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Meeting Report

Abstracts of the 25th Biennial International Congress on Thrombosis †

Vittorio Pengo [1,*] and Paolo Prandoni [2]

[1] Dept. Cardiac Thoracic and Vascular Sciences, Thrombosis Center, University Hospital Padova, via Giustiniani 2, 35128 Padova, Italy
[2] Clinica Medica 2, University of Padova, Via Ospedale 105, 35128 Padova, Italy; paolo.prandoni@unipd.it
* Correspondence: vittorio.pengo@unipd.it
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Abstract: This Issue collates the abstracts presented at the 25th Biennial International Congress on Thrombosis held on 23–26 May 2018. Prevention and treatment of thromboembolic events is a main issue in medicine that involves all the components of the health care system. Recently, a strong boost in this field came from the introduction of new antithrombotic agents whose use is expanding with the need for more information obtained by real-life studies. Thus, ICT 2018 was an important venue to compare clinical experiences and learn new advances in basic and pharmacological sciences.

Keywords: pharmacological sciences; thromboembolic; antithrombotic

1. Posters

1.1. Animal, Cellular and Molecular Research in Thrombosis

1.1.1. C0196 Effect of Cooling Environment in the State of Hemostasis System in Rats

Natalia Lycheva Alexandrovna

ZAO (Closed Joint Stock Company), St. Peterburg Institute of Pharmacy, Toxicology, St. Petersburg, Russia

Background

Hypothermia causes multi-organ failure or frostbite, which causes disability. We aimed to study hemostatic system in pre-reactive period of a cold injury that occurred during air and water-immersion cooling.

Methods

In the study we used 43 laboratory Wistar rats. Single air hypothermia was modulated by placing animals into a cooling chamber at a temperature −25 °C. The animals stayed in a chamber until rectal temperature was 30 °C. This is a moderate degree of hypothermia. Water-immersion cooling was modulated by placing animals into water at a temperature 5 °C and air −7 °C. Animals stayed in the water until rectal temperature was 27–30 °C. We assessed the state of vascular-platelet and plasma hemostasis as well as physiological state of anticoagulant and fibrinolytic systems. To perform the studies we used routine techniques and an integral method–thromboelastography.

Results

We stated that during water-immersion cooling experimental animals developed thrombocytosis and activation of their aggregation function. Laboratory parameters characterizing the initial stages of plasma hemostasis as well as external and internal activation pathways were not changed in such intensity of hypothermic effect. In contrast, we registered expressed thrombinemia at the final stage, that was confirmed by a significant increase of the concentration of soluble fibrin monomer complexes and decrease of the time of their self-assembly. Moreover, we observed the inhibition of fibrinolytic plasma activity on the background of the decrease of antithrombin III concentration. In this case, single air hypothermia accompanied by rectal temperature 30 °C also caused significant changes in hemostatic system. Vascular-platelet hemostasis responded to the intervention by the significant decrease of platelet aggregation activity. Plasma hemostasis was involved in the final stage of coagulation, which was manifested by hypocoagulation shifts. Along with this, we registered expressed inhibition of fibrinolytic activity in blood plasma.

Conclusions

Thus, rectal temperature +30 °C during immersion cooling was accompanied by the expressed activation of coagulation and registration of the state of thrombotic readiness. During air-cooling when rectal temperature reached +30 °C, secondary hypocoagulation shifts were recorded.

The reported study was funded by RFBR, according to the research project 16-34-60054 mol_a_dk.

1.1.2. C0197 a Comparative Characteristic of the State of the Hemostasis System in Rats under the Action of a Single Immersion Hypothermia Immediately and a Day after They Reached an Super Deep Degree of Hypothermia

Natalia Lycheva Alexandrovna

ZAO (Closed Joint Stock Company), St. Peterburg Institute of Pharmacy, Toxicology, St. Petersburg, Russia

Background

To study the state of hemostatic system in rats during hypothermic and post-hypothermic periods.

Methods

The studies were performed on 40 male Wistar rats, weighing 300 ± 15 g. Immersion hypothermia was modeled by placing the animals in individual cells in water at a temperature of 5 °C and air of 7 °C. The criterion for cessation of exposure was the achievement by experimental animals of a rectal temperature of 10–16 °C, which corresponded to an ultra-deep degree of hypothermia. Exposure time was individual and was 55 ± 5 min. The control was the blood of 20 animals, obtained after they were placed in water in individual cells in water at a temperature of 30 °C and air 22–25 °C. Exposure time corresponded to the cooling time of animals of the experimental group. In the future, all animals were divided into 4 groups. In the animals of the 1st group (control), the blood was taken immediately after removal from the water. In the animals of the 2nd group (experimental), immediately after reaching the super-deep degree of hypothermia. In the third group—the blood was collected 24 h after extraction from the water (control). In the fourth group, blood was collected 24 h after the cooling stopped (experimental).

Results

Comparative analysis of the results showed that immediately after the end of a single cold exposure, an increase in platelet aggregation activity and development of hypocoagulation shifts, a decrease in antithrombin III concentration against a background of increased fibrinogen concentration and inhibition of fibrinolytic system activity were observed. The described

hemostasiological status fits into the picture of the formation of a distress reaction in response to a single action of the stimulus. One day after the experimental animals reached the critical temperature of the nucleus, the hypocoagulation shifts were maintained in the bloodstream and the concentration of fibrinogen increased and thrombinemia markers were recorded. Thus, one day after the general supercooling, the risk of developing a state of thrombotic alert remained and the state of distress increased.

Conclusions

Signs of impaired hemostasiological properties of the blood, recorded immediately after the cessation of cooling, are aggravated in 24 h by the appearance of thrombinemia markers in the bloodstream.

The reported study was funded by RFBR, according to the research project 16-34-60054 mol_a_dk.

1.1.3. C0198 Comparative Characteristics of the Hemostasis System State in Rats during Hypothermic and Early Reactive Periods of General Cold Trauma

Natalia Lycheva Alexandrovna

ZAO (Closed Joint Stock Company), St. Peterburg Institute of Pharmacy, Toxicology, St. Petersburg, Russia

Background

The damaging effect of cold on the tissue is accompanied by the development of frostbite and multiple organ failure.

Methods

Male Wistar rats (53 individuals) were used in the study. The animals of the experimental groups underwent single immersion cooling in water at a temperature of 5 °C until profound hypothermia was reached. The control group of the animals was placed in water at a temperature of 30 °C. In the animals of the first group, blood was taken immediately after reaching profound hypothermia. In the second group blood was taken 24 h after cooling stopped.

Results

Comparative analysis of the results showed that immediately after the end of a single cold exposure, there was a significant increase in platelet aggregation activity, appearance of thrombinemia markers in the bloodstream and inhibition of fibrinolytic system activity. 24 h after the experimental exposure, these parameters returned to the initial values. When assessing the activity of external and internal ways of coagulation immediately after the termination of cooling, the development of hypocoagulation was established, both with routine tests and from thromboelastogram data. At the end of a 24-h period, hypocoagulation, recorded immediately after reaching the rectal temperature of the sought-for value, was preserved. Thus, after the end of a 24-h period after cold exposure termination, most of the parameters of the hemostatic system that had deviated from the normal level returned to it immediately after the end of the experiment. The delayed effect of hypothermia in this cold exposure regime manifested itself only by reduced coagulation activity at the initial steps of coagulation.

Conclusions

Signs of abnormal hemostasiological blood properties, recorded immediately after the cooling termination, disappear within 24 h and only hypocoagulation remains in the bloodstream. The reported study was funded by RFBR, according to the research project? 16-34-60054 mol?

1.1.4. C0205 Influence of the Peptide Trp-Thr-Ala-Glu-Glu-Arg-Gln-Leu on Hemostas

Alexandr Stepanov A. V. Stepanov, V. L. Tsepelev

Chita State Medical Academy, Chita, Russia

Background

The peptide Trp-Thr-Ala-Glu-Glu-Arg-Gln-Leu influences immunity. It stimulates the expression of clusters of CD19, CD21, CD22, CD23, CD38 and CD72 on lymphocytes, restores immunity to embryonic bursectomy. In animal experiments, the peptide affects hemostasis. Establish the mechanism of peptA22 ide action on hemostasis.

Methods

From the blood of patients with burns mononuclear cells were isolated. The peptide was added to the mononuclear culture at a concentration of 5 pmol/mL. Cells were cultured for 6 h. Growth medium was tested in hemostasis and fibrinolysis tests.

Results

The Trp-Thr-Ala-Glu-Glu-Arg-Gln-Leu peptide possessed a procoagulant effect. The main exact application of it is the external pathway for the formation of prothrombinase. Mononuclears under the influence of the peptide are isolated into the culture medium by protease inhibitors. This peptide mechanism explains its effect in vivo. In experimental models (embryonic bursectomy and thymectomy), the Trp-Thr-Ala-Glu-Glu-Arg-Gln-Leu peptide eliminates hypercoagulation. Another explanation of the effect of peptide on hemostasis is the immune regulation of hemostasis. Fibrinolysis did not reveal the effects of this peptide.

1.2. Antithrombotic drugs

1.2.1. C0071 Varying Response to Rivaroxaban and Apixaban in Individuals Measured Over Time

Suzanne Zwaveling [1], Joke Konings [2], Hilde Kelchtermans [2], Bas de Laat [2], H. Coenraad Hemker [2], Saartje Bloemen [3]

[1] *Maastricht University, Maastricht, Limburg, The Netherlands*
[2] *Synapse Research Institute, Maastricht, Limburg, The Netherlands*
[3] *Maastricht University, Department of Biochemistry Maastricht, Maastricht, Limburg, The Netherlands*

Background

Because of their presumed stable pharmacokinetics and -dynamics, direct oral anticoagulants (DOACs) are prescribed at fixed dosage without monitoring of their effect. However, both the relation between the dose and plasma levels, as that between plasma levels and the effect on thrombin generation (TG), have been shown to be highly variable between individuals. Here we investigated how stable the individual response to a fixed, spiked concentration of DOAC is over time.

Methods

Twelve consenting, healthy donors were included. Blood was collected every two months to a total of six samples. TG was determined in platelet poor plasma in the presence of 5 pM tissue factor and 4 μM phospholipid vesicles, with or without addition of 300 nM rivaroxaban or 200 nM apixaban. The response to DOACs was expressed as the percentage of inhibition of endogenous thrombin potential (ETP) or peak relative to the uninhibited sample.

Results

The effect of a fixed concentration of rivaroxaban or apixaban on TG parameters in a single individual appeared to be far from stable over time. The ETP varied around the individual average between 13.1–41.2% for rivaroxaban and 5.8–35.0% for apixaban; the peak between 1.1–6.2% and 2.7–15.4%, respectively. The differences of the uninhibited values over time were much less pronounced, particularly for the ETP (CV per donor over 6 time points between 3.4–14.2% for ETP and 1.2–8.5% for peak).

Conclusions

Previously we have shown that the in vitro response to a fixed DOAC concentration is highly variable between different individuals (CV up to 30.2%). Here we show that also within the same donor there is a large variation in response over time. The apparently low variation of the peak is due to the particular shape of the TG curve induced by the presence of direct factor Xa inhibitors, which makes that, contrary to the ETP, the peak is very sensitive at low, but not at higher concentrations of the inhibitor. Therefore, at values where the ETP is inhibited around 40–80%, the variation in the peak is minor.

We stress that the variations observed here are those of the response to a fixed spiked concentration around IC_{50}, in vivo the considerable pharmacokinetic variation will superimpose upon this pharmacodynamic variability. We postulate that, where a fixed dose DOAC regimen is found to be non-inferior to controlled vitamin K antagonist treatment, controlled DOAC treatment could be significantly superior.

1.2.2. C0099 One Time Point Measure Is Enough? Proposal Approach for a DOAC Patient Card

Simone Lorenzo Romano, Ilenia Scataglini, Tiziana Pavia, Giovanni Pellegrini, Lucia Ruocco

Ambulatorio Antitrombosi, U.O. Laboratorio Analisi Cliniche, Azienda Ospedaliera Pisana, Pisa, Italy,

Background

Although direct oral anticoagulants (DOACs) measurement is indicated in some clinical situations, none study found a useful laboratory cut-off.

The aim of the study was to set up a DOAC patient card considering a cohort of patients (pts) admitted to the Thrombosis Centre for follow up.

Methods

From 2013 to 2016, a total of 295 consecutive pts were enrolled for assessment of inter-individual variability (IV) and 114 for intra-IV. 37 pts were on dabigatran (23 and 14 taking 150 mg or 110 mg respectively), 39 were on rivaroxaban (30 and 9 taking 20 mg or 15 mg), 34 on apixaban (22 and 12 taking 5 mg or 2.5 mg) and 4 on edoxaban (60 mg). Blood was taken at peak (2 h after intake) and trough (12 h for dabigatran/apixaban or 24 h for rivaroxaban/edoxaban). Quality Control (QC) with 2 level concentrations of internal controls was performed. Diluted-thrombin-time (dTT-Werfen®) calibrated for dabigatran and anti-FXa (Stago®) for rivaroxaban, apixaban and edoxaban were carried. Inter-IV and intra-IV were determined by % coefficient of variation (CV). Renal function was assayed by creatinine/eGFR.

Results

114 pts (age 44–91) 55.3% males were followed. For all drugs, mean CV Inter-IV was lower at peak (41) then at trough (61); mean CV intra-IV was: at peak 22.4 and trough 20.3. Dabigatran showed the greatest CV intra-IV: at 150 mg (peak 23; trough 29.4), at 110 mg (peak 33.8, trough 30.2); rivaroxaban showed less variation both at 20 mg (peak 19.6; trough 22.4) and 15 mg (peak 21, trough 21.5); apixaban also at 5 mg (peak 10.1, trough 18.2), and 2.5 mg (peak 15.6 trough 7.4); edoxaban showed peak 12.5 and trough 13.4. The correlation with the eGFR was poor for all drugs. In all drugs

a cut-off was not found for inter-IV, nor in dabigatran for intra-IV. We set a personal card for DOACs, with the following data: surname, name, disease, drug (type and dose), drug concentration (range at peak and trough).

Conclusions

Our study confirmed the wide range of inter-IV of DOACs, with lower variance at peak than at trough. It is of clinical interest the DOAC measure in particular conditions, but the lack of a cut-off made a single dosage negligible. Moreover, the eGFR did not correlate with any drugs. The study showed a possible cut-off for intra-IV trough and peak level for all DOACs except for dabigatran. A personal range for DOACs could be useful for a specific clinical management. Our goal is to use a personal DOAC patient card but further studies are needed to verify it.

1.2.3. C0101 Safety and Efficacy of Anti Vitamin K Treatment Managed by Anticoagulation Clinic in the Era of Direct Anticoagulants

Cesare Manotti, Maria Ilaria Tassoni, Maria Lombardi, Piera Maria Ferrini, Gaetano Carolla, Carmine Siniscalchi, Pasquale Rubino, Anna Rocci, Tiziana Pasquariello, Pietro Rossetti, Roberto Quintavalla

Internal Medicine, Angiology and Coagulation Unit University Hospital, Parma, Italy

Background

In the era of Direct Oral AntiCoagulants (DOACs), that proven non-inferior or superior to Anti Vitamin K drugs (AVK) in preventing thromboembolism AVK are still used. The use of DOACs is growing but AVK are still used in particular conditions (DOACS contraindications, patients with Atrial Fibrillation and Valvular Disease, Mechanical Heart Valve Prosthesis and arterial disease). In these patients it is necessary to guarantee an adequate AVK treatment to prevent adverse events. The aim of this study was to verify safety and efficacy of care in rigorously controlled patients in AVK treatment delivered by an Anticoagulation Clinic.

Methods

Safety and efficacy of AVK treatment was evaluated by a cohort, observational, prospective study in all non-selected patients managed by our Anticoagulation Clinic from 1 January 2014 to 30 June 2016. Clinical endponts were major bleedings (MB), minor bleedings (MI), thrombo-embolic incidents (TE) and TTR (Time in Therapeutic Range) according to Rosendaal method.

Clinical outcome data was obtained through hospital discharge medical records using ICD 10 codes and dedicated data base of computerized AVK decision support system (DSS), TTR was acquired from DSS.

Results

The study included 5334 unselected AVK patients, observational period 8800.2 p/y. Mean age was 74.9 years. Indication treatment proportion were for NVAF 61.4%, Venous thromboembolic disease 21.4%, other indications 12.2. In whole population MB, MI, TE were respectively 1.78, 1.14 and 1.74% p/y and TTR 71.4%. Adverse events were higher in patients with TTR < 71% vs. > 71%. Patients in TTR < 71% group were 2736 with a follow up of 3791.2 p/y and 2598 for 5009.2 p/y in TTR > 71% group. Respectively MB, MI, TE were 2.58, 1.48, and 2.32% p/y in TTR < 71% group and 1.18, 0.88 and 1.30 in TTR > 71% group

Conclusions

Well-managed AVK, when patients spend a high proportion of time in the therapeutic range TTR > 71%, is safe and effective and may be a valid option in the era of DOACs, in particular in patients in which DOACs cannot be used.

1.2.4. C0107 WCM (Warfarin Composite Measure) a Method to Improve Anti Vitamin K Patients Management

Cesare Manotti [1], Maria Ilaria Tassoni [1], Maria Lombardi [1], Piera Maria Ferrini [1], Carmine Siniscalchi [1], Gaetano Carolla [1], Pasquale Rubino [1], Anna Rocci [1], Tiziana Pasquariello [1], Pietro Rossetti [1], Federico Banchelli [2], Roberto Quintavalla [1]

[1] *Internal Medicine, Angiology and Coagulation Unit University Hospital, Parma, Italy*
[2] *Statistics Unit, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio, Emilia, Italy*

Background

TTR is universally used to describe the quality of warfarin therapy in AVK patients and it has been associated with clinical outcomes. TTR reflects only intensity but not variability so it has a limited ability to predict individual complications risk. INR variability (Variance Growth Rate, VGR) has been studied however, it is unable to predict completely adverse events. Recently a new method WCM, which summarizes TTR and VGR, incorporating intensity and variability of INR has been proposed to better identify patients of risk complication. We studied whether WCM can improve AVK management better predicting patients at risk than TTR or VGR used independently.

Methods

We evaluated the ability of TTR, VGR and WCM in predicting adverse events by a cohort, observational, prospective study in all non-selected patients, in AVK therapy for at least six months, managed by our Anticoagulation Clinic from 1 January 2014 to 30 June 2016.

Clinical endpoints were major bleedings (MB), thromboembolic events (TE). Therapeutic quality control was evaluated by TTR according to Rosendaal method, VGR and WCM with methods proposed by Fihn, 1996 and Rouzuki, 2015. We divided patients into quintiles (Q) based on their level for TTR, VGR and WCM. (Q I the worst and progressively to the best QV) and MB and TE were stratified by the calculated Q.

Results

The study included 3452 AVK patients (7432.7 p/y). Mean age was 74.7 years. In the whole population MB, TE were respectively 1.27 and 1.56% p/y and mean TTR 70.7% (ds 20.1) with mean INR from Q I (41.7) to Q V(96.3). HR QI vs. Q V and Q II vs. Q V for MB was respectively for TTR, VGR, WCM 3.89, 2.78, 4.09 and 1.85, 3.27, 3.95. The HR for TE demonstrated the same difference between the worst and best Q: using WCM (Q I vs. Q V and Q II vs. Q V) 4.04, 2.19 as compared to TTR 2.8, 1.65 and VGR 4.56, 1.78.

Conclusions

WCM HR for MB and TE demonstrates a significant difference between excellent control and poorest control quintiles (QI and Q II) compared to TTR and VGR. This data suggests effectiveness of WCM in identifying AVK patients at risk of complications, who can benefit from closer INR control or other clinical and social support. We would suggest implementing in CDSS WCM together with TTR and VGR and making quality control patient data available in real time so as to improve the quality of AVK therapy.

1.2.5. C0170 Intracranial Haemorrhages during Vitamin K Antagonist Therapy for Non-Valvular Atrial Fibrillation: A Case-Control Study

Luca Zanella, Giacomo Zoppellaro, Gentian Denas, Seena Padayattil Jose, Vittorio Pengo

Department of Cardiac, Thoracic and Vascular Sciences, Padova, Italy

Background

Intracranial haemorrhages (ICHs) are the most fearful side effect of oral anticoagulant therapy. It is still not clear which risk factors are involved in the developing of ICHs in patients treated with vitamin K antagonists (VKAs) and if commonly used bleeding risk scores are able to predict which patients will develop ICHs.

Methods

This is a retrospective case-control study in a single Thrombosis Centre. During a seven years period (From 1 January 2006 to 31 December 2012), patients with non-valvular atrial fibrillation (NVAF) who developed ICHs during VKA treatment were identified as cases. Four control patients matched for gender, age and length of VKAs were assigned to each case. We collected information about the index event, including its localization, its cause (spontaneous or post-traumatic), INR value at the time of the event, and case fatality. Haemoglobin level, platelets count and creatinine values were also collected. TTR of the six months preceding the case's index event was calculated. In order to calculate CHA_2DS_2-VASc ischemic risk score, HAS-BLED, ATRIA and ORBIT bleeding risk scores, exposure to relevant risk factors was assessed for each patient. The association between considered risk factors and ICHs was evaluated using a linear logistic regression method. Receiver Operator Characteristic (ROC) curves to assess the predictive ability of bleeding risk scores were also evaluated.

Results

Fifty-one cases of ICHs most of whom (72.5%) 80 years of age or older were retrieved. Case fatality rate was 27.5% (14 cases). The median time from beginning of VKAs to ICHs was approximately 26 months, ranging from 15 to 55 months. INR value was in target range at the time of the event (mean INR: 2.8 ± 0.9) in most patients (80%). Five cases out of 51 were above and five below the therapeutic range, respectively. Compared to 204 controls, no individual risk factor was associated with ICHs (Table 1).

Ischaemic risk score CHA_2DS_2-VASc and bleeding risk scores HAS-BLED, ATRIA and ORBIT did not show statistically significant differences between cases and controls (Table 2).

These scores showed a poor ability to predict ICHs using ROC curves (Table 3).

Conclusions

ICHs during therapy with VKAs are frequent in very elderly, hardly predictable and apparently not associated with known risk factors or commonly used risk scores. NOACs might be preferred for ICHs prevention in very elderly population with NVAF.

1.2.6. C0171 Different Safety Profiles of Oral Anticoagulants in Very Elderly Non-Valvular Atrial Fibrillation Patients: A Propensity Score Matched Cohort Study

Giacomo Zoppellaro [1], Luca Zanella [2], Gentian Denas [2], Nicola Gennaro [3], Eliana Ferroni [3], Ugo Fedeli [3], Seena Padayattil Jose [2], Giorgio Costa [4], Maria Chiara Corti [3], Margherita Andretta [4], Vittorio Pengo [2]

1 *Padua University Hospital*
2 *Department of Cardiac, Thoracic and Vascular Sciences, Padova, Italy*
3 *Epidemiological Department (SER), Veneto Region, Padova, Italy*
4 *Unified Pharmaceutical Coordination Centre (CRUF), Veneto Region, Venezia, Italy*

Background

Non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in non-valvular atrial fibrillation (NVAF) are the first-line therapy according to guidelines. Data in comparison to vitamin K antagonists (VKAs) in very elderly patients are scanty.

Methods

This is a population-based retrospective cohort study including NVAF patients with ≥80 years of age, who initiated oral anticoagulants for stroke prevention in a region with well-managed VKA therapy. NOACs and VKAs cohorts were identified using Anatomical Therapeutic Chemical (ATC) codes, while excluding other indications for anticoagulation therapy using ICD-9CM codes. Event-rates were assessed using both *intention to treat* and *as treated* analyticalapproaches.

Results

15,136 elderly naïve patients (2882 treated with NOACs and 12,254 with VKAs) were identified. Overall, ischaemic stroke and major bleeding were not different for NOACs and VKAs with both approaches. However, the two groups showed a different major bleeding profile: in the *as treated* analysis, gastrointestinal bleeding was significantly higher (HR 1.81, 95% CI 1.12–2.94) and intracerebral bleeding significantly lower (HR 0.32, 95% CI 0.16–0.65) in patients taking NOACs. Gastrointestinal bleeding was especially frequent from the lower tract in the NOAC group (HR 3.48, 95% CI 1.51–8.05). Mortality was similar between groups, with a trend for reduction in NOACs.

Conclusions

In comparison to well-managed VKA therapy, NOACs in very elderly patients with NVAF reduce intracerebral haemorrhage and increase gastrointestinal bleeding, mostly from the lower tract.

1.3. Angiogenesis and Vascular Biology

C0233 The Role of GDF15 Protein in the Development of Hypercoagulation in Essential Hypertension

Alexandr Stepanov A. V. Stepano, S. O. Davydov, B. I. Kuznik, Y. N. Smolyakov, E. S. Guseva

Chita State Medical Academy, Chita, Russia

Background

GDF15 protein plays an important role in the development of essential hypertension. In recent years, a number of studies have shown that this protein is a marker of the severity of cardiovascular diseases. This study is aimed at clarifying the role of GDF15 protein in the formation of thrombogenic potential in essential hypertension.

Methods

Our observations were made on women with stage II arterial hypertension with a high risk of cardiovascular complications, voluntarily agreeing to participate in the study. We studied the concentration of GDF15, lipid spectrum, blood coagulation. In addition, the spatial growth of the fibrin clot was investigated with Thrombodynamics Analyzer T2.

Results

Our observations showed that in women with essential hypertension, the concentration of GDF15 increases significantly. In stage II hypertension, the coagulation and fibrinolysis indexes do not differ from the norm. However, in these patients, the initial and steady-state rate of the fibrin clot formation and its dimensions are significantly increased. The presented facts testify to a distinct increase in the thrombus formation process in hypertensive patients.

Significant changes are revealed in the lipid spectrum—the concentration of total cholesterol, triglycerides and very low density lipoproteins increases, as well as the atherogenic index.

We found numerous correlations from weak to strong between the concentration of GDF15 and the studied parameters of hemostasis and lipid metabolism.

Conclusions

All submitted data indicate the extremely important role of GDF15 protein in the formation of thrombogenic potential in women suffering from hypertension. There is no doubt that the use of drugs or procedures aimed at lowering blood concentration of GDF15, will be a pathogenetic basis of therapy of hypertension and its complications.

1.4. Antithrombotic Drugs

1.4.1. C0099 One Time Point Measure Is Enough? Proposal Approach for a DOAC Patient Card

Simone Lorenzo Romano, Ilenia Scataglini, Tiziana Pavia, Giovanni Pellegrini, Lucia Ruocco

Ambulatorio Antitrombosi, U.O. Laboratorio Analisi Cliniche, Azienda Ospedaliera Pisana, Pisa, Italy,

Background

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The aim of the study wasto set up a DOAC patient card considering a cohort of patients (pts) admitted to the Thrombosis Centre for follow up.

Methods

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1.4.2. C0101 Safety and Efficacy of Anti Vitamin K Treatment Managed by Anticoagulation Clinic in the Era of Direct Anticoagulants

Cesare Manotti, Maria Ilaria Tassoni, Maria Lombardi, Piera Maria Ferrini, Gaetano Carolla, Carmine Siniscalchi, Pasquale Rubino, Anna Rocci, Tiziana Pasquariello, Pietro Rossetti, Roberto Quintavalla

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Methods

Safety and efficacy of AVK treatment was evaluated by a cohort, observational, prospective study in all non selected patients managed by our Anticoagulation Clinic from 1 January 2014 to 30 June 2016. Clinical endpoints were major bleedings (MB), minor bleedings (MI), thrombo-embolic incidents (TE) and TTR (Time in Therapeutic Range) according to Rosendaal method.

Clinical outcome data was obtained through hospital discharge medical records using ICD 10 codes and dedicated data base of computerized AVK decision support system (DSS), TTR was acquired from DSS.

Results

The study included 5334 unselected AVK patients, observational period 8800.2 p/y. Mean age was 74.9 years. Indication treatment proportion were for NVAF 61.4%, Venous thromboembolic disease 21.4%, other indications 12.2. In whole population MB, MI, TE were respectively 1.78, 1.14 and 1.74% p/y and TTR 71.4%. Adverse events were higher in patients with TTR < 71% vs. > 71%. Patients in TTR < 71% group were 2736 with a follow up of 3791.2 p/y and 2598 for 5009.2 p/y in TTR > 71% group. Respectively MB, MI, TE were 2.58, 1.48, and 2.32% p/y in TTR < 71% group and 1.18, 0.88 and 1.30 in TTR > 71% group

Conclusions

Well-managed AVK, when patients spend a high proportion of time in the therapeutic range TTR > 71%, is safe and effective and may be a valid option in the era of DOACs, in particular in patients in which DOACs can not be used.

1.4.3. C0107 WCM (Warfarin Composite Measure) a Method to Improve Anti Vitamin K Patients Management

Cesare Manotti [1], Maria Ilaria Tassoni [1], Maria Lombardi [1], Piera Maria Ferrini [1], Carmine Siniscalchi [1], Gaetano Carolla [1], Pasquale Rubino [1], Anna Rocci [1], Tiziana Pasquariello [1], Pietro Rossetti [1], Federico Banchelli [2], Roberto Quintavalla [1]

[1] *Internal Medicine, Angiology and Coagulation Unit University Hospital, Parma, Italy*

[2] *Statistics Unit, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio, Emilia, Italy*

Background

TTR is universally used to describe the quality of warfarin therapy in AVK patients and it has been associated with clinical outcomes. TTR reflects only intensity but not variability so it has a limited ability to predict individual complications risk. INR variability (Variance Growth Rate, VGR) has been studied however, it is unable to predict completely adverse events. Recently a new method WCM, which summarizes TTR and VGR, incorporating intensity and variability of INR has been proposed to better identify patients of risk complication. We studied whether WCM can improve AVK management better predicting patients at risk than TTR or VGR used independently.

Methods

We evaluated the ability of TTR, VGR and WCM in predicting adverse events by a cohort, observational, prospective study in all non selected patients, in AVK therapy for at least six months, managed by our Anticoagulation Clinic from 1 January 2014 to 30 June 2016.

Clinical endponts were major bleedings (MB), thromboembolic events (TE). Therapeutic quality control was evaluated by TTR according to Rosendaal method, VGR and WCM with methods proposed by Fihn, 1996 and Rouzuki, 2015. We divided patients into quintiles (Q) based on their level for TTR, VGR and WCM. (Q I the worst and progressively to the best QV) and MB and TE were stratified by the calculated Q.

Results

The study included 3452 AVK patients (7432.7 p/y). Mean age was 74.7 years. In the whole population MB, TE were respectively 1.27 and 1.56% p/y and mean TTR 70.7% (ds 20.1) with mean INR from Q I (41.7) to Q V (96.3). HR QI vs. Q V and Q II vs. Q V for MB was respectively for TTR, VGR, WCM 3.89, 2.78, 4.09 and 1.85, 3.27, 3.95. The HR for TE demonstrated the same difference between the worst and best Q: using WCM (Q I vs. Q V and Q II vs. Q V) 4.04, 2.19 as compared to TTR 2.8, 1.65 and VGR 4.56, 1.78.

Conclusions

WCM HR for MB and TE demonstrates a significant difference between excellent control and poorest control quintiles (QI and Q II) compared to TTR and VGR. This data suggests effectiveness of WCM in identifying AVK patients at risk of complications, who can benefit from closer INR control or other clinical and social support. We would suggest implementing in CDSS WCM together with TTR and VGR and making quality control patient data available in real time so as to improve the quality of AVK therapy.

1.4.4. C0170 Intracranial Haemorrhages during Vitamin K Antagonist Therapy for Non-Valvular Atrial Fibrillation: A Case-Control Study

Luca Zanell, Giacomo Zoppellaro, Gentian Denas, Seena Padayattil Jose, Vittorio Pengo

Department of Cardiac, Thoracic and Vascular Sciences, Padova, Italy

Background

Intracranial haemorrhages (ICHs) are the most fearful side effect of oral anticoagulant therapy. It is still not clear which risk factors are involved in the developing of ICHs in patients treated with vitamin K antagonists (VKAs) and if commonly used bleeding risk scores are able to predict which patients will develop ICHs.

Methods

This is a retrospective case-control study in a single Thrombosis Centre. During a seven years period (From 1 January 2006 to 31 December 2012), patients with non-valvular atrial fibrillation (NVAF) who developed ICHs during VKA treatment were identified as cases. Four control patients

matched for gender, age and length of VKAs were assigned to each case. We collected information about the index event, including its localization, its cause (spontaneous or post-traumatic), INR value at the time of the event, and case fatality. Haemoglobin level, platelets count and creatinine values were also collected. TTR of the six months preceding the case's index event was calculated. In order to calculate CHA_2DS_2-VASc ischemic risk score, HAS-BLED, ATRIA and ORBIT bleeding risk scores, exposure to relevant risk factors was assessed for each patient. The association between considered risk factors and ICHs was evaluated using a linear logistic regression method. Receiver Operator Characteristic (ROC) curves to assess the predictive ability of bleeding risk scores were also evaluated.

Results

Fifty-one cases of ICHs most of whom (72.5%) 80 years of age or older were retrieved. Case fatality rate was 27.5% (14 cases). The median time from beginning of VKAs to ICHs was approximately 26 months, ranging from 15 to 55 months. INR value was in target range at the time of the event (mean INR: 2.8 ± 0.9) in most patients (80%). Five cases out of 51 were above and five below the therapeutic range, respectively. Compared to 204 controls, no individual risk factor was associated with ICHs (Table 1).

Ischaemic risk score CHA_2DS_2-VASc and bleeding risk scores HAS-BLED, ATRIA and ORBIT did not show statistically significant differences between cases and controls (Table 2).

These scores showed a poor ability to predict ICHs using ROC curves (Table 3).

Conclusions

ICHs during therapy with VKAs are frequent in very elderly, hardly predictable and apparently not associated with known risk factors or commonly used risk scores. NOACs might be preferred for ICHs prevention in very elderly population with NVAF.

1.4.5. C0171 Different Safety Profiles of Oral Anticoagulants in Very Elderly Non-Valvular Atrial Fibrillation Patients: A Propensity Score Matched Cohort Study

Giacomo Zoppellaro [1], Luca Zanlla [1], Gentian Denas [1], Nicola Gennaro [2], Eliana Ferron [2], Ugo Fedel [2], Seena Padayattil Jose [3], Giorgio Costa [1], Maria Chiara Corti [3], Margherita Andretta [1], Vittorio Pengo [3]

[1] *Department of Cardiac, Thoracic and Vascular Sciences, Padova, Italy*
[2] *Epidemiological Department (SER), Veneto Region, Padova, Italy*
[3] *Unified Pharmaceutical Coordination Centre (CRUF), Veneto Region, Venezia, Italy*

Background

Non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in non-valvular atrial fibrillation (NVAF) are the first-line therapy according to guidelines. Data in comparison to vitamin K antagonists (VKAs) in very elderly patients are scanty.

Methods

This is a population-based retrospective cohort study including NVAF patients with ≥80 years of age, who initiated oral anticoagulants for stroke prevention in a region with well-managed VKA therapy. NOACs and VKAs cohorts were identified using Anatomical Therapeutic Chemical (ATC) codes, while excluding other indications for anticoagulation therapy using ICD-9CM codes. Event-rates were assessed using both *intention to treat* and *as treated* analyticalapproaches.

Results

15,136 elderly naïve patients (2882 treated with NOACs and 12,254 with VKAs) were identified. Overall, ischaemic stroke and major bleeding were not different for NOACs and VKAs with both approaches. However, the two groups showed a different major bleeding profile: in the *as treated*

analysis, gastrointestinal bleeding was significantly higher (HR 1.81, 95% CI 1.12–2.94) and intracerebral bleeding significantly lower (HR 0.32, 95% CI 0.16–0.65) in patients taking NOACs. Gastrointestinal bleeding was especially frequent from the lower tract in the NOAC group (HR 3.48, 95% CI 1.51–8.05). Mortality was similar between groups, with a trend for reduction in NOACs.

Conclusions

In comparison to well-managed VKA therapy, NOACs in very elderly patients with NVAF reduce intracerebral haemorrhage and increase gastrointestinal bleeding, mostly from the lower tract.

1.4.6. C0182 Intentional Intoxication with Rivaroxaban and Carvedilol: Clinical Evaluation and Monitoring of Anticoagulation Effect of Rivaroxaban

Luciana Goncalves Ricca [1], Ana Leite [1], Ines Garcia [2], Dina Hortela [2], Carmo Koch [1]

[1] *Transfusion Medicine and Blood Bank, Centre of Thrombosis and Hemostasis, Sao Joao University Hospital, Porto, Portugal*

[2] *Emergency Department, Sao Joao University Hospital, Porto, Portugal*

Background

Rivaroxaban is a direct factor Xa inhibitor, increasingly used for prevention of thrombotic events. An overdose is expected to lead to significant coagulopathy and increased bleeding risk. Carvedilol is a vasodilating beta-blocker indicated for the treatment of heart failure. An overdose can be associated to bradycardia, hypotension, cardiac insufficiency and hypoglycemia. Few cases of overdose with both drugs have been reported, limiting the clinical experience in these situations. We report the case of a patient with an intentional overdose of rivaroxaban and carvedilol.

Methods

A 74 years old female patient under carvedilol due to heart failure and rivaroxaban due to pulmonary embolism was admitted at the emergency department, 90 min after ingestion of 280 mg of rivaroxaban (20 mg × 14 tablets) and 350 mg of carvedilol (25 mg × 14 tablets). At admission she was conscious, with heart rate 80 bpm, oxygen saturation 98%, but with hypotension (blood pressure 65/47 mmHg). No signs of bleeding were present.

The initial laboratory evaluation revealed: normal full blood count, serum creatinine 0.62 mg/dL, serum glucose 140 mg/dL, aPTT 38.2 s, PT 16.9 s. Rivaroxaban concentration determined by a specific anti-FXa chromogenic assay was 367 ng/mL. Carvedilol concentrations were not analysed.

Few minutes after admission, intravenous infusion of fluids (sodium chloride 0.9% solution and glucagon) and oral activated charcoal (50 g) were administered.

Results

Blood pressure was normal 3 h after admission (113/70 mmHg) and patient remained asymptomatic with normal vital signs.

Six hours after admission laboratory tests were: aPTT 32.6 s, PT 13.7 s, rivaroxaban concentration 79 ng/mL, serum glucose 90 mg/dL. Twelve hours after admission rivaroxaban concentration was 13 ng/mL.

Signs of bleeding were never detected.

Conclusions

Though the patient ingested an excessive dose of rivaroxaban, she did not have any bleeding complication or significant coagulopathy. The prompt administration of oral activated charcoal certainly contributed to prevent a major increase of rivaroxaban plasma concentration. The excessive ingestion of carvedilol was also efficiently managed. Patient was discharged 24 h after this intoxication and sent to a psychiatric clinic.

1.4.7. C0189 Thrombin Generation Detects a Hypercoagulable Effect of "In Vitro"; Added Idarucizumab to Normal Plasma Samples

Mojca Krivec, Nina Vene, Alenka Mavri, Mojca Bozic Mijovski

University Medical Centre, Ljubljana, Slovenia

Background

Idarucizumab is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with dabigatran when reversal of the anticoagulant effects are needed. It has been suggested that the "in vitro" addition of idarucizumab to plasma from patients treated with dabigatran could fully neutralize the effects of dabigatran and thus facilitate the diagnosis of coagulation defects or extensive thrombophilia screening. There is little knowledge about the effect of the "in vitro" addition of idarucizumab to normal plasma samples. The aim of this study was to assess this effect on thrombin generation.

Methods

Blood was drawn from 44 patients, centrifuged immediately and platelet-poor plasma stored at −70 °C until analysis. Thrombin generation was measured before and after the addition of idarucizumab to plasma (final concentration of 125 mg/L) with Technothrombin TGA RC Low reagent and Technothrombin substrate (both Technoclone, Austria). Lag time, time to peak thrombin (TTP), peak thrombin and area under the curve (AUC) were recorded.

Results

The "in vitro" addition of idarucizumab to normal plasma samples significantly shortened the thrombin generation lag time and TTP, while Thrombin and AUC increased, implying a prothrombotic state (Table 1).

Table 1. Thrombin generation before and after the "in vitro" addition of idarucizumab to normal plasma samples. Means ± standard deviations are shown with paired *T*-Test *p* values.

Thrombin Generation	Before	After	% Change	*p*
Lag (min)	17.2 ± 3.3	16.2 ± 3.3	−5.8	<0.001
Thrombin (nM)	203 ± 86	230 ± 90	13.3	<0.001
TTP (min)	24.6 ± 4.7	23.3 ± 4.4	−5.3	<0.01
AUC	3400 ± 726	3912 ± 677	15.1	<0.001

Conclusions

Our study showed a slight but significant hypercoagulable effect of the "in vitro" addition of idarucizumab to normal plasma samples. This effect should further be studied in other coagulation assays.

1.4.8. C0190 the Hypercoagulable Effect of "In Vitro"; Added Idarucizumab on Thrombin Generation

Mojca Krivec, Nina Ven, Alenka Mavri, Mojca Bozic Mijovski

University Medical Centre, Ljubljana, Slovenia

Background

It has been suggested that the "in vitro" addition of idarucizumab to plasma fully neutralizes the effects of dabigatran. The aim of this study was to assess the influence of "in vitro" addition of idarucizumab on thrombin generation in plasma samples from patients treated with dabigatran.

Methods

Blood was drawn from 44 patients before initiation of therapy with dabigatran (baseline) and then twice at trough and twice at peak dabigatran concentration. In plasma thrombin generation was measured before (DABI) and after the addition of idarucizumab to plasma (final concentration of 125 mg/L, DABI+I) with Technothrombin TGA RC Low reagent and Technothrombin substrate (both Technoclone, Austria). Lag time, time to peak thrombin (TTP), peak thrombin and area under the curve (AUC) were recorded. Dabigatran concentration was measured with the in-house modified thrombin time.

Results

Dabigatran correlated positively with thrombin generation lag time ($r = 0.50$, $p < 0.001$) and TTP ($r = 0.43$, $p < 0.001$), and negatively with AUC ($r = -0.38$, $p < 0.001$), while there was no association between dabigatran and peak thrombin. The addition of idarucizumab significantly shortened lag time and TTP, both to the levels comparable to baseline. Idarucizumab significantly increased the amount of thrombin formed, as AUC was significantly lower in DABI and significantly higher in DABI+I samples compared to baseline. Peak thrombin was similar in DABI and baseline samples, but significantly increase in DABI+I (Table 1).

Table 1. Thrombin generation in "ex vivo" samples with dabigatran (DABI), after the addition of idarucizumab (DABI+I) and baseline samples. Means ± standard deviations are shown with ANOVA p values.

Thrombin Generation	DABI	DABI + I	Baseline	*p*
Lag time (min)	36.4 ± 9.6 *	16.0 ± 4.2	17.2 ± 3.3	<0.001
Thrombin (nM)	208 ± 102	270 ± 94 *#	203 ± 86	<0.001
TTP (min)	43.3 ± 10.6 *	22.5 ± 5.8	24.6 ± 4.7	<0.001
AUC	2184 ± 1126 *	4138 ± 692 *	3400 ± 726	<0.001

* Post-hoc $p < 0.001$ compared to baseline values; # post-hoc $p < 0.001$ compared to DABI.

Conclusions

Our study showed a significant hypercoagulable effect of the "in vitro" addition of idarucizumab to plasma samples from patients receiving dabigatran as shown by the increased peak thrombin and AUC of a thrombin generation assay.

1.4.9. C0203 Dabigatran Reversal with Idarucizumab for Thrombolysis after Acute Ischemic Stroke: Case Report

Federico Martinez Sabio [1], Luisa Fonseca [2], Luciana Gonçalves [1], Carla Monteiro [1], Ana Leite [1], Maria Koch [1]

[1] *Centre of Thrombosis and Haemostasis, Centro Hospitalar de Sao Joao, Porto, Portugal*
[2] *Stroke Unit, Centro Hospitalar de Sao Joao, Porto, Portugal*

Background

The likelihood of a total recovery after an acute ischemic stroke (AIS) is significantly improved by reperfusion either by intravenous thrombolytic treatment or endovascular mechanical thrombectomy. The use of intravenous thrombolysis is limited by the short treatment window and the need to assess individual balance of benefit and risk of symptomatic intracranial haemorrhage. Current guidelines do not recommend thrombolysis in patients under non-vitamin K antagonists (NOACs), due to intracranial bleeding risk, unless the last dose of NOAC is taken >48 h before and anticoagulation tests are normal. Idarucizumab is a monoclonal antibody fragment approved for immediate reversal of dabigatran anticoagulation, in patients with life-threatening bleeding or needing urgent invasive procedures. The use in patients with AIS candidates for thrombolytic

therapy has been rarely used. We report the case of a patient with AIS anticoagulated with dabigatran who received idarucizumab for allowing urgent thrombolysis.

Methods

A 76 years-old male patient with atrial fibrillation, under dabigatran 110 mg bid for stroke prevention, was admitted in the emergency department with aphasia, right hemiparesis, dysarthria, right homonymous hemianopsia, NIHSS 15. Symptoms onset occurred 3 h before admission. A CT angiography detected a distal thrombus in left middle cerebral artery. Laboratory evaluation was: normal full blood count, CrCl 72 mL/min, aPTT 28.5 (N: 24–36 s), PT 13.1 (N: 9.9–13.8 s). According to his wife, he took the last dose of dabigatran 10 h before admission. It was decided to give idarucizumab 2.5 g EV (half-dose due to normal aPTT); immediately after infusion he received thrombolytic therapy (alteplase iv).

Results

NIHSS was 10 in the end of alteplase and 2 twenty-four hours after alteplase. Patient did not present any bleeding complication. He was discharged 4 days later to a local hospital without sequels, under enoxaparin and AAS. He resumed the anticoagulation with dabigatran 150 mg bid 2 weeks later

Conclusions

Reversal of dabigatran with idarucizumab in this patient requiring thrombolysis was efficient and safe. However further studies need to be done to corroborate the good results that have been obtained in several case reports. It is important to emphasize that this patient was under-treated with dabigatran, according to the guidelines, highlighting the need to prescribe the right dose to the right patient to improve efficacy and safety of dabigatran.

1.4.10. C0215 Reduced Variability to Aspirin Antiplatelet Effect by the Coadministration of Statins in Individuals with Established Cardiovascular Disease or with Cardiovascular Risk Factors

Melania Dovizio [1], Stefania Tacconelli [1], Luigia Di Francesco [1], Alessandra Meneguzzi [2], Ilaria Díagostino [1], Virgilio Evangelista [3], Marta Luciana Capone [1], Stefano Manarini [3], Linda Grossi [1], Ettore Porreca [1,2,3,4], Concetta Di Febbo [4], Annalisa Bruno [1], Patrizia Ballerini [1], Giacomo Levantes [5], Cristiano Fava [2], Pietro Minuz [2]

1 *"G. d'Annunzio" University of Chieti, Chieti, Italy*
2 *University of Verona and Policlinico ìG.B. Rossiî, Verona, Italy*
3 *Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy*
4 *SS. Annunziata Hospital, Chieti, Italy*
5 *San Pio da Pietrelcina Hospital, Vasto, Chieti, Italy*

Background

A virtually complete suppression of platelet cyclooxygenase (COX)-1 activity by low-dose aspirin, via the acetylation at serine-529 which persists throughout dosing interval, is mandatory to fulfil its cardioprotective effect. In fact, even small concentrations of thromboxane (TX)A2 have been shown to cause platelet activation.

Methods

We studied the influence of cardiovascular(CV) risk factors, previous CV events, and co-treatments with preventive medicines, on residual platelet thromboxane(TX)B2 production in serum of 182 individuals with established CV disease(CVD) or with CV risk factors (dyslipidemia, hypertension and diabetes) who were chronically treated with enteric coated (EC)-aspirin 100 mg/day. In a control group of 13 individuals with comparable age and gender treated for a week with

low-dose EC-aspirin, the upper limit value of serum TXB2 for an adequate response to aspirin was defined as 3.90 ng/mL, i.e., the mean value ±2 SDs. In a subgroup of patients, the systemic TXA2 biosynthesis (by assessing the urinary levels of 11-dehydro-TXB2, TX-M) and arachidonic acid-induced platelet aggregation were evaluated.

Results

Residual serum TXB2 levels exceeded the upper limit value for an adequate response to aspirin in 14% of individuals. This phenomenon was detected at 12 h after dosing with aspirin, thus excluding the influence of an accelerated platelet turnover. In a subgroup of individuals with serum TXB2 values >3.9 ng/mL, median values of urinary TX-M and AA-induced platelet aggregation were significantly higher than in the individuals with serum TXB2 < 3.9 ng/mL. The co-administration of statins was an independent predictor of residual serum TXB2 levels, and the percentage of patients with enhanced values was significantly lower in statin users vs. nonusers (9.00 vs. 22.00%, $p < 0.05$). We provide evidence in vitro that atorvastatin (the most used statin in our patient population) reduced residual TXB2 generation by increasing the extent of acetylation of platelet COX-1 by aspirin.

Conclusions

The coadministration of atorvastatin, and possibly other statins, may counter the mechanisms associated with the CVD which translate into reduced bioavailability of low-dose EC aspirin in some individuals. The results of the present study may contribute to give a mechanistic interpretation of the additional effects in reducing cardiovascular events by the co-administration of low-dose aspirin and statins.

1.4.11. C0220 Low Drug Levels and Thrombotic Complications in High Risk Atrial Fibrillation Patients Treated with Direct Oral Anticoagulants

Sophie Testa [1], Oriana Paoletti [1], Cristina Legnani [2], Claudia Dellanoce [1] Emilia Antonucci [3], Benilde Cosmi [3], Vittorio Pengo [4], Daniela PoliI [2], Rossella Morandini [5], Roberto Testa [6], Armando Tripodi [7], Gualtiero Palareti [8]

1 *Centro Emostasi e Trombosi, Cremona, Italy*
2 *Angiologia AOU Sant'Orsola Malpighi, Bologna, Italy*
3 *Fondazione Arianna Anticoagulazione, Clinical Trial Bologna, Bologna, Italy*
4 *Universitá di Padova, Padova, Italy*
5 *Centro Emostasi e Trombosi, Cremona, Italy*
6 *INRCA-IRCCS, Ancona, Italy*
7 *Centro Emofilia e Trombosi, Universitá di Milano, Milano, Italy*
8 *Fondazione Arianna Anticoagulazione, Bologna, Italy*

Background

Direct oral anticoagulants (DOACs) are administered at fixed dose without need for dose adjustment by lab testing. A high inter-individual variability in the drug blood levels was shown with all DOACs. To evaluate a possible relationship between DOAC C-trough anticoagulant levels and thromboembolic events, 565 consecutive naïve patients with atrial fibrillation (AF), were enrolled in this study performed within the START-Laboratory Registry

Methods

DOAC specific measurements [diluted thrombin time (dTT) or anti-FIIa calibrated for dabigatran; anti-FXa calibrated for rivaroxaban or apixaban] at C-trough were performed locally at steady state within 15–25 days from starting treatment. For each DOAC, the interval of C-trough levels, from the limit of quantification to the highest value, was subdivided into 4 equal classes and

results were attributed to these classes; the median values of results were also calculated. Thromboembolic complications occurring for 1 year follow up were recorded.

Results

Thromboembolic events (1.8%) occurred in 10 patients who had baseline C-trough levels in the lowest class of drug levels. The incidence of thromboembolic events among patients with DOAC C-trough results in the lowest level class was 2.4%, while it was 0% in the remaining groups. The patients with thrombotic complications also had a mean CHA_2DS_2-VASc score higher than the total patient population (5.3 ± 1.4 vs. 3.0 ± 1.4).

Conclusions

In this study cohort, thrombotic complications occurred only in DOAC-treated AF patients who had very low C-trough levels, with relatively high CHA_2DS_2-VASc score. Larger studies are warranted to confirm these preliminary observations.

1.4.12. C0222 High Risk for Reoperation among Patients with Bioprosthetic Heart Valves and Indication for Long-Term Anticoagulation

Daniela Poli [1], Emilia Antonucci [2], Vittorio Pengo [3], Elisa Grifoni [4], Niccolo Maggini [1], Sophie Testa [5], Arturo Cafolla [6], Paolo Pedico [7], Antonio Insana [8], Angelo Santoro [9], Francesco Marongiu [10], Carmelo Paparo [8], Eugenio Bucherini [11], Pasquale Pignatelli [12], Lucilla Masciocco [13], Andrea Toma [14], Luigi Ria [15], Gualtiero Palareti [16]

1 *AOU Careggi, Firenze, Italy*
2 *Fondazione Arianna Anticoagulazione, Clinical Trial Bologna, Bologna, Italy*
3 *Universitá di Padova, Padova, Italy*
4 *Med Interna Ospedale di Empoli, Empoli, Italy*
5 *Centro Emostasi e Trombosi, Cremona, Italy*
6 *Policlinico Umberto I, Roma, Italy*
7 *Med Trasfusionale, Barletta, Italy*
8 *Osp Moncalieri, Moncalieri, Italy*
9 *Osp Perrino Brindisi, Brindisi, Italy*
10 *Universitá di Cagliari, Cagliari, Italy*
11 *Ospedale di Faenza, Faenza, Italy*
12 *Universitá Sapienza, Roma, Italy*
13 *Ospedale di Lucera, Lucera, Italy*
14 *Ospedale di Arzignano, Arzignano, Italy*
15 *Ospedale di Gallipoli, Gallipoli, Italy*
16 *Fondazione Arianna Anticoagulazione Bologna, Bologna, Italy*

Background

Several factors should be considered when a prosthetic heart valve, bioprosthetic (BV) or mechanical (MV), is to be implanted: thrombogenicity, life-expectancy and the risk of reoperation.

Methods

We conducted an observational retrospective multicenter study among Italian Thrombosis Centers on patients with BV on long-term VKA treatment to evaluate the risk of reoperation and the rate of bleeding and thrombotic events.

Results

We analyzed 612 patients (median age 71.8 years) with BV on long-term VKA treatment for the presence of AF (78.4%) or other indications (21.6%). Thirty-four major bleeding events (rate 1.1 × 100

pt-yrs) and 29 thromboembolic events (rate 0.9 × 100 pt-yrs) were recorded, and 46 patients (rate 1.5 × 100 pt-yrs) undergo reoperation. The percentage of reoperation was higher among younger patients: 32.9% among patients <60 years and 3.9% among patients ≥60 years [RR 3.8 (2.1–7.2) p = 0.0001]. When patients were analyzed according to age < or ≥65 years and < or ≥70 years, younger patients still were at higher risk for reoperation [RR 3.1 (1.7–6.0), p = 0.0001 and 3.7 (1.7–8.6), p = 0.0001, respectively.

Conclusions

Our findings suggest that the threshold of 65 years for implanting a BV should be carefully evaluated, considering the high risk for reoperation and the high risk of AF occurrence with persisting need for long-term anticoagulation. The high risk for reoperation of young patients implanted with BV and the availability of a safer and easier way to conduct VKAs treatment such as the use of point-of-care devices, should be considered when the type of valve must be chosen.

1.4.13. C0238 Thrombin Generation in Routine Clinical Practice Patients Receiving Dabigatran

Mojca Krivec, Nina Vene, Alenka Mavri, Mojca Bozic Mijovski

University Medical Centre, Ljubljana, Slovenia

Background

The impact of dabigatran on in vivo anticoagulation effect is not fully elucidated. The aim of this study was to assess thrombin generation in routine clinical practice patients receiving dabigatran.

Methods

Blood was drawn from 44 patients before initiation of therapy with dabigatran (baseline) and then twice at trough and twice at peak dabigatran concentration. In platelet-poor plasma thrombin generation was measured with Technothrombin TGA RC Low reagent and Technothrombin substrate (both Technoclone, Austria). Lag time, time to peak thrombin (TTP), peak thrombin and area under the curve (AUC) were recorded.

Results

No difference in thrombin generation parameters or biological variation (CV) was noted between patients receiving 150 (n = 23) or 110 mg dabigatran (n = 21) twice daily. Thrombin generation lag time and TTP were significantly longer at trough and peak compared to baseline. There was no difference in lag time or TTP between trough and peak. Dabigatran had no effect on peak thrombin as there was no significant difference between baseline, trough or peak values. AUC was significantly lower at trough compared to baseline and at peak compared to trough (Table 1). Biological variation was quite high (up to 41%) and was similar at trough and at peak, except for TTP with significantly lower variation at peak concentration compared to trough CV.

Table 1. Thrombin generation in "ex vivo" samples before therapy initiation (baseline), at trough and at peak dabigatran levels. Means ± standard deviations are shown with ANOVA p values for comparison between baseline, trough and peak.

Thrombin Generation	Baseline	Trough	Peak	p	Trough CV (%)	Peak CV (%)
Lag time (min)	17.1 ± 3.3	31.7 ± 7.7 #	31.3 ± 12.4 #	<0.001	19 ± 14	16 ± 12
Peak Thrombin (nM)	204 ± 86	210 ± 96	163 ± 91	NS	37 ± 29	32 ± 32
TTP (min)	24.5 ± 4.7	38.7 ± 9.3 #	37.0 ± 14.5 #	<0.001	19 ± 13	13 ± 11 *
AUC	3410 ± 720	2299 ± 1069 #	1693 ± 1023 #*	<0.001	28 ± 28	41 ± 38

* p < 0.01 between Peak and Trough or between Peak CV and Trough CV; # post-hoc p < 0.001 compared to baseline.

Conclusions

Among the parameters of thrombogram recorded in our study AUC was the most sensitive to dabigatran with the lowest values at peak dabigatran concentrations. Lag time and TTP were also prolonged in samples containing dabigatran, but there was no difference between trough and peak. Dabigatran had no effect on peak thrombin levels.

1.4.14. C0247 Influence of Rivaroxaban on Rotational Thromboelastometry in Samples from Routine Clinical Practice Patients

Mojca Bozic Mijovski, Nina Vene, Alenka Mavr

University Medical Centre, Ljubljana, Slovenia

Background

Rotational thromboelastometry (ROTEM®), that provides a point-of-care analysis of the viscoelastic properties of clot formation and dissolution, is widely implemented in the management of bleeding and coagulopathy. ROTEM® is affected by anticoagulant drugs, such as warfarin and heparin. The aim of this study was to assess the effect of rivaroxaban on different ROTEM® parameters in samples from routine clinical practice patients.

Methods

Sixty patients with atrial fibrillation were included in the study who were receiving either 20 mg (n = 30) or 15 mg (n = 30) of rivaroxaban daily. From each patient blood was collected three times at trough and three times at peak rivaroxaban blood concentration. In whole blood ROTEM® EXTEM and a modified ROTEM® test with a lower tissue factor concentration (LowTF) were performed on ROTEM® delta analyzer (all Tem International GmbH, Germany) within one hour of blood collection and the following parameters were recorded: clotting time (CT), clot formation time (CFT), alpha angle, amplitude at 10 min (A10) and maximum clot firmness (MCF). Plasma rivaroxaban levels were measured with an anti-Xa assay (BIOPHEN® DiXaI, Hyphen Biomed).

Results

All ROTEM® parameters except EXTEM MCF were significantly higher at peak compared to trough rivaroxaban concentrations. ROTEM® EXTEM CT was the parameter that most closely correlated with rivaroxaban concentration (r = 0.86, p < 0.001).

Table. Rivaroxaban concentrations and ROTEM® parameters at trough and peak. Average ± standard deviation or median (first to third quartile) is given.

	Trough	**Peak**	***p***
Rivaroxaban (ng/mL)	37 ± 33	251 ± 102	<0.001
EXTEM CT (s)	88 ± 20	202 ± 36	<0.001
EXTEM CFT (s)	71 ± 14	78 ± 12	=0.002
EXTEM MCF (mm)	66 ± 4	65 ± 4	NS
LowTF CT (s)	284 ± 34	450 ± 65	<0.001
LowTF CFT (s)	104 ± 18	141 ± 22	<0.001
LowTF MCF (mm)	63 ± 5	61 ± 5	=0.04

Conclusions

In this study on routine clinical practice patients both ROTEM® EXTEM and LowTF ROTEM® were shown to be affected by rivaroxaban. The possible clinical use of LowTF ROTEM® should be further evaluated in clinical studies.

1.4.15. C0261 Direct Oral Anticoagulants: For All Patients of an Internal Medicine Ward?

Francesco Marongiu [1], Paola Schirru [1], Valentina Moledda [1], Antonella Mameli [2], Mariagrazia Porru [2], Doris Barcellona [3], Francesco Marongiu [3]

[1] *University of Cagliari, Department of Medical Science and Public Health Monserrato, Cagliari, Italy*
[2] *AOU di Cagliari, Cagliari, Italy*
[3] *Policlinico Universitario, Department of Medical Science and Public Health, Cagliari, Italy*

Background

Prescription of Direct Oral Anticoagulants (DOAC) is increased over time. However, is not still known whether these drugs are suitable for patients with atrial fibrillation (AF) or venous thromboembolism (VTE) admitted to an internistic clinical ward coming from an emergency room. The aim of this study was the evaluation for DOAC prescription in a group of patients consecutively hospitalized.

Methods

A total of 2041 patients were admitted to our Internal Medicine ward from 1 January 2015 to 30 November 2017. Patients with a clear indiction to oral antcoagulation were 402 (19.7%), 193 men and 209 women (age: 82, 29–101 years). In 333 patients (82.8%) indication for oral anticoagulation was AF while in 69 (17.2%) it was VTE. AF and VTE was already known in 315 patients while a new diagnosis of both conditions was made in 87. At admission patients were treated with Anti-Vitamin K (AVK), DOAC, Aspirin, LMWH or nothing. Exclusion criteria were the following: MDRD < 30 mL/min, platelet count < 100.000/mm^3, AST e ALT > 3 times normal values, Hb < 10 g/dL, active cancer, unreliable adherence and persistance, gastro-intestinal conditions at risk of bleeding, cardiac mechanic prosthesis, splancnic thrombosis, anti-phospholipid syndrome and severe mitral stenosis. At the end of the study period 4 of us reviewed independently the data base to detect whether a concordance could be accepted with what was decided at discharge.

Results

At discharge DOAC prescription was decided for 182/402 (45.3%) patients. A total of 62 out of of 166 (37.3%) already treated with anti-vitamin K could be swiched to DOAC. The interclass correlation coeffcient among the 4 reviewers was 0.881 (95% CI: 0.862–0.898). HASBLED > 4 and comorbidities > 3 were significant associated to a non prescription od DOAC (3.01, 1.79–5.07 and 2.50, 1.45–4.33 rispectively).

Conclusions

In our clinical daily practice less than 50% of patients with a clear indication to oral antcoagulation can be suitable for DOAC prescription. This percentage is even lower when we considered patients already treated with AVK. The presence of both high bleeding risk and comorbidities can affect the final decison of DOAC perescription other than the exclusion criteria which could be reduced in the future by dedicated clinical studies. The good concordance among the physicians of our group is worth noting. Concordance test should be carried out in every clinical unit to avoid discrepancies in the approach to the anticoagulant therapy.

1.4.16. C0262 Aspirin Effectiveness and Safety Evaluation in Children with Arterial Ischemic Stroke

Olga Lvova [1], Kuznetsov Nikolay [2], Anastasia Dron [3], Ekaterina Kazakova [2]

[1] *Ural Federal University, Laboratory of Brain and Neurocognitive Development, Yekaterinburg, Russia*
[2] *Ural State Medical University, Yekaterinburg, Russia*
[3] *City Clinic Pediatric Hospital 9, Yekaterinburg Russia*

Background

Aspirin is often used for secondary prevention in children with arterial ischemic stroke (AIS). The effectiveness of 1–5 mg/kg/day dosage was proved (Class IIb-III, Level of Evidence B-C, Management AHA/ASA, 2008). However, aspirin is still unsafe for children as it might cause severe complications, therefore aspirin remains "off label" in many countries.

Methods

Case control study. 75 children with AIS have been prescribing aspirin for 24 months as the secondary prevention medicine. The initial dose was 1–2 mg/kg/day. We recorded complications such as bleeding on any localization of the body using questioning, skin and mucosa examination, CBC, ultrasound and MRI. The effectiveness of aspirin was studied by the presence of repeated thrombotic events (AIS or TIA) and by the results of platelets aggregation with arachidonic acid (ASPI test). ASPI test was performed with the help of impedance Multiplate analyzer (Roche, Switzerland) after 1–3 months, 6–7 months, 22–24 months later after aspirin administration. ASPI test was considered effective when results of aggregation showed 30 U and less in it. Any result higher than 30 U leaded to aspirin dose increase up to 2–3 mg/kg/day.

There were 77 children in the control group with AIS, who did not receive aspirin within 24 months. None received tissue plasminogen activator or endovascular treatments. AIS in both groups were confirmed by brain CT (MRI) scan; all patients signed informed consent form.

Results

The observation showed that nobody had complications or side effects related to aspirin (macro and micro bleeding). Platelets aggregation data are presented in Table 1.

Table 1. The observation of ASPI test levels in patients with AIS (*n* = 75).

Follow-Up Stage	ASPI Test Data, (M ± m)	ASPItest (0–30 U), *n* (%)	ASPI Test (above 30 U), *n*	Increased Dosage, *n*
1–3 months	20.1 ± 1.01	53 (70.7)	22	11
6–7 months	23.3 ± 1.08	55 (73.3)	20	10
22–24 months	18.2 ± 1.05	55 (73.3)	20	12

Tthere were 5 recurrent episodes of TIA/AIS, which occurred in group with aspirin, and also 12 recurrent episodes in control group without aspirin during 24 month, RR = 2.43 (95% CI 0.88–8.24, Fisher 0.040).

Conclusions

Children with AIS can be prescribed aspirin as a safe and effective secondary prevention medicine, which is capable of decreasing the risk of recurrent TIA/AIS in 2 times within first 24 months after AIS occurred. Dosage titration must start from 1–2 mg/kg/day and be supervised under the laboratory indicators of effectiveness.

1.4.17. C0285 Prevalence of New Oral Anticoagulants Use in Patients Admitted to University Department of Traumatology

Ana Bronic, Srecko Sabalic

University Hospital of Traumatology Zagreb, Zagreb, Croatia

Background

New oral anticoagulants (NOAC) recently were introduced in the clinical practice as an alternative to warfarin for the prevention and treatment of thrombosis. Majority of published investigations dealt with comparison of NOAC efficacy in relation to warfarin but there is less

information on how frequently these agents were prescribed in the clinical practice. The purpose of this study was to analyse frequency and trends of NOACs prescription in patients admitted to the University Department of Traumatology, Sestre Milosrdnice University Hospital Center in Zagreb, Croatia during last four years.

Methods

Medical records of inpatients admitted to University Department of Traumatology, Sestre Milosrdnice University Hospital Centre from 1 January 2014 to 31 December 2017 were retrospectively reviewed. Data related to prescribed NOACs, including, direct thrombin and factor Xa inhibitors, age, gender and ICD-10 diagnosis on admission were recorded.

Results

Of all inpatients admitted during four years (N = 22,029), prescription of NOACs was recorded in 511 patients, 305 females and 208 males, aged 16–91 year. In 482/511 (94.3%) patients NOAC was prescribed at the Department whereas 29/511 (5.7%) patients already admitted to Department with prescribed NOAC, mainly due to previous diagnosis of atrial fibrillation. Dabigatran was medication of choice in 365/511 patients whereas rivaroxaban was prescribed in 146/511 patients. According to ICD-10, dabigatran was mainly used in patients admitted with diagnosis of gonarthrosis (M17; N = 162) or knee injuries (S80-S89; N = 17), coxarthrosis (M16; N = 120), hip injuries (S70-S79; N = 38) whereas all other related ICD-10 diagnosis were less in common (N < 5). Rivaroxaban was used mainly in patients with coxarthrosis (M16; N = 100), hip injuries (S70-S79; N = 8) or knee injuries (S80–89; N = 15), whereas gonarthrosis (M17; N = 13) or knee injuries (S80-S89; N = 14) were less common diagnosis. All other related ICD-10 diagnosis were less represented (N < 5). NOAC prescription to inpatients in 2014, 2015, 2016 and 2017 was recorded as 84/5394 (1.6%), 48/5506 (0.9%), 122/5398 (2.2%) and 256/5593 (4.6%) respectively.

Conclusions

We have recorded the increased trend of prescribing NOACs since 2014 indicating an uptake in their prescription in the patients with injuries and disorders of the knee and hip. However, further investigations should be performed in order to provide insight into optimal implementation of NOACs into everyday practice.

1.4.18. C0323 Egina: A New Excellence Model for the Management of Anticoagulation with Doacs in Southern Italy

Alessandro Ciavarella [1], Antonio Ciampa [2], Giovanni Dirienzo [2], Caterina Ledda [3], Giacomo Lucarelli [5], Giuseppe Malcangi [1], Paolo Pedic [4], Luigi Ria [8], Rita Santoro [6], Nicola Ciavarella [7]

1 *Azienda Ospedaliera Universitaria Consorziale Policlinico di Bari, Medicina Interna, Bari, Italy*
2 *Centro Emostasi di Avellino, Avellino, Italy*
3 *Bureau Veritas, Italy*
4 *Centro Trombosi di Acquaviva delle Fonti, Fonti, Italy*
5 *Centro Emostasi e trombosi di Barletta, Barletta, Italy*
6 *Centro Emofilia e trombosi di Catanzaro, Catanzaro, Italy*
7 *APTEA, Italy*
8 *Centro Trombosi di Gallipoli, Gallipoli, Italy*

Background

During the last 40 years, in Italy the oral anticoagulant therapy has been managed in patients with atrial fibrillation and venous thromboembolism by a network of Anticoagulation Centers (ACs). These have acquired extensive experience in the prevention of complications related to the use of AVK anticoagulants. From 2013 onwards, a new approach to anticoagulation has been made

available, thanks to the introduction of new direct oral anticoagulants (DOACs). They have proven non-inferiority in preventing stroke or venous thromboembolism, and no statistical differences in the rates of major bleeding, ensuring clinical benefits and cost-effectiveness. Nowadays it is possible to choose among four DOACs, monitored by clinical but not laboratory evaluations.

Methods

We created a new model named EGINA (Excellence model for the Integrated Management of New Anticoagulants) to be used by ACs for the management of the treatment with DOACs. It included an innovative follow-up system introduced by ACs which was capable to achieve the ISO9001 certification, attested by the "Bureau Veritas" company, an international certification agency. This agency was involved in the evaluation of ACs through different elements, such as clinical indicators, the adherence to international guidelines and others like the amount of outpatient visits and instrumental tools examinations. The data were collected in 19 ACs in Southern Italy through software like "Parma" and "Prometeo", offering a widespread electronic chart. Each ACs recruited at least 60 patients previously treated with AVK or naïve patients.

Results

Preliminaries data came from 10 out of 19 ACs, showing good clinical practice, adherence to guidelines and patients compliance and satisfaction. The whole group achieved both the ISO9001 certification and the award of excellence given by "Bureau Veritas". In the upcoming months other centers will be added, with the aim of involving the largest number of Italian ACs.

Conclusions

The EGINA model for the management of oral anticoagulation meets the need to set an ACs standard for ensuring company organization, appropriateness in medical decisions and cost optimization, defining a new way to take care of anticoagulated patients. Concurrently it follows the modern trend of scientifically measuring the crucial parameters of a health care establishment with the purpose of improving the quality and ensuring the international standards compliance.

1.4.19. C0342 Alterations of Thrombin Generation and Tf-Triggered Whole Blood Thromboelastometry in Patients with Idiopathic Venous Thromboembolism Treated with Rivaroxaban or Apixaban. A Prospective Observational Study

Katerina Nikolopoulou [1], Stella Salta [1], Loula Papageorgiou [1], Amir Khaterchi [2], Ismail Elalamy [1], Grigoris T Gerotziafas [1]

[1] *Sorbonne Universitè, Faculty of Medicine, Cancer, Haemostasis and Angiogenesis Research Group, INSERM UMR S938, Paris, France*

[2] *Service Díhèmatologie Biologique Hôpital Tenon, Hôpitaux Universitaires de líest Parisien, Paris, France*

Background

The orally active direct and specific inhibitors of activated factor X (FXa), apixaban and rivaroxaban are licensed for VTE treatment. They both inhibit free and clot-bound FXa, as well as prothrombinase activity thereby inhibiting thrombin generation and prolonging clotting times. They differ regarding their affinity for FXa and pharmacokinetic properties. The present study compared the impact of rivaroxaban or apixaban treatment on thrombin generation process, clot formation kinetics and clot firmness.

Methods

In total 412 patients with idiopathic VTE were prospectively included in the study; 331 patients were on rivaroxaban (20 mg/o.d.) and 81 patients on apixaban (5 mg bid). The control group consisted

of 30 healthy individuals age- and sex-matched. Plasma concentrations of rivaroxaban and apixaban were measured with the commercially available assay (DiXal; Biophen France). Thrombin generation (TG) in platelet poor plasma was assessed with the Calibrated Automated Thrombogram (CAT®) using the PPP-reagent 5 pM TF (Stago France). Whole blood thromboelastometry was assessed with ROTEM® instrument (Werfen France). Coagulation was triggered with 5 pM of TF (Innovin diluted 1/200).

Results

Treatment with rivaroxaban or apixaban significantly inhibited TG in CAT® and prolonged clotting time (CT) in ROTEM®. In rivaroxaban treated patients 95% had TG inferior to the Lower Normal Limit (LNL) and 70% had CT longer than the Upper Normal Limit (UNL). Respectively, 78% of apixaban treated patients had TG inferior to the LNL and 50% had CT longer than the UNL. This effect in both assays was not correlated with Apixaban or Rivaroxaban plasma concentrations. Interestingly, a minimum blood concentration of 5 ng/mL in rivaroxaban treated patients and 10.5 ng/mL in apixaban treated patients was able to maintain the TG peak below the LNL. A CT longer than the UNL was observed with 2.2 ng/mL of rivaroxaban and 10.5 ng/mL of apixaban anti-Xa activity. Neither apixaban nor rivaroxaban had any detectable effect on clot firmness.

Conclusions

Based on TG and ROTEM assays, we have shown that both apixaban and rivaroxaban have a detectable anticoagulant effect at very low concentrations with a wide interindividual variability.

1.4.20. C0346 Frequency, Predictors and Impact of Combined Antiplatelet Therapy on Venous Thromboembolism in Patients with Symptomatic Atherosclerosis

Ilaria Cavallari [1], David A Morrow [2], Mark A Creager [3], Jeffrey Olin [4], Deepak L Bhatt [5], P Gabriel Steg [6], Robert F Storey [7], Marc Cohen [8], Benjamin S Scirica [5], Gregory Piazza [9], Erica L Goodrich [5], Eugene Braunwald [5], Marc S Sabatine [5], Marc P Bonaca [5]

[1] *Cardiovascular Science, Rome, Italy*
[2] *TIMI Study Group, Brigham and Women's Hospital, Boston, MA, USA*
[3] *Dartmouth-Hitchcock Heart and Vascular Center, Geisel School of Medicine at Dartmouth, Lebanon, PA, USA*
[4] *Wiener Cardiovascular Institute and Marie-Jose and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, NY, USA*
[5] *TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[6] *French Alliance for Cardiovascular Trials, Département Hospitalo-Universitaire Fibrosis, Inflammation, Remodeling, HÙpital Bichat, Assistance Publique-Hôpitaux de Paris, INSERM UnitÈ 1148, Paris, France and Université Paris-Diderot, Sorbonne Paris Cité, Paris, France*
[7] *Department of Infection, Immunity and Cardiovascular Disease, University of Sheffeld, Sheffeld, UK*
[8] *Cardiovascular Division, Department of Medicine, Newark Beth Israel Medical Center, Rutgers-New Jersey Medical School, Newark, NJ, USA*
[9] *Cardiovascular Division, Brigham and Womenís Hospital, Harvard Medical School, Boston, MA, USA*

Background

Observational studies suggest that symptomatic atherosclerosis may be associated with risk of venous thromboembolism (VTE). Prior randomized studies have demonstrated a significant reduction in recurrent VTE with aspirin monotherapy. Whether VTE risk is associated with more severe symptomatic atherosclerosis and whether more intensive antiplatelet therapy reduces VTE risk beyond aspirin monotherapy is unknown.

Methods

TRA2P-TIMI 50 (vorapaxar) and PEGASUS-TIMI 54 (ticagrelor) were blinded, randomized placebo-controlled trials of antiplatelet therapy for prevention of ischemic events in stable patients with symptomatic atherosclerosis. Two blinded vascular specialists systematically identified symptomatic venous thromboembolic events in both trials.

Results

Of 47,611 patients with stable vascular disease followed for three years in both studies there were 343 VTE events in 301 patients (KM rate at 3 years 0.9% for placebo). The risk of VTE was independently associated with age, body mass index, polyvascular disease, chronic obstructive pulmonary disease and malignancy. The burden of atherosclerosis manifested as increasing number of symptomatic vascular territories was associated with a graded increase in the 3-year rates of VTE (0.76% for one, 1.53% for two and 2.45% for three territories). More intensive antiplatelet therapy (vorapaxar and ticagrelor pooled) significantly reduced the risk of VTE by 29% compared with background antiplatelet therapy, from 0.93% to 0.64% at 3 years (HR 0.71, 95% CI 0.56–0.89; $p = 0.003$).

Conclusions

The rate of VTE in patients with atherosclerosis is ~0.3% per year while on treatment with at least one antiplatelet agent with increased risk independently associated with the number of symptomatic vascular territories. More intensive antiplatelet therapy reduces the risk of VTE. These data suggest a relationship between atherosclerosis burden and VTE risk and support inclusion of VTE as a prospective endpoint in long-term secondary prevention trials evaluating the risks and benefits of antiplatelet therapies in patients with atherosclerosis.

1.4.21. C0349 Meta-Analysis Comparing the Safety and Efficacy of Dual vs. Triple Antithrombotic Therapy in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

Ilaria Cavallari [1], Giuseppe Patti [2]

[1] *Cardiovascular Science, Rome, Italy*
[2] *Campus Bio-Medico University of Rome, Rome, Italy*

Background

In atrial fibrillation (AF) patients undergoing percutaneous coronary intervention (PCI), the effectiveness and safety of dual compared to triple antithrombotic therapy are a matter of debate, especially when considering the prevention of endpoints at low incidence, such as myocardial infarction (MI), stent thrombosis or mortality.

Methods

This study-level meta-analysis included 4 controlled randomized trials and 6036 patients with a clinical indication to chronic oral anticoagulation (OAC) after PCI, mainly for AF. Patients receiving dual therapy with a single antiplatelet agent, essentially a P2Y12 inhibitor, plus OAC were compared to those treated with triple therapy (aspirin, a P2Y12 inhibitor and OAC). The incidence of the following outcomes was evaluated: TIMI major and minor bleeding, MI, stent thrombosis, stroke, cardiovascular and all-cause death.

Results

Occurrence of TIMI major bleeding wassignificantlylower in patients treated with dual therapy: 1.97% vs. 3.53% in those on triple therapy (OR 0.55, 95% CI 0.39–0.78, $p = 0.0007$); rates of minor bleeding were also decreased in the former (57% relative reduction). With dual therapy there was not a statistically significant difference in all-cause and cardiovascular mortality (3.81% vs. 4.01%, $p = 0.37$ and 1.62% vs. 2.02%, $p = 0.42$, respectively). Incidence of MI (3.25% vs. 2.78%, $p = 0.61$), definite stent

thrombosis (0.92% vs. 0.66%, $p = 0.46$) and stroke (1.28% vs. 1.32%, $p = 0.85$) was similar in the two treatment strategies.

Conclusions

In patients with long-term indication to OAC after PCI, compared to triple therapy, dual antithrombotic therapy reduces bleeding, without an excess in thromboembolic and ischemic cardiac events.

1.4.22. C0351 Prevalence and Predictors of Dual Antiplatelet Therapy Prolongation beyond One Year in Patients with Acute Coronary Syndrome: Insights from the Real-World Start-Antiplatelet Registry

Ilaria Cavallari [1], Giuseppe Patti [2], Emilia Antonucci [3], Paolo Calabró [4], Plinio Cirillo [5], Paolo Gresele [6], Gualtiero Palareti [3], Vittorio Pengo [7], Pasquale Pignatelli [8], Elisabetta Ricottini [2], Rossella Marcucci [9]

[1] *Cardiovascular Science, Rome, Italy*
[2] *Campus Bio-Medico University of Rome, Rome, Italy*
[3] *Arianna Anticoagulazione Foundation, Bologna, Italy*
[4] *Division of Cardiology, Monaldi Hospital and "Luigi Vanvitelli" University of Campania, Naples, Italy*
[5] *Department of Advanced Biomedical Sciences, School of Medicine, "Federico II" University, Naples, Italy*
[6] *Department of Medicine, Division of Internal and Cardiovascular Medicine, University of Perugia, Perugia, Italy*
[7] *Department of Cardiothoracic and Vascular Sciences, University Hospital of Padua, Padua, Italy*
[8] *Department of Internal Medicine and Medical Specialties, La Sapienza University of Rome, Rome, Italy*
[9] *Department of Experimental and Clinical Medicine, Center for Atherothrombotic diseases, University of Florence, Florence, Italy*

Background

To date, there are limited real-world data regarding prevalence and predictors of prolongation of dual antiplatelet therapy (DAPT) with aspirin plus a P2Y12 inhibitor beyond one year after acute coronary syndrome (ACS). We have explored such issue in the START-ANTIPLATELET, a branch of the START-Register (ClinicalTrials.gov Identifier: NCT02219984).

Methods

START-ANTIPLATELET is a prospective, observational, multicenter, Italian registry including patients admitted for ACS and followed up to one year. For the purpose of this analysis, we have included only patients receiving DAPT throughout one year after ACS and we have considered separately patients according to the decision of the treating cardiologist to continue or not DAPT beyond one year.

Results

596 out of 840 ACS patients completed 12-month follow-up on DAPT; DAPT was prolonged beyond one year in 13% of patients ($N = 79$). The strongest predictors of DAPT continuation were further cardiovascular events after the index admission (OR 3.3, 95% CI 1.4–7.7), the absence of bleeding complications (OR 3.2, 95% CI 1.2–8.3) and no anemia during one-year follow-up (OR 2.6, 95% CI 1.1–5.9). Other independent predictors of DAPT prolongation were at least moderate renal failure (OR 2.5, 95% CI 1.3–5.0) and peripheral artery disease (OR 1.8, 95% CI 1.1–3.0). The choice of DAPT prolongation was not associated with younger ager, diabetes status, coronary angioplasty as initial treatment strategy or drug-eluting stent implantation.

Conclusions

This study provides a real-world snapshot on the factors influencing the option to continue DAPT beyond one year after ACS; moreover, it may be useful to illustrate the relative contribution of low bleeding risk versus high ischemic risk features for DAPT prolongation.

1.4.23. C0075 New Insights on the Role of Neutrophils Activation in Peripheral Artery Disease: Findings from a Case-Control Study

Silvia Galliazzo [1], Lucia Mazzolai [2], Andreas Erdmann [2], Maxime Pellegrin [2], Catherine Amstutz [2], Monique Salvi [2], Elisabetta Faggin [3], Marcello Rattazzi [4], Paolo Pauletto [4]

[1] *Ponzano Veneto, Italy*
[2] *Service d'Angiologie du CHUV, Lausanne Switzerland*
[3] *Dipartimento di Medicina Clinica e Sperimentale, Dipartimento di Scienze Mediche e Chirurgiche, Universitá degli Studi di Padova, Padova, Italy*
[4] *Department of Internal Medicine, Universitá di Padova, Ospedale Ca' foncello, Treviso, Italy*

Background

Nowadays atherosclerosis is universally considered as a focal chronic inflammatory disorder of elastic and muscular large and medium sized arteries. Over the past two decades the role of neutrophils has gained evidence in the pathophysiology of atherosclerosis. Neutrophils have been described into plaque lesions affecting coronary and carotid arteries. Little evidences are available about neutrophils role in atherosclerotic low extremities artery disease (LEAD). We aimed at investigating the role of neutrophils in LEAD. For this purpose, we carried out an observational case-control study to compare neutrophils count and their circulant degranulation markers between symptomatic LEAD patients and healthy controls.

Methods

We recruited 39 age- and sex-matched consecutive cases and controls. Cases were represented by symptomatic consecutive LEAD patients (ABI ≤ 0.9 or TBI ≤ 0.6). Neutrophils count, neutrophils to lymphocytes ratio, serum levels of neutrophil elastase (NE), proteinase 3(PR3), lactoferrin (LactoFe) and neutrophils gelatinase associated lipocalin (NGAL) were compared between cases and controls. In the group of cases we also investigated the relation between neutrophils, neutrophils degranulation proteins and disease clinical marker such as ankle-brachial index (ABI), toe-brachial index (TBI), flow-mediated dilatation (FMD) and pulse wave velocity (PWV).

Results

Neutrophils count was higher among cases as compared with control (4851.3 ± 297.3 vs. 3430 ± 197.2/mm^3, $p = 0.0001$), as well as neutrophils to lymphocytes ratio (2.7 ± 0.2 vs. 1.8 ± 0.1; $p = 0.0001$), PR3 (573.6 ± 60.6 vs. 201.9 ± 25.3 ng/mL, $p = 0.0001$) and NE levels (197.1 ± 23.7 vs. 94.7 ± 11.9 ng/mL, $p = 0.0001$). Among cases PR3 and NGAL were significantly increased in patients with FMD < 7% compared to the ones with FMD > 7% (712.2 ± 81.7 vs. 450.2 ± 92 ng/mL, $p = 0.04$ and 313.2 ± 76.5 vs. 161.6 ± 18.7 $p = 0.05$ respectively). At a multivariable analysis higher neutrophils count was inversely correlated with ABI/TBI ($\beta = -0.37$; $p = 0.04$).

Conclusions

In LEADS patients circulate neutrophils and their degranulation markers are increased. They might take part to the atherosclerosis -related vascular inflammatory response favoring both plaque progression and arterial endothelial dysfunction in the lower limbs.

1.4.24. C0199 Methylenetetrahydrofolate Reductase Gene Polymorphism in Young Stroke Patients from the South of Tunisia

Mbarek Lamia [1], Megdiche Fatma [1], Dammak Mariem [2], Gaddour Hssan [1], Krichen Imen [1], B. Rhouma Mahdi [1], Masmoudi Ahmed [1], Mhiri Chokri [2], Kallel Choumous [1]

[1] *Laboratory of Hematology, Hospital University Habib Bourguiba, Sfax, Tunisia*
[2] *Department of Neurology, Hospital University Habib, Sfax, Tunisia*

Background

Ischemic stroke, which represents the third public health problem causing death, is a multifactorial disease that may imply a wide range of risk factors. In fact, hyperhomocysteinemia should be investigated as an independent risk factor of ischemic stroke and could be explained by genetic factors such as the C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene whose association with stroke is actually controversial.

The objective of this study was to evaluate the frequency of the C677T MTHFR genotype for young patients with unexplained ischemic stroke in the South of Tunisia.

Methods

100 patients from the South of Tunisia, with young-onset stroke and less than sixty years old, were enrolled in this study. DNA extraction was done by standard procedures. Molecular genotyping was carried out by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using specific primers and a restriction enzyme named '*HinfI*'.

Results

Among the one hundred young stroke cases, there were 48 women and 52 men. The mean age was 28 years old ±18, 16. The C677T MTHFR polymorphism was detected in 60 cases with an overall allele frequency of 60% including a C677T MTHFR TT genotype's frequency of 25% (15 cases/60) and a C677T MTHFR CT genotype's frequency of 75% (45 cases/60), respectively. Added to that, the C allele frequency was 0.625 and the T frequency was 0.375.

Conclusions

Our results highlight that the MTHFR C677T homozygosity is common among South Tunisian young patients with ischemic stroke ad may lead to hyperhomocysteinemia which is an obvious risk factor for stroke. A large study is needed in order to draw a comprehensive MTHFR allele analysis and to investigate a likely involvement of the C677T MTHFR polymorphism in the risk of ischemic stroke in order to help to reduce stroke's morbidity and to ensure a better patient care.

1.4.25. C0224 Thrombophilia Testing in Patients with Ischemic Stroke

Touil Soumaya, Cheikhrouhou Mariem, Hanachi Majdi, Kaabar Mohamed Yassine, El Elmi Alia, Gabsi Sirine, Guermazi Sami

Charles Nicolle Hospital, Tunis, Tunisia

Background

Congenital thrombophilia's implication in the occurrence of ischemic stroke in young patients is still debated. Among acquired disorders, antiphospholipid syndrome is considered as a risk factor for arterial and venous thrombosis.

Aim: To establish the prevalence of hereditary and acquired thrombophilia and its different types in patients with a history of ischemic stroke.

Methods

It is a retrospective descriptive study from 2012 through 2017 including patients aged up to 60 years with non-cardiac ischemic stroke and no anticoagulant treatment. A thrombophilia testing was performed on STA Compact® coagulation analyzer (Stago, France). We evaluated antithrombin activity (AT), protein C activity (PC), free protein S (PS), and activated protein C resistance (APCR). Lupus anticoagulant (LA) screening was performed using PTT-LA® reagent and dRVVT Screen®. When positive, we confirmed the antiphospholipid specificity using Staclot® LA and/or dRVVT Confirm®.

Results

Our study enrolled 123 cases. The mean age was of 39.9 years [1–60 years]. The prevalence of thrombophilia was 21.1% (26 cases), with a mean age of 33.6 years [1–56 years] and a sex ratio of 0.85. The difference in age between thrombophilic and non-thrombophilic groups was statistically significant ($p = 0.041$). PS deficiency (<60%) was diagnosed in 8.9% (11 cases) of the study population, PC deficiency (<60%) in 4.9% (6 cases), LA in 2.4% (3 cases), and AT deficiency (<70%) in 1.6% (2 cases). APCR was found in 5.7% (7 cases), which is similar to its prevalence in the general Tunisian population (data not shown). Combined disorders were identified in 2.4%, broken down as follows: PC and PS deficiencies (2 cases); LA and APCR (1 case).

Conclusions

In our work, congenital and acquired thrombophilia is relatively frequent in patients with ischemic stroke, particularly in the young. However, protein S deficiency could be transient, in relation to an inflammatory syndrome. Even though thrombophilic disorders are rarely incriminated in the occurrence of this vascular pathology, their diagnosis is crucial in order to evaluate the recurrence risk. Our thrombophilia investigation should be completed by screening for prothrombin G20210A mutation and plasma homocysteine measurement in young patients with non-cardiac ischemic stroke.

1.4.26. C0364 Restenosis Is a Predictor of Poor Outcome in Patients Undergoing Endovascular Intervention for Peripheral Arterial Disease

Benilde Cosmi

Fondazione Arianna Anticoagulazione, Clinical Trial Bologna, Bologna, Italy

Background

Few data are available on long term atherothrombotic events in patients who underwent peripheral vascular intervention (PVI) for peripheral arterial disease (PAD). We speculated that restenosis after PVI is a predictor of poor outcome, being restenosis a marker of a more aggressive atherothrombosis. Aim of the present study was to ascertain if restenosis after PVI was associated with higher risk of cardiovascular events in patients with PAD.

Methods

A longitudinal study of 251 patients who underwent PVI for PAD (Fontaine's stages: II through IV; aged 70 ± 11 years, male/female 149/102). Major adverse cardiovascular events (MACE) were the composite end-point. The study started after the PVI and patients were seen after one month, six months, one year and every year thereafter. At each visit, clinical examination, ABI measurement and duplex sonography (DUS) were performed. Primary patency was maintained until restenosis defined by a peak systolic velocity (PSV) ratio >2.4 and >70% diameter reduction was documented by DUS. Patients were followed-up for an average time of 1207 ± 904 days.

Results

102 (40.6%) patients developed restenosis. Restenosis was more frequent in patients with diabetes, critical limb ischemia and after femoro-popliteal PVI. Age, sex, hypertension, total cholesterol, and ABI before PVI were similar among patients with restenosis vs. those without, whereas ABI post PVI was lower in patients with restenosis vs. those without (0.78 ± 0.23 vs. 0.87 ± 0.25, $p = 0.008$) During the follow-up, MACEs ($n = 127$) were more frequent in the patients with restenosis versus those without (79.4 vs. 30.9% log-rank $p < 0.001$). According to Cox regression analysis, diabetes (RR 1.84 95% CI: 1.24–2.74, $p = 0.003$), ABI post PVI (RR 1.97 95% CI: 1.17–3.33, $p = 0.011$), heart ischemic disease (RR 1.94 95% CI: 1.34–2.80, $p = 0.001$) and restenosis (RR 2.94 95% CI 2.01–4.29, $p = 0.001$) were predictors of MACE.

Conclusions

The presence of restenosis at DUS in patients who underwent PVI for PAD is associated with increased risk of arterial thrombotic events. Intervention trials are required to show the benefit of different therapeutic approaches in such patients at high risk of clinical deterioration.

Keywords: Peripheral arterial disease; percutaneous transluminal angioplasty; peripheral vascular intervention; thrombosis; cardiovascular outcome; restenosis; Duplex sonography

1.5. Atrial Fibrillation

1.5.1. C0128 Persistence with Oral Anticoagulation in Naœve Patients with Non-Valvular Atrial Fibrillation: Preliminary Result of a Real-World Study

Giorgio Costa [1], Nicola Gennaro [2], Eliana Ferroni [2], Gentian Denas [3], Giacomo Zoppellaro [3], Seena Padayattil [3], Ugo Fedeli [4], Maria Chiara Corti [4], Margherita Andretta [1], Vittorio Pengo [3]

[1] *Health Technology Assessment Department, Veneto Region, Padua, Italy, Health Technology Assessment Department, Veneto Region, Padua, Italy*
[2] *Epidemiological Department, Veneto Region, Padua, Italy*
[3] *Cardiology Clinic, Department of Cardiac, Thoracic and Vascular Sciences, Padua University Hospital, Padua, Italy*
[4] *Epidemiological Department, Veneto Region, Padua, Italy*

Background

Persistence with oral anticoagulation is essential to prevent thromboembolic complications in patients with non-valvular atrial fibrillation (NVAF). The real-life study of patients' characteristics and persistence is functional to better understanding the actually treated population and the therapeutic compliance.

Methods

We performed a population-based retrospective cohort study in the Veneto Region (north-eastern Italy, about 5 million inhabitants) using the regional health system databases. The naïve patients initiating direct oral anticoagulants (DOACs) for stroke prevention in NVAF from July 2013 to December 2016 were included in the study. The patients were identified using Anatomical Therapeutic Chemical (ATC) codes, excluding other indications for anticoagulation therapy using ICD-9CM codes. Treatment persistence was defined as the time from initiation to discontinuation of the therapy, distinguishing any therapeutic switches. We did Kaplan-Meier persistence curves and described the characteristics and comorbidities of the patients initiating DOACs.

Results

The naïve patients initiating direct oral anticoagulants (DOACs) for stroke prevention in NVAF identified in a 3.5-year period are 12,829. In the three groups (dabigatran, rivaroxaban and apixaban), some baseline characteristics appear to be different with statistical significance. Indeed, the percentages of patients with previous stroke/transient ischemic attack/thromboembolism and those with previous bleeding are respectively: 22.3% and 3.1% for dabigatran, 16.4% and 2.6% for rivaroxaban, 26.9% and 4.6% for apixaban. After one year, the persistence to the DOACs is 74.1%. Approximately 9.0% of the discontinuations are due to the switch to the vitamin k antagonists (VKAs). The switch among DOACs affects 2.6% of treated patients; consequently, the persistence to the single active substance is 71.5%.

Conclusions

Preliminary real-world results show that more than a quarter of naive patients stop treatment with DOACs within 12 months. There are some differences in terms of initial characteristics of the treated patients. Further investigations are needed in order to analyze persistence by single active substance, the predictors of discontinuation and the main causes of discontinuity.

1.5.2. C0257 Event Rate with Oral Anticoagulation in Low Risk Patients with Atrial Fibrillation

Gentian Denas [1], Nicola Gennaro [2], Eliana Ferroni [2], Ugo Fedeli [2], Mario Saugo [2], Giacomo Zoppellaro [3], Seena Padayattil Jose [3], Giorgio Costa [4], Maria Chiara Corti [2], Margherita Andretta [4], Vittorio Pengo [3]

[1] *Padova University Hospital, Cardiac, Thoracic, and Vascular Sciences, Padova, Italy*
[2] *Epidemiological Department (SER), Veneto Region, PD, Italy*
[3] *Padua University Hospital, PD, Italy*
[4] *Unified Pharmaceutical Coordination Centre (CRUF), Veneto Region, Italy*

Background

There remains a clinically important uncertainty in treating atrial fibrillation (AF) patients at low risk of stroke, those with one non-gender related (1 NGR) risk factor. Among such patients, the benefits of anticoagulation may not exceed the risks of bleeding. The aim of our study was to assess the incidence of stroke and major bleeding in a cohort of AF patients with 1 NGR risk factor.

Methods

We performed a population-based analysis on linked claims data in the Veneto Region. NOAC and VKA cohorts were identified using ATC codes, while AF patients were identified by excluding other indications for anticoagulation using ICD-9CM codes. Study endpoints were major bleeding including intracranial haemorrhage (ICH), and ischaemic stroke.

Results

Overall, 6518 low risk AF patients receiving oral anticoagulants were identified. Of these, 37.3% were female, 53% were 65 years old, and 43.3% had hypertension. Eighty-percent were treated with VKAs, the rest with NOACs. Follow up extended for 5079 patient-years. Major bleeding incidence was 0.98% patient-years (0.86 and 1.03% patient-years with NOACs and VKAs, respectively; HR 0.91, 95% CI 0.46–1.80), intracranial haemorrhage was 0.37% patient-years (0.31 and 0.39% patient-years with NOACs and VKAs, respectively; HR 0.93, 95% CI 0.30–2.87). Stroke incidence was 0.24% patient years (0.08 and 0.29% patient-years with NOACs and VKAs, respectively; HR 0.25, 95% CI 0.03–1.99). No differences were found between individuals with ICH versus those without, despite a trend towards more ICH in individuals <65 years.

Conclusions

We found an overall elevated risk of major bleeding and intracranial haemorrhage in low risk AF patients. NOACs had a better safety profile, although ICH incidence was similar with both NOACs and VKAs.

1.6. Coagulation and Tissue factor

1.6.1. C0066 TF (Tissue Factor) and TFPI (Tissue Factor Pathway Inhibitor) in Patients with Intracranial Tumors.

Danuta Rosc [1], Bierwagen Maciej [2], Wiercinski Mariusz [2], Góralczyk Krzysztof [3], Kulwas Arleta [3], Ruszkowska-Ciastek Barbara [3]

[1] *Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Kuyavian-Pomeranian, Poland*
[2] *Ward of Neurosurgery and Traumatology, University Hospital No. 2 in Bydgoszcz, Bydgoszcz, Kujawsko-Pomorskie, Poland*
[3] *Department of Pathophysiology, Faculty of Pharmacy, Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Kujawsko-Pomorskie, Poland*

Background

In patients with intracranial tumors, hypercoagulability is observed due to brain tissue and tumor cells being the source of tissue factor. The aim of the study was to assess antigen and activity of tissue factor (TF), tissue factor pathway inhibitor (TFPI) in the plasma and tumor homogenate in patients with intracranial tumors.

Methods

The study included 69 patients; 21 patients were diagnosed with glioma, 18 patients with meningioma and 30 patients with metastatic tumors; mean age 54 years. The material for the study was the plasma 351 years. In the plasma of all the participants and in tumor tissue homogenate, the concentrations of TF-Ag and TFPI-Ag and activity of TF and TFPI and the concentration of total protein were measured. The results were converted per mg of protein.

Results

In patients with intracranial tumor, elevated concentrations of TF-Ag, TFPI-Ag and TF, TFPI activity were noted, also after the conversion per mg of protein. A 80-fold higher concentration of TF-Ag per 1 mg of protein and 15-fold higher activity of TF were found in tumor tissue compared to the patients plasma. In tumor tissue homogenate, a lower TFPI concentration and activity were recorded.

Conclusions

The study confirmed the essential prothrombotic properties in the blood of patients with intracranial tumors, expressed with an elevated TF level and activity as well as a tremendous amount of TF in tumor tissue homogenate derived from tumors. It seems that lower TFPI levels are associated with the enormous TF value in tumor tissue homogenates.

1.6.2. C0067 Haemostatic Profile Depends on Age and Menopausal Status in Breast Cancer Patients

Rhone Piotr [1], Danuta Rosc [2], Bielawski Kornel [3], Ruszkowska-Ciastek Barbara [3]

[1] *Clinical Ward of Breast Cancer and Reconstructive Surgery, Oncology Centre Prof. Franciszek Łukaszczyk Memorial Hospital, Bydgoszcz, Kujawsko-Pomorskie, Poland*
[2] *Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Kuyavian-Pomeranian, Poland*

[3] *Department of Pathophysiology, Faculty of Pharmacy, Nicolaus Copernicus University w Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Kujawsko-Pomorskie, Poland*

Background

It is well-established that thrombosis is a common complication of malignancy. The aim of the study was to evaluate the concentrations and activities of selected haemostatic parameters in the plasma of patients diagnosed with breast cancer depends on age and menopausal status.

Methods

The study involved eighty-five women aged 45–66 (mean age 55) with primary breast cancer without distant metastases (M0). Forty-eight of cases were aged ≥55 and 68% of patients were postmenopausal. Histological grading and immunohistochemistry ER/PR/HER-2/Ki-67 evaluation were measured in this cohort of patients using standard criteria and procedures. Fifty-eight were diagnosed with luminal-A-type breast cancer, 88% of patients had invasive breast ductal carcinoma. Haemostatic profile expressed by concentrations and activities of tissue factor (TF) and its inhibitor (TFPI) as well as concentrations of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) was measured applying immunoassay techniques.

Results

A significantly higher concentration of tissue factor pathway inhibitor in breast cancer patients over 55 than in the younger patients was obtained. Furthermore, a significantly higher pro-coagulant potential expressed by TF/TFPI concentration ratio was recorded in younger women with breast cancer, even though the concentration of tissue factor did not differ significantly in those women. Additionally, positive correlations were reported between TFPI and age as well as between tissue plasminogen activator and age, whereas, a negative correlation between TF activity and age was observed. Finally, an essential growing tendency towards a higher concentration of TFPI and a significantly higher concentration of tissue plasminogen activator (t-PA) were noted in post-menopausal breast cancer patients as compared to pre-menopausal cases.

Conclusions

Our findings suggest an opposite dynamic of breast cancer biology dependent on age- and hormonal status. Haemostatic profile could, therefore, be a relevant indicator of the cancer nature. Indeed, younger women with breast cancer are more predisposed to cancer-related thrombosis and worse prognosis because TF express non-coagulant functions in cancer biology by promoting tumour proliferation, angiogenesis activity, and metastasis. Whereas, older women present enhanced tendency to fibrinolysis activation and better controlling tissue factor-dependent blood coagulation

1.6.3. C0068 Tissue Factor-Dependent Coagulation Activation in Patients with Type 2 Diabetes Mellitus Complicated by Diabetic Foot Syndrome

Kulwas Arleta [1], Ruszkowska-Ciastek Barbara [1], Jundzill Wieslaw [2], Góralczyk Krzysztof [1], Jawien Arkadiusz [2], Danuta Rosc [3]

[1] *Department of Pathophysiology, Faculty of Pharmacy, Nicolaus Copernicus University w Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Kujawsko-Pomorskie, Poland*

[2] *Department of Vascular Surgery and Angiology, Faculty of Medicine, Nicolaus Copernicus University w Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Kujawsko-Pomorskie, Poland*

[3] *Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Kuyavian-Pomeranian, Poland*

Background

Diabetes including types 1 and 2 is associated with hypercoagulable state. Tissue factor is the main activator of the extrinsic coagulation process. Diabetic foot syndrome (DFS) is a major complication of diabetes mellitus. A review of the applicable literature indicates lack of the studies concentrated on analysis of hemostatic profile in diabetic foot syndrome. The aim of the study was to evaluate the concentration of selected hemostatic parameters including tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in the plasma of patients with DFS.

Methods

This was a prospective, single-centre study comprising 93 Caucasian individuals. The investigation group consisted of 63 patients with diabetic foot syndrome (DFS); (males/females 40/23) aged between 35–89 (mean age of 64 ± 11.06). Subjects were admitted to the Department of Vascular Surgery and Angiology. The control group consisted of 30 healthy volunteers (14 females and 16 males) at a mean age of 59 ± 11.16. In the citrate plasma the concentrations of tissue factor (TF), tissue factor pathway inhibitor (TFPI), thrombin-antithrombin complexes (TAT), thrombin activatable fibrinolysis inhibitor (TAFI) were measured applying immunoassay techniques.

Results

There were observed significantly higher concentrations of tissue factor, tissue factor pathway inhibitor and thrombin-antithrombin complexes in subjects with diabetic foot syndrome relative to healthy individuals. However, significantly lower concentration of TAFI in diabetic foot syndrome patients as comparison to the control group was noted.

Parameters [Units]	Subjects with Diabetic Foot Syndrome $N = 63$	Control Group $N = 30$	p-Values
TF [pg/mL]	$Q_1 = 200.00$ $Me = 440.00$ $Q_3 = 570.00$	$Q_1 = 83.08$ $Me = 108.49$ $Q_3 = 144.52$	<0.0001
TFPI [ng/mL]	$Q_1 = 86.80$ $Me = 186.20$ $Q_3 = 302.20$	$Q_1 = 70.32$ $Me = 87.29$ $Q_3 = 96.92$	<0.0001
TAFI [ng/mL]	$Q_1 = 5.55$ $Me = 8.80$ $Q_3 = 14.10$	$Q_1 = 32.03$ $Me = 42.98$ $Q_3 = 59.55$	<0.0001
TAT [ng/mL]	$Q_1 = 3.08$ $Me = 5.42$ $Q_3 = 7.99$	$Q_1 = 1.42$ $Me = 2.49$ $Q_3 = 3.92$	<0.0002

Conclusions

In patients with diabetic foot syndrome high activation of extrinsic coagulation pathway was observed expressed by increased the concentration of TF, TAT complexes. However, essential inhibitory potential of the extrinsic coagulation pathway was found in those patients, based on the higher concentration of TFPI.

1.6.4. C0111 Activated Factor X Generation Assays Indicate Hypercoagulability Features in Cad Patients with High Plasma Levels of Activated Factor VII-Antithrombin Complex

Marcello Baroni [1], Filippo Stefanoni [2], Barbara Lunghi [1], Annalisa Castagna [2], Giovanna Marchetti [3], Oliviero Olivieri [2], Francesco Bernard [1], Nicola Martinelli [2]

[1] *Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy*
[2] *Department of Medicine, University of Verona, Verona, Italy*
[3] *Department of Biomedical and Specialty Surgical Sciences, University of Ferrara, Ferrara, Italy*

Background

High plasma levels of activated Factor VII-Antithrombin (FVIIa-AT) complex have been associated with an increased risk of total and cardiovascular mortality in patients with stable coronary artery disease (CAD), as well as with an enhanced thrombin generation.

Methods

The assessment of activated factor X generation (FXaG) in plasma with an ample range of tissue factor (TF) concentrations was performed in 40 male CAD patients (mean age 62.4 ± 10.0 years) characterized for FVIIa-AT levels by ELISA. The analyses were enriched by the set up of novel fluorogenic FXaG assays, based on inhibition of thrombin and TFPI through specific aptamers.

Results

In FXaG at low TF concentration, the area under the curve (AUC) increased progressively across FVIIa-AT quartiles ($p = 0.007$ by ANOVA, confirmed after adjustment for traditional cardiovascular risk factors). In FXaG at high TF concentration an inverse correlation between FVIIa-AT and lag time was observed. After thrombin inhibition and potentiation of FXaG by anti-thrombin and anti-TFPI aptamers respectively, the FXaG lag time was shorter in the highest than in the lowest FVIIa-AT quartile ($p = 0.009$). These data pointed out increased FXaG activity in the initiation phase of coagulation, prompting us to explore thoroughly FXaG rate. The highest relative difference in FXaG rate across FVIIa-AT quartiles was present at the early times ($p = 0.001$) and progressively decreased over time.

Conclusions

Conclusions: In male subjects with CAD high plasma levels of FVIIa-AT were associated with an increased FXaG, specifically detectable in the initiation coagulation phase and potentially produced by increased concentration of activated factors. Our data support the evaluation of the FVIIa-AT complex as a marker of hypercoagulability.

1.6.5. C0122 "An Old Friend for New Friends": The D-Dimer Is Not Influenced by the Assumption of the Doac Therapy

Simone Lorenzo Roman, Tiziana Pavia, Claudia Novi, Simona Bartoli, Vincenzo Cioffari, Giovanni Pellegrini, Lucia Ruocco

Ambulatorio Antitrombosi, U.O. Laboratorio Analisi Cliniche, Azienda Ospedaliera Pisana, Pisa, Italy, Dipartimento di Medicina di Laboratorio PISA (Italy), Italy

Background

The D-dimer (DD) test is a non-invasive and rapid blood assay, commonly used in venous thromboembolism (VTE). Two types of threshold can be used for DD values: 1-conventional reference value, 2-cutoff established in clinical studies of patients (pts) with suspected VTE, as decision value in clinical field. Both are strictly dependent on the method and on the laboratory kit used. The role of the DD is under-explored in Direct Oral Anticoagulants (DOACs) monitoring. This study aimed to check the DD levels in DOACs therapy pts.

Methods

DOACs were assayed by d-TT (Werfen®) and anti-FXa (Stago®) through a calibration for each specific drug, DD by enzyme linked fluorescence assay (Vidas®), all at trough and peak time after assumption. Data were analyzed by sex, age group (G1 < 50 years, G2 < 60 years, G3 < 70 years, G4 < 80 years, G5 < 90 years, G6 < 100 years) and disease (VTE pts vs. Atrial Fibrillation-AF). Student *t*-test, Mann Whitney test and one-way ANOVA for multiple data were performed.

Results

A total of 109 pts (female 47.7%) in follow-up for DOAC therapy at the Thrombosis Center, were enrolled: 26 pts were on dabigatran (11 on 110 mg, 15 on 150 mg), 53 on rivaroxaban (12 on 15 mg, 41 on 20 mg), 32 on apixaban (12 on 2.5 mg and 20 on 5 mg) and 9 on edoxaban (1 on 30 mg, 8 on 60 mg). Pts were distributed by age groups: G1: 5 pts; G2: 11 pts; G3: 15 pts; G4: 45 pts; G5: 31 pts; G6: 2 pts. No significant differences were found comparing sex or different DOAC drugs in DD. Statistical significant differences across age groups (G2 vs. G3, $p = 0.05$; G3 vs. G4, $p = 0.004$; G4 vs. G5, $p = 0.002$) were found. No significant statistical differences were found also comparing DD value at trough vs. peak time. Pts affected by VTE showed significant lower DD values than pts with AF (M ± SD: 0.5 ± 0.6 vs. 0.64 ± 0.7 respectively, $p = 0.014$).

Conclusions

The study confirms the difference of DD levels in groups stratified by age as reported in literature, also in pts with DOAC therapy: all pts showed DD age-related normal values. VTE pts revealed lower DD values than AF pts: this observation must be confirmed by further investigations. Our data support the use of an age-adjusted DD cut-off also in pts with DOACs therapy. Nevertheless, additional studies in larger patient populations are necessary to strengthen these preliminary findings.

1.6.6. C0251 Factor XIII as a Predictor of Intramyocardial Haemorrhage in Patients with St Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A Prospective Pilot Study

Gentian Denas, Alessia Bracco, Andrea Gualtiero Cavicchiolo, Jozef Luli, Giacomo Zoppellaro Seena Padayattil Jose, Elisa Bison, Vittorio Pengo

Padova University Hospital, Cardiac, Thoracic, and Vascular Sciences, Padova, Italy

Background

Intramyocardial haemorrhage (IMH) in ST elevation myocardial infarction (STEMI) is an independent predictor of adverse left ventricular remodelling, independently of the initial infarct size, and predicts future major adverse events. Blood coagulation factor XIII (FXIII) is thought to play a role in wound healing and tissue repair. Previous work has shown that FXIII levels were diminished in STEMI patients, with the nadir of reduction on day 5 after the acute event. We hypothesise that FXIII decay in the first week after STEMI might be related to IMH extension.

Methods

In this pilot study, we prospectively collected data on STEMI patients admitted in the Padua University Hospital Coronary Care Unit undergoing primary percutaneous coronary intervention (PCI) and Cardiac magnetic resonance imaging (CMR) during hospital stay. FXIII levels were measured using homemade ELISAs on blood samples collected at admission and on day 5. CMR for the detection of IMH was performed on day 5 in all patients.

Results

Thirty patients were included in the final analysis. Mean age was 61.1 ± 10.0 years and 3 were female. Mean basal FXIII levels were 100.3 ± 31.7. A reduction of the mean FXIII levels on day 5 was observed, 98.6 ± 34.8, without reaching statistical significance. IMH was detected in 12 (30%) patients. Day 5 FXIII levels were significantly lower in patients with IMH as opposed to patients without IMH (73.5 vs. 96.4, $p = 0.003$). No independent predictor of IMH was found on multivariate analysis although FXIII levels nearly reached statistical significance (OR 0.8, 95% CI 0.7–1.0, $p = 0.096$). There was a strong, positive correlation between day 5 FXIII levels and IMH ($r = 0.577$, $n = 10$).

Conclusions

In this pilot study, we found a positive correlation between day 5 FXIII levels and the presence of IMH in STEMI patients undergoing PCI. This correlation may lay the future basis for the use of FXIII as a prognostic marker in STEMI.

1.6.7. C0283 Clinical and Biological Features of Inherited Bleeding Disorders: A Monocentric Study

Bahri Dhouha Baccouche Héla, Chakroun, Manai Zeineb, Mahjoub Sonia, Ben Romdhane Neila

Rabta Hospital, Department of Hematology, Tunis, Tunisia

Background

Bleeding disorders are heterogeneous diseases that are mostly acquired. Inherited bleeding disorders (IBDs) include frequent entities like hemophilia A and B, Von Willebrand disease and rare bleeding disorders (RBDs) including factor I (FI), factor II (FII), factor V (FV), combined FV and factor VIII (FVIII), factor VII (FVII), factor X (FX), factor XI (FXI), factor XIII (FXIII) and vitamin K dependent clotting factors.

In this study, we aimed to describe clinical and biological presentation of patients with IBDs suspicion.

Methods

Our study is retrospective concerning all the patients addressed to our biological hematology department during a period of 4-year [2013–2017] for hemostasis investigation.

Global coagulation tests were performed for each patient on an STA® automate. Factor II, V, VII, VIII, IX, X and XI assays were performed by chronometric technique on STA Compact Stago®. Chromogenic assay for FXIII and Willebrand factor analysis were performed on SYSMEX CS-2100i. Clot weight of fibrinogen was done in case of decreased functional activity of fibrinogen.

Results

Among 729 hemostasis samples sent for hemostasis disorder, 67 cases (9%) were found to be inherited. The median age was 27.5 years [10 days–71 years]. The sex ratio was 1.5.

Diagnosis of the IBDs was made during a systematic laboratory investigation in 44 patients (66%), in a context of family investigation in 6 patients (10%) and in 17 patients (24%) with hemorrhagic symptomatology.

Hemophilia A and B as well as Von Willebrand disease were found in 7 cases (10%).

A RBD was paradoxically found in the others 60 cases (91%). The most common RBD was FVII deficiency found in 26 cases (38%). The median rate of FVII was 21%. Seven cases had a severe FVII deficiency with FVII < 5% but were all asymptomatic. FXI and FXII deficiencies were found in 8 cases (13%) each one with a median rate factor of 14% and 16%, respectively. The others RBDs were: FV deficiency (n = 5), FX deficiency (n = 7), dysfibrinogenemia (n = 3), afibrinogenemia (n = 1), FXIII deficiency (n = 1), combined FXI and FXII (n = 1).

Conclusions

IBDs were notably discovered during a systemic assessment. RBDS were more frequent than hemophilia and Von Willebrand disease. This finding is explained by a selection bias as our institution is draining adult patients and is essentially composed by surgery departments. The preoperative laboratory assessment is a common circumstance of RBDs diagnosis.

1.7. Coronary, Cerebrovascular and Peripheral Vascular Disease

1.7.1. C0040 Prognostic Role of Purine Catabolites in Coronary Artery Restenosis Formation

Dana Taizhanova Zhumagalievna, Larisa Muravlyova, Olga Visternichan

Karaganda State Medical University, Karaganda, Kazakhstan

Background

The coronary heart disease is the global problem having not only the medical but the social meaning. The prognosis this disease is connected with immediate prevention of complications and myocardial revascularisation on time. There is the risk of the development of restenosis. More often these complication resulted in activisation of inflammatory factors and progress atherosclerotic process in the stenting zone. Thus, the search of new biochemical markers of early diagnostics of coronary restenosis is very actual. The aim—to estimate the dynamic changes of purine catabolites concentration in blood plasma of the patients with acute coronary syndrome before and after coronary stenting.

Methods

Determination of intermediates of purine catbolism guanine, hypoxanthine, adenine, xanthine and uric acid in plasma before stenting and after 3 days after this procedure was performed. 35 patients with acute coronary syndrome were examined (age 40–75). The patients with diabetes mellitus, chronic obstructive pulmonary disease, gout, with severe renal dysfunction were excluded. Conditionally healthy 35 persons were included into control group. Metabolites of purine metabolism were determined in blood plasma by the method of Oreshnikov E.V. and co-authors (2008). Statistical analysis of the data was performed using the software package STATISTICA version 10.0.

Results

In plasma samples taken from the patients with acute coronary syndrome prior to stenting, there was a tendency to increase the concentration of guanine (p-0.001), hypoxanthine (p-0.002) adenine (p-0.0003), xanthine (p-0.000003) and uric acid (p-0.000001) relative to the upper limit of the physiological norm were reviled. In plasma samples taken from the same patients on the third day after stenting, there was more marked elevation of the guanine (p-0.000001), hypoxanthine (p-0.000001) adenine (p-0.0000001), xanthine (p-0.000001) and uric acid (p-0.0000001) concentration were reveled.

Conclusions

1. Marked tendency to the elevation of purine catabolites concentration in blood plasma in patients with acute coronary syndrome can be caused by their insert into the blood plasma as the result of cell damage during the development of myocardial ischemia.
2. Significant increase in the concentration of catabolites of purine metabolism after stenting may be due to the development of aseptic inflammation in the stenting area, which is also accompanied by the migration of inflammatory factors to the stented part of the coronary artery.

1.7.2. C0093 Comorbid Dominants for Thrombogenicity in Patients with Chronic Cerebrovascular Diseases

Eugene Roitman [1], Alla Shabalina [2], Marine Tanashyan [2], Irina Kolesnikova [3]

[1] *RSS Clinical Hemostasiology, Office Moscow, Moscow, Russia*
[2] *Research Center of Neurology, Moscow, Russia*
[3] *Pirogov Russian National Research Medical University, Moscow, Russia*

Background

Comorbidity increases the risk of thrombosis and complicates the antithrombotic prevention. Chronic cerebrovascular disease (CCVD) are not rarely comorbided with myeloproliferative neoplasms (MPNs). The contribution from each of them in overall thrombotic risk remains of an interest.

Methods

We examined blood coagulation, hemorheology and inflammatory activities in 136 patients with MPNs in remission; group I), in 193 patients with CCVD (group II), and in 96 patients with CCVD associated with MPNs in remission (group III).

Results

The association CCVD with MPNs showed hemoglobin level, erythrocytes and leukocytes similar for CCVD. Platelet count became significantly higher compared to MPNs and to CCVD but platelet aggregation appeared low like in patients with MPNs isolated. Thus MPNs takes a leadership in effect on platelets.

Considered comorbidity had not any effects mediated with factor XII, probably, due to lower pro-inflammatory response which was more similar to the CCVD than to the MPNs. Group III contains more youngest patients, and only here the inflammatory level showed significant correlation to patient's age.

In group III, % prothrombin was lower compared to the MPNs and became approximately equal to CCVD patients. This picture is explained due to joint changes with different directions: lowered fVIIa together with simultaneously elevated fVIIIa and Protein S whereas both fVa and Protein C had no changes in compare to group I.

Patients with comorbidity demonstrated more activated fibrinolysis due to increased plasminogen and t-PA together with lowered PAI-1 in compare to group I. Alfa-2-antiplasmin have acquired intermediate between low level in MPNs and high values in CCVD.

All patients showed hyperviscosity trend but in group III hyperviscosity had approximately 25–30% lower level compared to other groups. This effect was as a result of (1) lower plasma viscosity due to more plasma diluting (estimated by ions and creatinine); and (2) lower hydrodynamic resistance of cell aggregates than under CCVD or under MPNs.

Conclusions

Seems that the overlap between CCVD and MPNs is indicating prevalent effect of CCVD on hemocoagulation pattern, however MPNs remains a leader in effect on platelets. The association of CCVD with MPNs does establish direction of causality that involves the preferred choice of antithrombotic therapy as for CCVD including the use of hemorheological correctors. However low PLT count and decreased platelet aggregation should be considered.

1.7.3. C0143 Gender-Linked Hemorheologic Features in Patients during and after Acute Stroke

Eugene Roitman [1], Alla Shabalina [2], Irina Kolesnikova [3], Marine Tanashyan [3]

[1] *RSS Clinical Hemostasiology, Office Moscow, Moscow, RUSSIA*
[2] *Research Center of Neurology, Moscow, Russia*
[3] *Pirogov Russian National Research Medical University, Moscow, Russia*

Background

Hemorheological conditions of blood flow play significant role in thrombogenicity and oxygen delivery in patients with stroke that affects morbidity and recovery. The study was aimed to find hemorheologic features which are related to gender in patients with stroke.

Methods

We studied blood rheology in 62 women and 112 men with acute stroke and within 12 months after the event. Hemorheological analyses was used rotational viscometry at shear rates 5–300 1/s (AKR-2, Russia) and assays for RBC aggregation/desaggregation and erythrocyte deformability with laser-assisted optical rotational cell analysis (LORCA, The Netherlands).

Results

As in the acute phase and after stroke no differences have discovered in cell counts, thrombogenicity, atherogenicity and renal function between men and women. Blood viscosity showed no overall critical excess in comparison with normal, but RBC aggregation was increased in general during acute stroke both in men and in women (AI 1.92 and 1.78, respectively).

In acute stroke men has showed higher blood viscosity (Relative Blood Viscosity: 5.0 vs. 4.39, respectively; $p < 0.05$) with more pronounced viscosity hysteresis at the range of low and middle shear rates than it was in women. This finding is evidenced more deep changes in blood rheologic behavior in men due to erythrocyte aggregation prevailed over RBC disaggregation with preferred formation of three-dimensional cell aggregates. In addition, red blood cells in women had slightly better RBC deformability than in men.

Within 12 months after stroke the blood viscosity in men has significantly reduced mainly at low and medium shear rates and did not show significant differences with blood viscosity in women. RBC disaggregation together with a predominantly linear aggregates have become predominant in men. Whereas blood viscosity in women at those time did not differ significantly with blood viscosity in acute stroke.

According statistical results with the using Chi-square criterion, hemorheological pattern mainly for the distribution of RBC aggregation amplitude showed gender-linked manner in men ($p < 0.05$) but not in women ($p > 0.05$).

Conclusions

The obtained results suggest the regulatory processes for hemorheological conditions are varied widely in men due to, apparently, deeper violations in RBC aggregability. Generally we assume that it is appropriate to consider gender-linked hemorheological features for the choosing of therapy to improve oxygen delivery.

1.7.4. C0194 a Time-Course Analysis of Activated Factor Vii-Antithrombin Complex Plasma Concentration in the Follow-Up of Patients with Angiographically-Demonstrated Coronary Artery Disease

Filippo Stefanoni [1], Annalisa Castagna [1], Marcello Baroni [2], Federica Tosi [1], Giovanni Poli [3], Barbara Lunghi [2], Stefania Gaino [3], Barry Woodhams [4], Giuseppe Lippi [3], Domenico Girelli [1], Oliviero Olivieri [1], Francesco Bernardi [2], Nicola Martinelli [1]

1 *Department of Medicine, University of Verona, Verona, Italy*
2 *Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy*
3 *Section of Clinical Biochemistry, University of Verona, Verona, Italy*
4 *Haemacon Ltd., Bromley, Kent, UK*

Background

Activated factor VII-antithrombin (FVIIa-AT) complex reflects tissue factor exposure to the blood, thus being a biomarker of prothrombotic diathesis, and has been associated with mortality in patients with coronary artery disease (CAD).

Methods

Within the original prospective study showing baseline levels of FVIIa-AT as a predictor of cardiovascular mortality, in 178 survived CAD patients (85.4% males, mean age 58.2 ± 8.5 years) a second blood drawn for FVIIa-AT evaluation was performed in occasion of an ambulatory visit (after a median follow-up of 63 months). FVIIa-AT plasma levels were measured by ELISA.

Results

During the follow-up 58 subjects reported angina symptoms, 7 had myocardial infarction (MI), and 35 underwent new coronary revascularization. FVIIa-AT levels at second control were significantly correlated with those at baseline ($R = 0.262$, $p < 0.001$) and were significantly higher than those at baseline ($p < 0.001$), except for patients having begun anticoagulant therapy with warfarin. Neither baseline nor second control FVIIa-AT levels were associated with angina, MI, or coronary revascularization. On the other hand, subjects with angina had a higher increase of FVIIa-AT levels from baseline to the second control (50.1 ± 55.9 versus 31.4 ± 54.4 pM, $p = 0.035$), as well as subjects with MI (79.4 ± 52.2 versus 35.8 ± 55.1 pM, $p = 0.040$), while no significant difference was found for coronary revascularization (49.9 ± 48.8 versus 34.4 ± 56.6 pM, $p = 0.139$). Subjects with an increase higher than the median value (>36.4 pM) had an about two-fold increased risk of angina/MI after adjustment for sex, age, time of follow-up, and warfarin therapy (OR 2.05 with 95% CI 1.05–4.02).

Conclusions

In the setting of secondary prevention of CAD a larger time-related increase of FVIIa-AT levels during follow-up is associated with angina and non-fatal MI.

1.7.5. C0284 the Effect of Antiplatelet Treatment in Patients with Different Pathogenetic Subtypes of Ishemic Stroke

Tatiana Vavilova Vladimirivna [1], Olga Rodionova [2], Victor Sorokoumov [2], Ludmila Isaeva [3], Yuliya Bogatenkova [3]

[1] *Almazov National Research Centre, Laboratory Medicine and Genetics, Saint-Petersburg, Russia*
[2] *Pavlov Medical University, Saint-Petersburg, Russia*
[3] *City Diagnostic Centre, Saint-Petersburg, Russia*

Background

According to current recommendations, all patients with non-cardioembolic stroke or transient ischemic attack (TIA) should be treated withantiplatelet agents. But at the moment, the issue of ineffectiveness/resistance to these drugs is increasingly being discussed. There are a number of factors that can lead to a decrease or absence of antiplatelet effect of aspirin and clopidogrel. The aim of this study was to find differences in the antiplatelet effect of aspirin and clopidogrel depending on the pathogenetic subtype of noncardioembolic ischemic stroke.

Methods

The study included 35 patients treated with aspirin (16 with lacunar and 19 with atherothrombotic stroke subtype) and 30 patients treated with clopidogrel (15 with unspecified and 15 with atherothrombotic stroke subtype). The selected subgroups are comparable by sex and age.

Platelet activity were measured in whole blood by the impedance agregatometry (CHRONO-LOG, Model 590, USA). ADP and collagen were used for induction at a final concentration of 10 mM/mL and 2 μg/mL, respectively. We evaluated the following parameters: Lag Time, the amplitude of the aggregation, the area under the aggregation curve (AUC).

Results

Patients with atherothrombotic stroke subtype with aspirin therapy develop better-marked hypoaggregation ($p < 0.05$) than patients with lacunar subtype, reflected in a smaller amplitude and area under the aggregation curve in the collagen- and ADP-induced platelet aggregation study.

Patients with an atherothrombotic stroke subtype on clopidogrel treatment also develop significantly better-marked hypoaggregation than patients with an unspecified subtype: increase in Lag Time (collagen) to 80.0 (62.0, 90.0) s, Lag Time (ADP) 43.0 (24.0, 83.0) s and decrease the collagen-induced amplitude up to 15.0 (7.0, 19.0) om, the AUC to 44.1 (23.8, 62.8) om*s.

Conclusions

Thus, our study revealed significant differences in the antiplatelet effect of aspirin and clopidogrel in various pathogenetic subtypes of stroke. This fact requires further study, but already now there is no doubt that the etiologic factor of cerebral circulation disorders affects the effectiveness of antiplatelet drugs and should be taken into account in the complex assessment of the patient and the choice of tactics.

1.7.6. C0321 Response to Aspirin and Thromboembolic Events in Patients Undergoing Eversion Carotid Endarterectomy

Tina Novakovic [1], Igor Koncar [1], Lazar Davidovic [2]

[1] *Clinical Centre of Serbia, Vascular Surgery Clinic, Belgrade, Serbia*
[2] *Clinical Centre of Serbia, Vascular Surgery Clinic, School of Medicine, University of Belgrade, Belgrade, Serbia*

Background

BACKGROUND: Antiplatelet therapy (AT) with acetylsalicylic acid has a key role in preventing thromboembolic events in patients with carotid stenosis submitted to eversion endarterectomy (EA). Aspirin might decrease the perioperative stroke rate and long term risk of thromboembolic events after surgery. It is well established that patient response to AT is variable depending on measuring method. It is not known if patient response to AT has impact on thrombotic event in carotid surgery.

AIM of this paper was to observe correlation between low responding to AT with neurological complication of carotid surgery.

Methods

METHODs: This was retrospective review of consecutive patients undergoing EA at university clinic for vascular surgery. Data including patient demographic, operative details, preoperative use of Aspirin, response on AT therapy and outcome were collected. Endpoints included thromboembolic events in hospital period. Platelet function was assessed by impedance aggregometry (Multiplate®, Roche Diagnostics). Anti-platelet therapy response was defined by the following AUC results: ASPI > 600 as no responders, ASPI < 600 as responders, ASPI < 300 as high responders. All patients were on chronic AT.

Results

RESULTS: During 4 months, 180 patients (125 men and 55 women, median age (min-max) 69 (50–85) years) undergoing EA were included. Good response to AT was recorded in 89 patients (49%), while 91 (51%) had shown no response to AT. Frequency of thromboembolic event was 5%. All of 9 patients with thromboembolic event had ASPI > 300 ($p = 0.401$), 5 (56%) of them were resistant to AT, ASPI > 600 ($p = 0.514$).

Conclusions

CONCLUSIONS: Based on our results non responders to AT are not at higher risk from neurological events after carotid surgery. These results should be tested in a prospective study on a higher number of patients.

1.8. Deep Vein Thrombosis and PE

1.8.1. C0006 Venous Thromboembolism Monitoring Program in Patients with Totally Implanted Central Venous Access System

Mikhail Cherkashin, Natalia Berezina, Alexey Serov, Daria Kuplevatskaya, Denis Puchkov, Mikhail Anishkin Natalia Nikitina

DTC IIBS N.A. S. Berezin, Saint-Petersburg, Russia

Background

Patients on long-term chemotherapy need to have adequate venous access for months and sometimes for years. Implantable central venous port catheter systems (CVC) provide this opportunity. But any central venous catheter is the well-known risk factor for VTE, about 15% of these patients have thrombotic complication (between 82–103 days after intervention) and in some hospitals active thrombosis monitoring programs were implemented

Methods

In 2013–2017 we have implanted 264 central venous port-systems for long-term chemotherapy (commonly by subclavian access under CT-navigation, in 5 case due to bilateral subclavian vein occlusion we use right femoral access).

Mean patients' age was 45 years old (27–61). After intervention every patients were included in observational program: visits to surgeon (1, 3, 6 and 12 months), subclavian and superior caval vein ultrasoundexamination and echocardiography. In case of pulmonary embolism suspicion—chest CT and pulmonary CT angiography were performed.

Results

In 21 patients (8.8%) venous thrombosis (device occlusion or subclavian vein involvement) occurred. All these patients received low-molecular weight heparin. In 7 cases local thrombolysis with active thrombotic masses aspiration was performed. In 2 patients we have performed device explantation due to absence of recanalization and risk of thrombosis progression. Mean time for venous thrombosis development was 3 months after port-system implantation. In 1 case non-massive pulmonary embolism was detected. Based on risk analysis male sex ($p < 0.05$) and head and neck cancer ($p = 0.03$) were detected as independent predictors for venous thrombosis. Additionally we have analysed snmall group of patients with implanted devices from other clinics ($n = 15$), transferred in our surgical department for port-systems explantation or replantation due to catheter malposition. These data were not included in risk analyisis, but in 7 of these patients (46.6%) thrombosis was revealed and we suggest device malposition as a serious risk factor for VTE.

Conclusions

Active VTE monitoring in oncologic patients with implanted central venous access systems for long-term chemotherapy is the important part of disease management. Aggressive strategy with device recanalization allows to continue life-saving chemotherapy. We suggest male sex, head and neck cancer and device malposition as additional risk factors for VTE.

1.8.2. C0031 Challenges in the Diagnosis of Sub-Segmental Pulmonary Embolism in Symptomatic Patients: A Case Report

Marta Milan [1], Lucia Sarolo [2], Paola Cozzolino [3], Paolo Prandoni [2]

[1] *Unit of Coagulopathies, University Hospital of Padua, Padua, Italy*
[2] *Unit of Coagulopathies, Padua, Italy*
[3] *Radiology Unit, Padua, Italy*

Background

Diagnosis of subsegmental pulmonary embolism (SSPE) is nowadays increasing due to the growing number of radiological examinations performed with multidetector-row computer tomography (MDCT) scanners. The reliability of the CT diagnosis of SSPE is still an unresolved issue.

Methods

We present the case of a woman evaluated for a thoracic pain, who had the diagnosis of SSPE by means of an angio-CT scan that was subsequently confuted by clinical and scintigraphic findings. New diagnostic algorithms for PE are briefly evaluated.

Results

A 74 years old woman referred to the Emergency department due to sub continuous, intercostal thoracic pain. She was otherwise healthy. The pre-test clinical probability of PE according to Wells score was 0. Biohumoral exams revealed a moderate increase of D-Dimer blood levels (579 μg/L [normal value 0–350 μg/L]). Because of the increase in the D-dimer levels a venous thromboembolic disease was suspected. She underwent a compression ultrasonography of the lower limbs that resulted negative and a pulmonary angio-CT that showed the presence of a SSPE (fig1). At admission in our department, we questioned the diagnosis of PE and decided to perform a V/Q lung scanning, which failed to show any perfusion defect compatible with the diagnosis of PE. After obtaining the patient consent, anticoagulation was stopped. The 3-months follow up was totally uneventful. Interestingly enough, a few days after discharge some vesicular skin lesions appeared with metameric distribution at the site of the chest pain, highly suggestive of the development of herpes zoster.

Conclusions

The patient we discuss was encouraged by Emergency Department physicians to perform a CT pulmonary angiography because of a positive D-dimer, in spite of a low pre-test clinical probability of PE, and the test led to the diagnosis of a small isolated sub-segmental embolus requiring full-dose anticoagulation for an unpredictable length. Had, however, the modern diagnostic algorithms, which rate the value of D-dimer according to age or to a simplified pre-test clinical probability been used, the patient could have safely avoided any anticoagulant treatment (see Table 1).

Table 1.

	Standard Algorithm	**ADJUST PE**	**YEARS STUDY**
Pre-test probability	LOW	LOW	0
D-dimer value	Positive	Negative	Negative
Indication for CT scan examination	YES	NO	NO

In conclusion clinical diagnosis of SSPE appeared to be a major challenge and clinical evaluation of patients according to new diagnostic algorithms is required.

1.8.3. C0042 Tranexamic Acid in Hip Fracture Surgery and Risk of Thromboembolic Disease

Maria Lourdes Posadas-Martinez, María Soledad Trasante Borches, Felipe Huaier Arriazu, Lucas Martín Seoane, Luis Roberto Basbus, Ana Lucìa Antivero Stock, Martìn Zarba, Fernando Javier Vázquez, Marina Valinotti, Marìa Belèn Bonella, Paula Guadalupe Gutièrrez, María Florencia, Grande Ratti, Gabriel Waisman, Diego Hernán Giunta

Hiba, Departamento de Investigacion bs as, Buenos Aires, Argentina

Background

Introduction: Tranexamic acid (AT) is an antifibrinolytic. In hip fractures, although its use to decrease in intra- and peri-operative bleeding, it is still controversial in terms of safety because it promotes a state of hypercoagulability.

Objective: To evaluate the association between the use of AT in preoperative anesthetic induction and thromboembolic events 90 days after hip fracture surgery.

Methods

Retrospective cohort of consecutive adult patients operated of hip fracture at the Hospital Italiano de Buenos Aires, between 30 May 2011 and 30 May 2016. Pathological fractures, dislocations and polytraumatisms were excluded. Each patient was followed for 90 days from admission. The events of thromboembolism (deep vein thrombosis DVT and pulmonary thromboembolism PET) confirmed at 90 days, transfusion requirement and change of hematocrit before and after surgery were detected. All information was obtained from the secondary database of the repository of electronic medical record data. The association between AT and thrombosis or bleeding will be evaluated with a Cox proportional hazards regression model.

Results

In the 5-year period, of the 1899 patients eligible for unscheduled surgery secondary to hip fracture, 1714 were included for the analysis. The baseline characteristics: 80.3% (1376) were female, with a median age of 84 years (interquartile range 78–88). Side fractures were 53.9%, medial 38.8% and periprosthetic 7.4%. The median score of charlson comorbidities was 0 (interquartile range 0–2). 89.7% (1538) received AT. Of the lateral fractures, 91.1% received AT, 89.3% of the medial fractures and 74.2% of periprosthetic fractures. The incidence of global ETV was 4.6% (n = 79, CI 0.5–5.7%). Within the group with AT 4.62% (71) presented ET and 4.55% (8) in the group without AT. The HR for thrombosis of AT was 1.14 (95% CI 0.52–2.47, p 0.747). 9.8% (151) of the patients with TA required transfusions and 22.2% (39) in the group without AT ($p < 0.001$). The mean change in hematocrit in the AT group was 4.1 (ds 0.14) and in the group without AT 3.2 (0.47) (p 0.1558).

Conclusions

The use of tranexamic acid in hip fracture surgery was not associated with an increase risk of thromboembolic disease within 90 days of admission. The transfusion requirement was lower in the group of patients who received tranexamic acid.

1.8.4. C0043 Incidence and Risk Factors of Venous Thromboembolic Disease and Thrombosis Portal in Patients Coursing Postoperative Hepatectomy in a Third Level Center: Cohorte Study

Maria Lourdes Posadas-Martinez, Juan Trobbiani, Veronica Peuchot, Fernando Vazquez, Diego Hern·n Giunta, Fernan Bernaldo Quiros, J. C. Iaquinand, J. Pekolj, Martin de Santibañes

Hiba, Departamento de Investigacion bs as, Buenos Aires, Argentina

Background

Thromboembolic disease (VTE) is one of the main complications in the postoperative of abdominal surgeries, with high morbidity and mortality and health costs. The use of thromboprophylaxis in patients with chronic liver disease decreases the risk of VTE without increasing complications due to bleeding. However, the indication of thromboprophylaxis in patients with hepatectomy is still controversial, especially because of the potential risk of postoperative bleeding.

Aim: To determine the incidence of thrombotic events (deep vein thrombosis (DVT)/pulmonary thromboembolism (PTE) and portal thrombosis (PT)) in patients undergoing postoperative hepatectomy and to identify associated risk factors.

Methods

Prospective cohort of all consecutive adult patients with hepatectomies during April 2012 and August 2015. Each patient was followed for 90 days or until the occurrence of the event of interest (DVT/PE, PT and/or death). Incident cases of DVT and PE were captured from the Institutional Registry of Thromboembolic disease. Factors associated with VTE were analyzed with a logistic regression model.

Results

During theperiod of interest, 287 patients were studied. 56% of the patients in the series (n = 161) received chemical thromboprophylaxis, which started on average 48 h after surgery. The incidence of global VTE (TVP and/or TEP) was 5% (n = 15, 95% CI 3–8). The incidence of DVT and PE was 4% (n = 12, 95% CI 2–7%) and 3% (n = 8, 95% CI 1–5%) respectively. TEP is diagnosed in 1 in 2 patients with DVT. The incidence of PD was 2.4% (n = 7, 95% CI 0.9–4.9). The risk factors for the development of VTE were surgery time, prolonged hospitalization and the presence of complications. Surgeries larger than 4 h multiply by 5 the risk of ETV compared to surgeries performed in less time (OR 5.62 IC 95% 1.55–20.40). Patients with hospitalizations greater than 7 days had a 4 times higher risk of presenting thrombotic events (OR 4.11 IC 95% 1.30–13) compared to those with shorter hospitalizations. The presence of postoperative complications increases the risk of suffering DVT/TEP by 4 times after adjusting with confounding factors (OR 3.9 CI 95% 1.2–13).

Conclusions

The incidence of post-hepatectomy VTE is high in this patients the subgroup of patients with complicated postoperative procedures is a high risk group for thrombotic events and could be a reason for new research, deepening earlier and more aggressive diagnostic and therapeutic measures for this disease.

1.8.5. C0044 Eosinopenia as a Marker of Mortality in Patients with Pulmonary Thromboembolism

Maria Lourdes Posadas-Martinez, Felipe Huaier Arriazu, Marìa Soledad Trasante Borches, Martìn Basbus, Ana Antivero, Marina Valinotti, Fernando Javier Vazquez, Gabriel Waisman, Juan Diaz, Diego Hernán Giunta

Hiba, Departamento de Investigacion bs as, Buenos Aires, Argentina

Background

Introduction: Eosinopenia is an independent marker of poor prognosis, associated with severe systemic inflammation, especially in sepsis/bacterial septic shock. Its behavior in pulmonary thromboembolism (PET) is not clear.

Objective: To evaluate the association between eosinopenia and mortality in adult patients with PE.

Methods

Materials and methods: We conducted a retrospective cohort study in patients diagnosed with PE of the Institutional Registry of Thromboembolic Disease of the Hospital Italiano de Buenos Aires (RIET), between 1 June 2012 and 31 March 2017. Pregnant women were excluded. Patients were followed up to 90 days, loss or death. Eosinophils were considered as the exposure variable at diagnosis. Eosinopenia was considered to be the absolute count of eosinophils less than <40 cells/mm^3. The association between eosinopenia and death was evaluated with a Cox proportional hazards regression model. The patients consented to their participation for the RIET. The protocol was approved by the ethics committee.

Results

Results: We included 766 patients with a median age of 72.5 (interquartile range, RIC 62–81), 41.2% (316) were male, and median Charlson comorbidities score was 2 (RIC 0–4). The median eosinophil count was 81.4 cells/mm^3 (RIC 190.25–20.6), of whom 35.3% (268) with eosinopenia. The median follow-up time was 306 days (RIC 53–692). 274 patients died during follow-up. The estimated survival at one year was 0.74 (95% CI 0.69–0.78) in patients without eosinopenia and 0.55 (95% CI 0.48–0.61). The HR of the eosinophil count for mortality was 0.99 (IC95% 0.99–1), for eosinopenia HR 1.99 (IC95% 1.57–2.53), for troponin HR 1.00012 (p 0.733) and that of pro BNP 1.00007 ($p < 0.001$). The HR of eosinopenia adjusted for age, sex, Charlson, total leukocytes, pro-BNP, troponins and DVT was 1.79 (95% CI 1.36–2.37, $p < 0.001$).

Conclusions

Discussion: Mortality was significantly higher among patients with PE and eosinopenia. The determination of eosinophils is widely available in almost all areas of care, and therefore could represent a marker of rapid, accessible, and economic severity in adult patients with PE.

1.8.6. C0051 Specific Thromboembolic Risk Factors and Venous Thrombosis Incidence in Patient with Lymphoma: One Center Experience

Carmen Sanchez-Martin [1], Olga Benitez-Hidalgo [2], Carola Diaz-Aizpun [2], Paloma Garcia-Martin [1], Manuel Espeso de Haro [2], Maria Eva Mingot Castellano [3]

[1] *Universidad de Malaga, Malaga, Spain*
[2] *Hospital Regional Universitario de Malaga, Malaga, Spain*
[3] *Regional University Hospital of Malaga, Hematology Malaga, Malaga, Spain*

Background

Incidence of venous thrombotic events (VTE) in patients with lymphomas is approximately 4%. There are a number of specific thrombotic risk factors (TRF), not been evaluated specifically in patients with lymphoma under non-hospitalization and on-hospitalization chemotherapy regimen. Objective:

- To evaluate the prevalence of general and specific TRF.
- To describe the incidence and characteristics of thrombosis and ischemic events in this group.
- To evaluate the safety of antiplatelet and anticoagulant treatment during chemotherapy treatment.

Methods

Retrospective, one center study. Patients with lymphoma diagnosed and treated in our center between January 2014 and December 2016. We analyzed age at diagnosis, histology, stage, chemotherapy (out-patient or not), prior vascular events, antiplatelet or antithrombotic prophylaxis, use of EPO, Hb < 100 g/L, platelets > 350 × 10^9/L, leucocyte > 11 × 10^9/L, immobilization, Charlson ≥ 3,

IMC > 35, dexamethasone, doxorrubicine, radiotherapy, catheters, incidence and characteristics of vascular events. Patients were followed for one year.

Results

171 subjects evaluated, median age 52.7 ± 18 years old, 45.6% females. Most frequent histology diffuse large B-cell lymphoma (34%). Most of patients advance disease, 61% were stages III or IV. In the serie, 23% received hospitalized chemotherapy, more frequent R-ESHAP, R-CHOP-MTX.

45% of patients had 3 or more TRF. All TRF except EPO, were more prevalent in patients under hospitalization chemotherapy ($p < 0.002$). Six patients presented VTE (2.2% of out-hospitalization chemotherapy, vs. 9.3% of hospitalized, $p < 0.04$): 1 pulmonary embolism, 2 lower limb and 3 upper limb venous thrombosis. 4 patients were under secondary antiplatelet prophylaxis for prior lymphoma arterial ischemia. One of them suffered from a gastrointestinal bleeding during chemotherapy. One of the 6 patients, who develop VTE after lymphoma, presented an upper gastrointestinal bleed. According to these, 2 of 10 patients under chemotherapy and antiplatelet or anticoagulant treatment presented grade 3 bleedings.

Conclusions

Incidence of VTE in patients with lymphoma could be influenced by the necessity of hospitalized chemotherapy. Upper limb thrombosis was the most frequent location, probably related with local administration of chemotherapy. Bleeding risk in patients with chemotherapy and antiplatelet or anticoagulant drugs have to be carefully evaluated.

1.8.7. C0057 Burden of Antiphospholipid Syndrome in a Thromboembolic Disease Registry

Maria Lourdes Posadas-Martinez, Aurelia Luissi, Marina Scolnik, Florencia Grande, Enrique Soriano, Fernan Quiros

Hiba, Departamento de Investigacion bs as, Buenos Aires, Argentina

Background

Prevalence of antiphospholipid antibodies in general population has been reported in about 5%. Impact of different thrombophilias in clinical thromboembolic disease is difficult to estimate. Our objective was to assess prevalence (global and in patients < 40 years) of Antiphospholipid Syndrome (APS) in a prospective Institutional Registry of Thromboembolic Disease at a tertiary university hospital.

Methods

A prospective cohort study evaluated all consecutive incident cases of pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT) confirmed in patients over the age of 18 between 1 January 2011 and 31 December 2014 at a university hospital. All patients with venous thromboembolic disease (VTED), confirmed by venous doppler ultrasound and/or multislice computed tomographic angiography and/or angioMRI and/or ventilation/perfusión scan and/or angiography, were included in the registry after given informed consent. A personal interview was performed and clinical (risk factors, comorbidities, etc) and laboratory data were collected. Patients were contacted annually after incident event in order to assess clinical status, treatments, adverse events, recurrence or death. Electronic medical records of all patients included in the registry were reviewed. APS prevalence was estimated and patients' characteristics were compared with other VTED etiologies.

Results

1294 patients with VTED were included in the registry in this period [females 54.9%, mean age 68.8 years (SD 15.7)]. VTED was attributed to APS in 23 patients [females 73.9%, mean age 59.6 (SD

18.2)], representing 1.8% of all patients and 3.8% of patients ≤40 years (Table 1). APS was associated with other autoimmune diseases in 7 patients (30.4%) (4 SLE, 2 RA, 1 overlap). Patients with APS and other thrombophilias were younger than patients with other etiologies ($p < 0.001$) (Table 2). Type of event and event mortality were similar across groups (Table 2). Having a prior/recurrent event was more frequent in patients with APS and other thrombophilias. In a multivariate logistic regression analysis, younger age (OR 1.03, CI 1.01–1.06), female sex (OR 1.64, CI 1.06–1.86) and a prior VTED event (OR 6.3, CI 2.5–16.1), were significantly associated with APS as the cause of the event.

Conclusions

APS- related VTED events represented 1.8% of total events in this registry. Younger age, female sex and having had a prior event were significantly associated with APS.

1.8.8. C0078 Antithrombotic Therapy for Cancer-Associated Venous Thromboembolism in Patients with Thrombocytopenia: A Retrospective Cohort Study

Silvia Galliazzo [1], Elena Rancan [2], Walter Ageno [2], Alessandro Squizzato [2]

[1] *Ponzano Veneto, Italy*
[2] *Department of Medicine and Surgery, University of Insubria, Ospedale di Circolo, Varese, Italy*

Background

Venous thromboembolism may occur even in thrombocytopenic cancer patients. Scant data are available on their optimal treatment. We aimed at describing the actual strategy of venous thromboembolism management and 3-months follow-up outcomes in this subpopulation of cancer patients.

Methods

Consecutive adult patients referring to our Thrombosis Center between 2006 and 2016 for an acute cancer-associated thrombosis (CAT) diagnosis and a concomitant thrombocytopenia were retrospectively analysed. Thrombocytopenia was classified according to platelets count in mild (100–149 × 10^9/L), moderate (50–99 × 10^9/L), and severe (<50 × 10^9/L). Low-molecular weight heparin (LMWH) was defined at therapeutic or intermediate or prophylactic dose, based on renal function and body weight. We reportedrecurrent VTE and major bleeding occurring in the first 3 months. Mild thrombocytopenic patients were used as a control group.

Results

82 patients were included (73 with deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and 9 with superficial vein thrombosis (SVT)). Mean age was 67 years, 36 (43.3%) were female, 67 (80%) were on chemotherapy, 4 (4.8%) had a glioblastoma, and 8 (9.6%) had cerebral metastasis. Thrombocytopenia was moderate in 27 cases (median count 78 × 10^9/L), severe in 7 (median count 37 × 10^9/L) and mild in 48 (median count 127 × 10^9/L). In moderate thrombocytopenic patients, 14 (51.8%) received a LMWH therapeutic dose, 12 (44.4%) an intermediate dose and 1 (3.7%) no anticoagulant treatment because of a limited SVT. At 3 months, 2 (7.4%) VTE recurrences and no major bleedings were reported. In severe thrombocytopenic patients, 5 (71.4%) received a therapeutic LMWH dose, 1 (14.2%) a prophylactic dose and 1 (14.2%) an inferior vena cava filter. At 3 months, 1 (14.2%) VTE recurrence and no major bleeding were reported.

In mild thrombocytopenic patients, 39 (81%) received a LMWH therapeutic dose, 7 (14.5%) an intermediate dose, 1 (2%) a prophylactic dose for a SVT and 1 (2%) an inferior vena cava filter for a concomitant hemopericardium. At 3 months, 4 (8.3%) recurrent VTE and 2 (4%) major bleedings were reported.

Conclusions

Management of CAT with thrombocytopenia is heterogeneous. About half of moderate thrombocytopenic patients received a LMWH intermediate dose without an apparent increased risk of recurrent VTE events as compared with mild thrombocytopenic patients. In patients with CAT and severe thrombocytopenia the anticoagulant strategy is controversial.

1.8.9. C0086 Clinical Outcome during the Course of VTE in Patients with High Grade Gliomas

José Portillo Sánchez, Iris Violeta de la Rocha

University General Hospital of Ciudad Real, Internal Medicine Ciudad Real, Ciudad Real, Spain

Background

Objectives: To analyze the clinical data and risk of venous thromboembolic disease (VTE), of patients affected by Glioblastoma (GBM). **Introducciton:** There is uncertainty about the optimal therapy, evolution, and risk factors of venous thromboembolism (VTE) in patients with (GBM). The ETV incidence 1.4 to 60% [1]. Prothrombotic condition is in 20–30% of patients with glioblastoma multiforme (GBM) [2]. Impac bleeding: 2–4% without/03.11% anticoagulated [3]. General risk factors VTE, dependent: patients, tumor and treatment. Risk assessment: Khorana scale: Very Low inclusion GBM. Importance functional status, Steroid. Predictive miomarkers in VTE: nº platelet, P-Selectin, D Dímer. **Bibliography: 1.** JR Perry. Neuro Oncol. September 2012; 14 Suppl 4:iv73–8; **2.** JoJT et al. Semin thromb hemos. April 2014; 40(3):325–31; **3.** T J Semrad. Californiaegistry Gliomas. Journal of Neurosurgery. April 2007; 106(4):601–8.

Methods

The cases of deep vein thrombosis (DVT) and pulmonary embolism were recorded in patients with glioblastoma diagnosed and treated in our hospital in the period 2012-14. We Use the statical Program SPSS.

Results

We found predominance of men, with average age lower than the cases without VTE. We did not find differences in the number of platelets or hemoglobin. Increased frequency of chemotherapy with Temodal and radiotherapy, in cases with TVE. The mean period from diagnosis to the TVE event of 11.84 weeks. Until data collection, the overall VTE indicence was 18.1%. The major hemorrhagic complication, especially cerebral, was low, without highlighting in patients with VTE treated, who were all, with light low molecular weight heparin (LWMH), not finding greater survival in the extended treatment. The Khorana index, of general risk of thrombosis in oncological patients, in this group of patients and pathology, did not correspond to the group of intermediate or high risk of VTE

Conclusions

Although the number of cases is limited, the data suggest that: (1) Patients with VTE were somewhat younger, with a higher incidence of COPD, and previous chemotherapy and radiotherapy; (2) The period of greatest incidence-risk of TVE would be in the first three months; (3) We did not find a greater incidence of major or cerebral hemorrhage in the cases with VTE treated with LWMH; (4) Extended treatment was not related to greater survival; (5) The Khorana index applied to other types of cancer may be less adequate, requiring studies of risk of thrombosis in patients with Glioblastom

1.8.10. C0088 Rivaroxaban for Scheduled Work-Up of Patients with Suspected Deep Venous Thrombosis; A Prospective Interventional Outcome Study Ñ the Ri-Schedule Study

Synne Fronas [1], Camilla Tøvik Jørgensen [2], Mohamed Qarbosh [2], Nezar Raouf [2], Jostein Gleditsch [2], Anders Dahm [3], Per Morten Sandset [4], Waleed Ghanima [2]

[1] *Sykehuset Østfold Hospital, Department of Internal Medicine Grålum, Østfold, Norway*
[2] *Ostfold Hospital Trust, Østfold, Norway*
[3] *Akershus University Hospital, Akershus, Norway*
[4] *Oslo University Hospital, Oslo, Norway*

Background

Scheduled work-up of deep vein thrombosis (DVT) can reduce the need for emergency diagnostic imaging and avert prolonged waiting for patients in the emergency room (ER). Current guidelines suggest using low-molecular-weight-heparin (LMWH) if the diagnostic work-up is expected to be delayed.

This abstract reports the study design and preliminary results on the feasibility of scheduled work-up after including 70% of the estimated sample size.

Methods

The Ri-Schedule study is a prospective outcome study (NCT02486445). The primary endpoint is safety of rivaroxaban (15 mg every 12 h, max 2 tablets) in the prediagnostic phase of DVT, which is a composite endpoint of serious bleeding and/or death related to bleeding occurring within 48 h after the last tablet is ingested if DVT is excluded, or until initiating anticoagulation therapy if DVT is confirmed.

The feasibility is defined as the proportion of patients who can be managed according to a scheduled work-up, where the patient receives rivaroxaban while awaiting further diagnostic testing. Inclusion criteria include: age ≥18, consent to the study, and fulfillment of the eligibility criteria. Work-up of suspected DVT includes Wells score, D-dimer and compression ultrasonography. Patients are recruited from the ER of Østfold Hospital, Norway. The study was approved by the Regional Ethics Committee and consent is acquired from all patients.

Results

Out of 1654 screened patients, 1194 have been included in 33 months. Of these, 442 (37%) patients met the predefined eligibility criteria and received rivaroxaban for scheduled work-up.

496 (42%) did not meet the criteria, and an additional 256 (21%) had already received prediagnostic LMWH.

DVT was diagnosed in 207 (17%) of the included patients. No death has been encountered so far in the study due to scheduled work-up.

Conclusions

Scheduled work-up was allowed in 37% of the patients according to the predefined eligibility criteria. This figure is likely to be higher if the final study results support the implementation of these criteria in the future.

1.8.11. C0119 Venous Thromboembolism and Immunothrombosis: Identification of New Biomarkers of Pathology

Pietro Rossetti [1], Antonio Mutti [2], Rosanna Vescovini [3], Paola Mozzoni [2], Matteo Goldoni [2], Ilaria Tassoni [4], Maria Lombardi [4], Gino Bernuzzi [5], Cesare Manotti [4], Roberto Quintavalla [4]

[1] *Angiology and Coagulation Unit, Department of Internal Medicine, University Hospital of Parma, Parma, Italy*
[2] *Department of Medicine and Surgery, University of Parma, Parma, Italy*
[3] *Department of Clinical and Experimental Medicine, University Hospital of Parma, Parma, Italy*
[4] *Department of Internal Medicine, Angiology and Coagulation Unit, University Hospital of Parma, Parma, Italy*
[5] *Immunohematology and Transfusion Center, University Hospital of Parma, Parma, Italy*

Background

Venous thromboembolism (VTE) is the third leading cause of death in Italian population. Immunothrombosis represents a new pathogenetic model of VTE. Recent studies propose some interleukins and microRNAs as molecules able to modulate endothelial inflammation and platelet hyperactivity

Methods

23 patients (18–65 years) were recruited with a new diagnosis of non-oncological VTE and free from chronic inflammatory diseases. Patients were matched 1:1 for age and sex with 23 healthy blood donors. Serum microRNAs (miR 126, 155, 17.92, 195), inflammatory cytokines (IL-6, TNF-alpha, IL-8) and lymphocyte subsets were evaluated in patients at the onset of pathology (T0) and in controls. In patients, clinical and instrumental follow-up was performed: ultrasound thrombotic vein residual, miRNA and interleukins evaluation at 3-month (T1), angio-TAC or pulmonary ventilary-perfusion scintigraphy at 4–6 months.

Results

Patients (T0) compared to healthy showed significant increased values of miRNA 126 [median (IQR 25–75): 0.026 (0.017–0.069) vs. 0.019 (0.011–0.026), $p = 0.01$], IL-8 [median (IQR 25–75): 3.4 (2.4–8.3) pg/mL vs. 2.4 (1.65–3.24) pg/mL, $p = 0.045$], monocytes [mean ± σ: 730 ± 306 cell/μL vs. 515 ± 181 cell/μL, $p = 0.007$], activated T lymphocytes [mean ± σ: 631 ± 242 cell/μL vs. 474 ± 138 cell/μL, $p = 0.011$], Treg lymphocytes [mean ± σ: 66 ± 24 cell/μL vs. 50 ± 16 cell/μL, $p = 0.018$]. IL-6 and miRNA 126 are significantly increased in pathological subjects at T0 compared to T1 [IL-6: median (IQR 25–75) 2.79 (2.43–9.91) pg/mL vs. 2.01 (1.18–2.14) pg/mL, $p = 0.003$ and miRNA 126: median (IQR 25–75) 0.026 (0.016–0.069) vs. 0.017 (0.014–0.029) $p = 0.014$]. In our study, high miRNA126 values at the onset (T0) would correlate with a significant overall thrombotic residual at 3–6 months follow-up (Spearman's Rho coefficient 0.646, p: 0.004).

Conclusions

Our data supports the idea that systemic inflammation is evident in the acute phase of VTE with increase in monocytes, activated T lymphocytes and IL-8. MiRNA 126 is highly active in mediating endothelial activation. These results suggest that miRNA 126 could modify at the onset the thrombus morphometry, conditioning response to therapy. MiR 126 would therefore represent a possible predictive biomarker of poor early recanalization. New efforts would better clarify the morphometric components of the thrombus and molecules modulating the various structural components.

1.8.12. C0125 Prognostic Role of Neutrophils to Lymphocytes Ratio in Patients with Acute Pulmonary Embolism: A Systematic Review and Meta-Analysis of the Literature

Silvia Galliazzo [1], Olga Nigro [2], Lorenza Bert [3], Luigina Guasti [3], Anna Maria Grandi [3], Walter Ageno [3], Francesco Dentali [3]

[1] *Ponzano Veneto, Italy*
[2] *Department of Oncology, University of Insubria, Ospedale di Circolo, Varese, Italy*
[3] *Department of Medicine and Surgery, University of Insubria, Ospedale di Circolo, Varese, Italy*

Background

The prognostic assessment of patients with acute pulmonary embolism (PE) is essential to drive its management. The search for new prognostic factors is a central issue for a more accurate estimate of short-term adverse events. Circulating neutrophils/lymphocytes ratio (NLR) has been suggested as prognostic biomarker for different cardiovascular diseases. Given the central role of inflammation and in particular of neutrophils in the pathogenesis of VTE and its clinical history, NLR could

represent a prognostic tool also in this setting. We performed a systematic review and meta-analysis of the literature to assess the prognostic role of NLR in patients with acute PE.

Methods

MEDLINE and EMBASE were searched up to 2017, week 21. Pooled results were reported as odds ratio (ORs) and were presented with the corresponding 95% confidence intervals (CIs). A bivariate random-effects regression approach was used to obtain summary estimate of accuracy of the high-NLR adjusting for inter-study variability.

Results

Six studies for a total of 1424 patient were included. High-NLR had a weighted mean sensitivity of 77% (95% CI 68–83) and a weighted mean specificity of 74% (95% CI 68–79). High-NLR positive and negative predictive values were 24.4% (95% CI 20.4–28.3) and 96.7% (95% CI 95.6–97.8) respectively.

Conclusions

The relevant impact of NLR on short-term mortality after an acute PE makes it a promising biomarker to better stratify patient prognosis.

1.8.13. C0216 Prevention of Venous Thromboembolism in Internal Medicine Wards—A Cross-Sectional Survey

Matija Kozak, Monika Ätalc, Tjaöa Viûintin Cuderman, Maja Boncelj Svetek, Uröka Bregar, Mirjam Gubenöek, Miodrag Janic, Ana Kovac, Barbara Krevel, Ana Spirkoska, Gregor Tratar, Martina Ravnikar, Mojca Élender

University Medical Centre, Ljubljana, Eslovenia

Background

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in hospitalized patients. Despite being a preventable disease, VTE prophylaxis is still largely underused in the hospital setting. The aim of this study was to establish the use of VTE prophylaxis in patients admitted to medical wards of the Division of Internal medicine at the University Medical Centre in Ljubljana, Slovenia.

Methods

On a pre-specified day, all patients hospitalized in the medical wards of the Division of Internal medicine were assessed for VTE risk using Padua prediction score and classified as low-risk or high-risk for VTE. Contraindications for pharmacological prophylaxis were assessed using an internally devised questionnaire. Based on VTE risk and contraindications for pharmacological prophylaxis the adequacy of VTE prophylaxis was determined by trained data abstractors. Prophylaxis prescription was determined as appropriate or non-appropriate. Attending physicians at the wards received no advance notification of the study.

Results

511 patients were enrolled (222 women, 289 men). In 245 patients VTE prophylaxis was not indicated, however, 17 (6.9%) patients classified as being low risk for VTE received prophylaxis nonetheless. Of 266 (52.1%) patients at high risk for VTE, 50% had a contraindication for pharmacological prophylaxis. In 133 high risk patients without contraindications VTE prophylaxis was prescribed correctly in 50 (37.6%) patients, 11 (8.3%) patients received wrong doses and 72 (52%) did not receive any prophylaxis.

Conclusions

On the day of the survey, in 81% of the patients hospitalized in medical wards of the Division of Internal Medicine wards at the University Medical Centre in Ljubljana the physicians' decision on VTE prophylaxis prescription was appropriate. However, since only 37% of the patients at high risk for VTE received recommended VTE prophylaxis, our data reinforce the rationale to implement measures to improve these results.

1.8.14. C0218 Prevention of Venous Thromboembolism in Trauma and Orthopaedics Patients—A Cross-Sectional Survey

Matija Kozak, Monika Ätalc, Tjaöa Viûintin Cuderman, Uröka Bregar, Miodrag Janic, Ana Kovac, Barbara Krevel

University Medical Centre, Ljubljana, Eslovenia

Background

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in hospitalized patients. Despite being a preventable disease, VTE prophylaxis is still largely underused in the hospital setting. The aim of this study was to establish the use of VTE prophylaxis in patients admitted to traumatologic and orthopaedic department at the University Medical Centre in Ljubljana, Slovenia.

Methods

On a pre-specified day, all patients hospitalized in traumatologic and orthopaedic department were assessed for VTE risk using Caprini risk prediction score and classified as low, medium or high-risk for VTE. Contraindications for pharmacological prophylaxis were assessed using an internally devised questionnaire. Based on VTE risk and contraindications for pharmacological prophylaxis the adequacy of VTE prophylaxis was determined by trained data abstractors. Prophylaxis prescription was determined as appropriate or non-appropriate according to the ACCP guidelines. Attending physicians at the wards received no advance notification of the study.

Results

148 trauma (70 women, aged from 16–95 years) and 71 orthopaedic (38 women, aged 28–85 years) patients were enrolled.

Table 1. The prescribed VTE prophylaxis in trauma and orthopaedic patients on a pre-specified day.

		Prophylaxis Prescribed; No. of Patients (%)		Prophylaxis Not Prescribed No. of Patients (%)		Contraindications No. of Patients (%)	
		Appropriate	Non-Appropriate	Appropriate	Non-Appropriate	Yes	No
Trauma	148 (100%)	59 (39.9%)	26 (17.6%)	48 (32.4%)	15 (10.1%)	118 (79.1%)	30 (20.3%)
Ortopaedics	71 (100%)	22 (30.1%)	1 (1.4%)	32 (45.1%)	16 (22.5%)	7 (9.9%)	64 (90.1%)

Conclusions

Taking into account indications and contraindications, in 107 (72.3%) trauma patients and 54 (75.1%) orthopaedic patients decision for VTE prophylaxis was appropriate. The results indicate that there is still place to improve VTE prophylaxis in our hospital.

1.8.15. C0223 Inherited Thrombophilia Testing in Patients with Unusual Site Thrombosis: Are Abnormalities Depending on Localization?

Gabsi Sirine [1], Kaabar Mohamed Yassine [2], El Elmi Alia [1], Cheikhrouhou Mariem [1], Hanachi Majdi [1], Touil Soumaya [1], Guermazi Sami [1]

[1] *Charles Nicolle Hospital, Tunis, Tunisia*

[2] *Charles Nicolle Hospital, Hematology Laboratory, Tunis, Tunisia*

Background

Deep venous thrombosis (DVT) is a multifactorial disorder classically occuring in the lower limbs. Rarely, atypical locations such as splanchnic venous thrombosis (SVT) and cerebral venous thrombosis (CVT) are reported. Implication of inherited thrombophilia is still debated. Our work aims to assess the prevalence of thrombophilia in patients with unusual site DVT (USDVT) at Charles Nicolle hospital–Tunisia.

Methods

This 5-year retrospective study (2013–2017) included patients with USDVT for whom thrombophilia testing was performed. Subjects with a prothrombin time <70% were excluded. Inherited thrombophilia screening assessed activated protein C resistance (APCR), free protein S (PS), protein C activity (PC) and antithrombin activity (AT). The corresponding deficiencies were defined for levels under 70% for AT and 60% for PC and PS. The retained cut-off for APCR was 120 s. All tests were performed using Diagnostics STAGO® reagents on STA Compact® automat. Statistical evaluation was performed using Chi-squared test.

Results

122 patients were included in our study. The mean age was 41 years. The sex ratio was 0.74. Almost half of the subjects (48%; $n = 59$) had SVT, 21% of them ($n = 25$) had CVT. Other locations were described in 31% of cases ($n = 38$). Thrombophilia screening was positive in 41/122 (34%). We found AT, PC and PS deficiency in respectively 19 cases (16%), 8 cases (7%), 16 cases (13%) and APCR in 8 cases (7%). In patients with SVT, AT deficiency was particularly frequent (15/59; 25%), versus 6 patients (10%) for PC and 9 patients (15%) for PS and only 1 case of APCR. We also remarked that AT level in SVT patients was lower than 60% in 10 cases. There was a strong association between AT deficiency and the splanchnic site ($p = 0.01$). In patients with CVT ($n = 25$), 20% ($n = 5$) had a positive APCR compared to 5% in the Tunisian general population (data not shown). This parameter was strongly associated to the cerebral location ($p = 0.008$). In this group, AT and PS deficiencies were found respectively in 4% ($n = 1$) and 8% ($n = 2$). In the third group ($n = 38$), 9 patients were positive for inherited thrombophilia without a particular trend.

Conclusions

In spite of the limitations of the sample size, our study shows interesting findings: some thrombophilia factors may be related to a specific location. This hypothesis should be tested in a larger cohort. Thrombophilia testing should also be completed with factor II mutation screening, lupus anticoagulant, Jak2 mutation and PHN clone.

1.8.16. C0266 Assessment of Thrombophilia Testing Request in a University Hospital. Haemostasis and Thrombosis Unit. "Hospital de Clõnicas" of Montevideo, Uruguay

Valentina Mèrola Ponce De León, Ana Carina Pizzarossa, Lorena Nicassio, Mariana Lorenzo, Matilde Boada, Sofia Grille, Pìa Oldán, Sabrina Ranero, Lilián Dìaz, Cecilia Guillermo, Rosario Martìnez

Hospital de Clínicas, Montevideo, Uruguay

Background

Introduction: Hereditary or acquired thrombophilia may increase the risk of venous thromboembolism (VTE) but it is only one of many risk factors in a clearly multifactorial entity. On the other hand, the utility of testing thrombophilia for decision making in VTE is controversial. The non selective study of thrombophilia not only lacks clinical impact but also causes unnecessary expenses and could cause harm. It is essential to try to optimize the request of these tests.

Methods

Methodology: In this retrospective study we included all patients with VTE assessed by our Unit between 2012 and 2017. Thrombophilia tests requested were analyzed according to age (cut off 50 years) and the categorization of the event according to 2016 ISTH recommendations (1). Two patient groups were established regarding thrombophilia testing: justified and non justified request. We considered justified testing the following situations: unprovoked events and provoked events by a minor transient risk factor in patients under 50 years of age, and/or with a family history of VTE. It was considered non justified request provoked events by major or persistent risk factors or patients older than 50 years. For this study, regarding hereditary thrombophilia Factor V Leiden, Prothrombin gene 20210 A/G, proteins C, S, antithrombin, homocysteine levelsor polymorphisms of MTHFR tests were included. Regarding acquired thrombophilia, antiphospholipid antibodies were evaluated. It is emphasized that many patients were studied prior admission to the Unit.

Results

Results: 185 patients were included. The justified request group included 48 patients, 47 of which (98%) were studied. The non justified included 147 patients, 44 (32%) of them were studied. Of these, 21 (47%) corresponded to unprovoked events in patients older than 50 years, 8 (18%) to events associated with a minor transient factor in patients over 50 years, 12 (27%) were associated to a major transient factor and 3 (6.8%) to a persistent factor. In the justified group 9/48 (18.8%) patients had one or more positive tests and 13/137 (9.5%) in the non justified group. None of these results changed the therapeutic behaviour.

Conclusions

Conclusions: Although, most of the tests were requested in the justified group, in more than a third of the patients thrombophilia testing was requested in clearly provoked events or in people older than 50 years. An effort on continue medical education about the role of thrombophilia in VTE is still necessary in our community.

1.8.17. C0274 Biovasc Score for Determining the Duration of Anticoagulant Therapy after a First Episode of Idiopathic Venous Thrombosis

Dargaud Yesim [1], Ninet Jacques [1], Desmurs Clavel Helene [1], Rugeri Lucia [2], Trzeciak Christine [2], GEMMAT Groupe [3]

[1] *Service de Medecine Interne, Hopital Edouard Herriot, Lyon, France*
[2] *Unite d'Hemostase Clinique, Hopital Cardiologique, Lyon, France*
[3] *Réseau Régional de Thrombose (Lyon-Saint Etienne), Lyon, France*

Background

Recurrence is common after an initial episode of venous thromboembolism (VTE) and is associated with high morbidity and mortality rates. The duration of anticoagulant therapy plays a key role in the fight against thrombosis recurrence. What the "optimal" duration of anticoagulation after the initial VTE episode might be is still unclear. A number of authors have developed models for predicting the risk of recurrence for personalized adjustment of anticoagulation duration. Three models have been published: the HERDOO-2 score, the DASH score and the Vienna score.

Methods

Using data from the literature and results from a recent translational study, we developed the BIOVASC score, a new tool for predicting the risk of VTE recurrence. The BIOVASC score is based on five criteria: male gender, obesity (BMI > 30 kg/m^2), D-dimer > 500 ng/mL, ETP > 1900 nM min, and estrogen/progestin therapy. The score aims to predict the risk of thrombosis recurrence, thus rendering it possible to halt anticoagulation safely if the score proves negative.

Results

The BIOVASC score was tested in 103 consecutive patients with a first episode of spontaneous proximal VTE with or without pulmonary embolism. The model is based partly on criteria used by existing prediction models and also data from the literature, while also integrating thrombin generation assay. Endogenous thrombin potential (ETP) is the area under the thrombin generation curve and represents enzymatic activity of generated thrombin or in other words the coagulation capacity of a given patient. In a recent prospective clinical study, our group revealed ETP > 1900 nM min to be an independent risk factor for recurrence. Several publications on thrombotic and bleeding disorders have reported ETP as a biological parameter that correlates in a better manner with patients' clinical signs of thrombosis or hemorrhages than the standard coagulation tests. Including this innovative parameter into the BIOVASC score provided us a negative predictive value of 97.7% for thrombosis recurrence, along with 94.7% sensitivity.

Conclusions

A multicentre prospective clinical cohort study, involving a larger sample size will be organized to evaluate whether or not the BIOVASC score may allow for a safer discontinuation of anticoagulant therapy in patients at low risk of recurrence and open new perspectives for personalized medicine in VTE.

1.8.18. C0350 Long-Term Echocardiographic Follow-Up after Pulmonary Embolism with Signs of Pulmonary Hypertension

Ÿyvind Jervan, Waleed Ghanima

The Hospital of Oestfold, Kalnes, Internal Medicine, Graalum, Norway

Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of pulmonary embolism (PE), affecting 3–4% of patients, and usually occurs within 2 years after PE. There is little evidence, however, regarding the optimal follow-up strategy for patients with slightly elevated systolic pulmonary artery pressure (sPAP) after PE. In this small follow-up study we re-evaluated 10 patients who had previously echocardiographic findings suggestive of pulmonary hypertension (PHT) after PE.

Methods

In 2013 we conducted a study in which we examined 170 patients with confirmed PE with echocardiography (mean time from PE diagnosis to TTE 5.3 years) to determine the long-term consequences of PE. Tricuspid regurgitation velocities >2.8 m/s, suggesting PHT, were observed in 19 patients (11%). However, some of these patients had significant comorbidity, including severe LV dysfunction and severe pulmonary disease probably contributing to PHT. In 2017 we sought to re-evaluate these patients with a second echocardiography.

Results

Of the 19 patients with signs of PHT, 2 patients had died, one of whom had confirmed CTEPH. Four patients were deemed ineligible for re-evaluation due to cognitive impairment, serious comorbidity or advanced cancer. We were unable to reach two patients and one did not wish to undergo further testing. Ten out of the 19 patients were re-evaluated with clinical examination and echocardiography. Using paired *t*-test we found no significant difference when comparing the estimated systolic pulmonary artery pressure (sPAP) with the results from 2013 (p-value = 0.9). However, 3 of the patients had a markedly increased sPAP (from 45, 43 and 43 mmHg to 70, 64 and 58 mmHg, respectively). None of these had been diagnosed with recurrent thromboembolic events since the initial echocardiographic examinations. Two of these had discontinued anticoagulation, and

had no other obvious cause of PHT suggesting CTEPH as the most probable cause. We are currently awaiting further diagnostic testing for verification of the diagnosis.

Conclusions

Our findings illustrate the importance of long-term follow-up after PE in the setting of even slightly elevated pulmonary artery pressure. Three out of the 10 patients examined had findings requiring further diagnostic work-up and altered therapeutic management.

1.8.19. C0360 How Common Is Thoracic Outlet Syndrome in upper Extremity Deep Vein Thrombosis? A Phlebographic Study

Alejandro Daniel Godoy [1], Alejandro Daniel Godoy [2], Romina Montivero [1], Aldo Hugo Tabares [1]

[1] *Hospital Privado Universitario de Córdoba, Córdoba, Argentina*
[2] *Hospital Privado Universitario de Córdoba, Medicina Vascular y Trombosis, Córdoba, Argentina*

Background

Upper extremity deep vein thrombosis (UEDVT) is an increasingly recognized clinical entity, particularly due to an increase in the use of indwelling central venous catheters and pacemakers. In patients with UEDVT without recognized risk factors for thrombosis, thoracic outlet syndrome (TOS) and thrombophilia might be etiologic factors. However, the prevalence of TOS in this population is unknown.

Vein compression by costo-clavicular o muscular structures is not easily assessed by clinical maneuvers, and imaging is required to document TOS

We studied the prevalence of TOS as assessed by functional venography in a cohort of patients with primary UEDVT

Methods

A retrospective, descriptive, observational study was conducted at the Hospital Privado Universitario de Córdoba from 1 January 2008 to 31 December 2017. UEDVT patients were idenfied by searching the interventional radiology databases, and the electronic medical records.

We excluded patients undergoing venography for the construction of arteriovenous fistulas (AVF), catheter placement for hemodialysis, pacemaker-associated and catheter related venous thrombosis, and patients undergoing thrombolysis.

Patients underwent venography by antegrade injection of nonionic iodinated contrast in the arm veins. Patients were evaluated with the arms in the resting position and during abduction to 90° and 170°. A positive result for TOS was considered when vein compression was present at 90 degrees abduction or less.

Results

During the study period a total of 307 upper limb venograms were performed; 276 were excluded: negative venogram 5, AV malformations 3, catheter for chemotherapy 9, pacemaker placement 23, AVF for hemodialysis 236

A total of 31 patients with primary UEDVT were evaluated, 22 patients (71%) were women with a median age of 36 years. A venographic diagnosis of TOS was present in 22 patients (71%). Among patients with TOS-associated thrombosis, 10 (47%) received oral contraceptives, and 7 (32%) had thrombophilia.

Conclusions

In the cohort of patients with unprovoked UEDVT studied, a high prevalence of TOS was found. TOS in conjunction with thrombophilic risk factors and the use of oral contraceptives might precipitate UEDVT

1.9. Diagnostic and Laboratory Methods

1.9.1. C0036 Increased Plasma Viscosity in Plasma Cell Dyscrasia and Whole Blood Viscosity in Polycythemia Vera

Hyun Kyung Kim

Department of Laboratory Medicine, Seoul, Korea

Background

Hyperviscosity syndrome in plasma cell dyscrasia (PCD) and thrombosis in myeloproliferative neoplasm (MPN) are major causes of morbidity and mortality. But measurement of blood viscosity has been underutilized. In this study, we investigated whether whole blood or plasma viscosity could reflect hyperviscosity syndrome in PCD, and whether WBC, RBC, and platelets influence on both viscosity in MPN. We also evaluated the influence of various laboratory markers on the blood viscosity.

Methods

A total 80 patients with hematologic diseases including PCD ($n = 26$), MPN ($n = 25$; Polycythemia vera (P. vera, $n = 5$), essential thrombocythemia (ET, $n = 7$), primary myelofibrosis (PMF, $n = 6$), chronic myelogenous leukemia (CML, $n = 7$)), acute leukemia ($n = 5$), and lymphoma ($n = 24$), and a total 104 healthy controls were investigated. In PCD patients, questionnaire survey about hyperviscosity symptoms was performed and the presence and degree of symptoms were arbitrarily scored. Whole blood/plasma and systolic/diastolic viscosity were measured by Hemovister (Ubiosis, Seongnam, Korea). We performed CBC, chemistry assays, coagulation assays and thrombin generation assays (TGA), and we evaluated the correlations with viscosity.

Results

In comparison with controls, PCD showed significantly high total protein, systolic and diastolic plasma viscosity (PV). In PCD patients with hyperviscosity score ≥2, the systolic and diastolic PV were significantly higher than controls. Among MPN, P. vera showed significantly high RBC counts, systolic and diastolic whole blood viscosity (WBV). ET showed significantly high platelet counts and CML showed significantly high WBC and platelet counts, but showed normal WBV. WBV showed significant positive correlation with RBC count and total protein, and negative correlation with ESR, factor VII and VIII. PV showed significant positive correlation with total protein and endogenous thrombin potential (ETP), and negative correlation with RBC count, albumin, total cholesterol, factor VIII and XI.

Conclusions

PCD showed high plasma viscosity and normal whole blood viscosity, and hyperviscosity symptoms are correlated with high plasma viscosity. Among MPN, P. vera exhibited high whole blood viscosity but ET and CML showed normal whole blood viscosity. To evaluate the hemorheologic disturbances and establish the therapeutic targets in PCD and MPN, the measurement of blood viscosity should be considered.

1.9.2. C0056 Age-Adjusted D-Dimer to Rule out Deep Vein Thrombosis in the Elderly: A Post-Hoc Analysis of the Palladio Study

Nicoletta Riva [1], Marc Righini [2], Giuseppe Camporese [3], Matteo Iotti [4], Eugenio Bucherini [5], Pieter Kamphuisen [6], Peter Verhamme [7], James Douketis [8], Chiara Tonello [3], Paolo Prandoni [3], Walter Ageno [1]

1 *Universidad de Insubria, Varese, Italy*
2 *Geneva University Hospitals, Geneva, Switzerland*
3 *University of Padua, Padua, Italy*

[4] *Reggio Emilia Hospital, Reggio Emilia, Italy*
[5] *Faenza Hospital, Faenza, Italy*
[6] *University Medical Center Groningen, Groningen, The Netherlands*
[7] *University of Leuven, Leuven, Belgium*
[8] *McMaster University, Hamilton, ON, Canada*

Background

The use of an age-adjusted D-dimer (DD) cut-off can increase DD specificity for the diagnosis of venous thromboembolism (VTE). Age-adjusted DD combined with clinical pre-test probability (PTP) was shown to be safe in a prospective management study of patients with suspected pulmonary embolism (PE). However, data regarding patients with suspected deep vein thrombosis (DVT) are still limited. We recently demonstrated that the PALLADIO algorithm using age-adjusted DD can decrease the need forcompression ultrasonography (CUS), but the advantage was limited (only 5% reduction). The aim of this study was to assess the accuracy of age-adjusted DD in the elderly.

Methods

PALLADIO (NCT01412242) was a prospective study that included outpatients with suspected DVT and validated a new diagnostic algorithm (combining PTP, DD according to manufacturers' cut-off, and CUS). Patients were divided into 3 groups with different diagnostic approaches: (1) unlikely PTP and negative DD: DVT was ruled out without further testing; (2) likely PTP or positive DD: limited-CUS; (3) likely PTP and positive DD: extended-CUS. A 3-month follow-up was performed if DVT was ruled out at baseline. For this post-hoc analysis we considered elderly patients (defined as 75 years or older) and age-adjusted DD (defined as age times 10 mg/L, or age times 5 mg/L for D-dimers with lower manufacturers' cut-off).

Results

Among the 1162 patients enrolled in the PALLADIO study, 403 were elderly (mean age 82 years, female 67.5%). According to the original PALLADIO algorithm, 18.1% were classified in group 1, 36.2% in group 2 and 45.7% in group 3. DVT at initial visit were detected in 1 (0.7%) patient in group 2 and 78 (42.4%) in group 3. Symptomatic VTE during follow-up occurred in 0% (95% CI, 0–5.0) in group 1; 1.41% (95% CI, 0.39–4.99) in group 2; 1.96% (95% CI, 0.54–6.87) in group 3.

Using the age-adjusted DD, 26.8% were classified in group 1 (no DVT at initial visit), 38.5% in group 2 (3 DVT) and 34.7% in group 3 (67 DVT). The incidence of symptomatic VTE during follow-up was similar: 0% (95% CI, 0–3.43) in group 1; 1.44% (95% CI, 0.40–5.09) in group 2; 2.86% (95% CI, 0.79–9.83) in group 3. The age-adjusted DD resulted in 8.68% (95% CI, 6.31–11.84) reduction of CUS.

Conclusions

The use of an age-adjusted DD cut-off can be especially beneficial in the elderly with unlikely PTP, allowing approximately 9% reduction of the CUS, but the safety of this approach should be confirmed in large prospective studies.

1.9.3. C0058 an Analysis of Deep Venous Thrombosis in Thermally Injured Patients (Materials of Doppler Ultpasound)

Borisov Valery, Sokolova E. P., Trofimova E. Y., Kaplunova M. Y., Mazhorova I. I.

Sklifosovsky Emergency Medicine Institute, Department of Health in Moscow, Moscow, Russia

Background

To study the incidence of deep venous thrombosis in burn patients which had of moderate and high risk of development thromboembolic disease

Methods

A total of 335 patients of thermal injury which had treatment inBurn Center of the Sklifosovsky Institute for Emergency Medicine, Moscow, Russia with II-III degree burns on the area from 10 to 60% TBSA. All patients had of moderate and high risk of development deep venous thrombosis (DVT) and should be included in the Samama scale for risk calculation in burn. 115 (34.3%) patients from 335 patients) developed DVT which was diagnosed on doppler ultrasound (DUS). Women was 54, 61 men, age 18 patients from up to 90 years. DUS of lower extremities was also performed on all patients on 8–15 day of admission with on devices Esaote Megas, Logiq-500 with a 7–12 MHz transducer. Imaged veins included external iliac, common femoral, superficial femoral, popliteal, anterior and posterior tibial. 10 (8.7%) patients developed pulmonary embolism (PE)

Results

At 62 (53.9%) on DUS were withdistal thrombosis with not occlusive and parietal character of fixation occurred: at 53 (46%)–occlusive and 22 (19.1%) with a floating. 12 (10 percent) patients had thrombosis with a floating proximal part of the thrombus from 1.0 to 7.5 cm the level of the popliteal vein, 10 (8.7%) at the level of femoral vein, thrombosis diagnosed 10 have double sided (8.7%) patients, unilateral u 105 (91.3%). All patients with burn injury in the first 7–14 days after trauma hadof bed rest, clinical indications vein thrombosis of the lower limbs have been identified. DUS study revealing pathological changes at 34.4%, to reliably determine the nature and extent of thrombosis, found a floating character of the thrombus at 19.1% patients

Conclusions

The appointment doppler ultrasound of patients with burns from a group of moderate and high risk development of venous thrombosis in lower limbs vein allows to identify and assess the character of thrombosis and began to start therapy when there were no clinical signs and symptoms DVT

1.9.4. C0060 Hemorheological Aspects of the Thromboembolic Complications in Severaly Burned Patients

Borisov Valery, Bitkova E. E., Khvatov V. B., Smirnov S. V., Kaplunova M. Y.

Sklifosovsky Emergency Medicine Institute, Department of Health in Moscow, Moscow, Russia

Background

To assess the rheological disorders, associated thrombotic complications of burn disease

Methods

31 patients with severe thermal injuries (Frank index more than 30). 12 (I group) developed thrombotic complications: deep venous thrombosis (n = 9); pulmonary embolism (n = 1), myocardial infarction (n = 2). The II group—19 non-thrombotic patients. The data of 45 healthy volunteers were included. Statistical processing was performed with calculation of criterion for Student and was performed using U-Mann-Whitney test. Whole blood rheology (viscosity and viscoelasticity) at three selected shear rates: 2.5 s^{-1}, 12.6 s^{-1}, 62.8 s^{-1} was assessed by BioProfiler (USA), red blood cell aggregation MA-1 (Myrenne GMBH, Germany) by the aggregation index in relation to the the shear rate 600 s^{-1} high shear range for desaggregation, 3 s^{-1} low shear range (M1), 0 s^{-1} stasis (M), hematocrit—in analyzer Act diff 2 Beckman Coulter (USA).

Results

In 1 day after injury in both groups showed significant elevated hematocrit and viscoelasticity in shear rate 12.6 s^{-1}, the I group showed a significant decrease M as well as vs. normal level and vs. II group. In 3 day in the I group significant decrease of hematocrit was observed: 29.5 ± 2.6% vs. 37.2 ± 2.2 vol.% in II group ($p \leq 0.05$). Whole blood viscosity in shear rate 2.5 s^{-1} decreased in I group for

40% ($p \leq 0.05$), in II group–for 20%. Viscoelasticity of erythrocyte membrane in shear rate 62.8 s^{-1} decreased in the I group to 0.21 ± 0.05 mPa s vs. 0.53 ± 0.13 mPa s in II group. In both groups there was an increase in M1 30% and 50% of normal, respectively. In 10 day enhanced M1 in both groups was continued, whole blood viscosity and viscoelasticity in a shear rate of 2.5 s^{-1} decreased in the I group to 50% in the II group 30%. In 20-day hematocrit level in the I group remained lower than in the II group was 37.7 ± 2.7% vs. 44.3 ± 1.3 vol.% ($p \leq 0.05$). Viscoelasticity in a shear rate of 62.8 s^{-1} in the I group of 45% of normal. To 30 days blood viscosity at shear rate 2.5 s^{-1}, 12.6 s^{-1} in the I group averaged 50% of normal, in the II group −60%, viscoelasticity in the I group was reduced at all shear rates, in the II group only at 2.5 s^{-1} at 40%

Conclusions

(1) In burn patients complicated by thrombotic processes, declining viscoelasticity blood in combination with the increase of the aggregation rate of red blood cells; (2) The most important hemorheological disorders observed from 3 to 20 days after injury

1.9.5. C0061 Morfofunctional Status of Platelets in Burn Patients with Severe Injury

Borisov Valery, Makarov M. S., Kaplunova M. Y.

Sklifosovsky Emergency Medicine Institute, Department of Health in Moscow, Moscow, Russia

Background

To study the morphofunctional characteristics of platelets from burn patients with severe injury.

Methods

A prospective study was conducted from 30 patients aged from 16 to 70 years: 22 men, 8 women who had treated at the Burn Center of the Sklifosovsky Institute for Emergency Medicine, Moscow from January 2017 to October 2017. All the patients had with burn wounds II-III degree from 22 to 75% ofthe TBSA. Platelets of patients investigated in first day after trauma, on the 3, 10, 20 and 30 days after injury. Analysis of the quality of platelets conducted using an original method (Patent No. 2485502). We to study stained cells in vivo with analysis in fluorescent microscope.

Results

On the 1–3 day treatment in 30 patients the content of biologically high-grade platelets (adhesive active cells with granules) did not comply with the normal (35–75%). 26 patients had platelets with granules in blood has been sharply reduced (0–9%), but 4 patients had higher rates adhesive active cells with granules (80–91%). All patients in the blood revealed a large number of platelets without granules with acute violations of the structure of membranes. Dynamics of morphological and functional characteristics of platelets it was different. So, 11 patients which were issued, biologically high-grade platelets gradually increased at 10, 20 and 30 day were a normal or about normal morphofunctional status of platelets. 5 patients which had more severe injury and were treated more than 30 days, level platelets with granules amounted 10–30% from the first to the last day of observation. 4 patients which had higher level platelets with granules (80–91%) on the first day, through 10 days it was a sharp decline platelets with active granules and then some rise this parameter the 30 day.

Conclusions

Morphofunctional characteristics of platelets can be used as a prognostic indicator of the severity burn trauma and criterion for outcome of burn disease in patients with severe thermal injury.

1.9.6. C0097 Blood Clot Properties Appearing after Transfusion Reflect Hemostatic Quality of Platelet Concentrates

Irina Kolesnikova [1], Alexander Kostin [2], Eugene Roitman [3]

[1] *Pirogov Russian National Research Medical University, Moscow, Russia*
[2] *N.V. Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia*
[3] *RSS Clinical Hemostasiology, Office Moscow, Moscow, Russia*

Background

Final platelet task is a hemostasis via good quality clot. Ongoing bleeding after platelet concentrates (PC) transfusion might be caused altered hemostatic activity of stored platelets. Additionally some role may play various subpopulations of platelets. Therefore the adjusted growth of circulating platelet count has limited diagnostic value as a criterion considering a success of transfusion. More interest belong to clot properties which are formed by recipient blood after PC.

Methods

Forty oncohematological patients with thrombocytopenia (platelet count 20–50 × 109/L) were examined before and after single PC transfusion aimed for hemorrhage prevention (group I; $n = 24$) and for bleeding therapy (group II; $n = 16$). Aggregation in stored platelet had evaluated as well as recipient clot quality, quantitative impact and quantitative value of PC-platelets assayed by different thromboelastographic methods. Additionally we used thromboelastography with own design basing on ADP mixed with some diluted solutions.

Results

Before PC transfusion Group II showed higher platelet count and better clot properties due to the fibrinogen contribution but not of the platelet investment. On contrary, after transfusion clot quality and platelet aggregation was higher in Group I.

The more days PC was stored, the less the platelets contributed to the patient's clot properties in Group II ($r = -0.548$; $p < 0.0001$) but the high in Group I ($r = 0.874$; $p < 0.0001$).

In Group II circulating platelet contribution to patient's clot properties depended positively on the quality of the clot, which PC forms in vitro mostly with the fibrin ($r = 0.898$; $p < 0.0001$) but negatively in Group I ($r = -0.422$; $p < 0.0001$).

Conclusions

It was shown that PC transfusion improved generally recipient clot quality but influenced reasons had differed. We assume that after prophylactic PC transfusion the main role belongs to aggregates-forming platelets to define the properties of recipient blood clot. In the bleeding cases the main role is given to platelet subpopulation carrying surface-expressed phosphatidylserine encouraging more active thrombin generation. Then it explains that the recipient clot quality improvement had developed mainly via fibrinogen/fibrin but not via the platelet way.

1.9.7. C0117 the Value of D-Dimer in Diagnosis of Thromboembolic Complications in Burn Patients

Borisov Valery, E. V. Klychnikova, E. V. Tazina, Kaplunova M. Y., A. S. Bogdanova, T. G. Spiridonova, E. A. Zhirkova

Sklifosovsky Emergency Medicine Institute, Department of Health in Moscow, Moscow, Russia

Background

The high prevalence of venous thromboembolic complications (VTE) among all hospitalized patients with thermal trauma reported in prospective and retrospective studies (from 0.4 to 23%).

Methods

We study to level of D-dimer in dynamics and to assess its in search for a practical and a reliable screening tool VTE in burn patients/A prospective study was conducted in the Department of Burns Sklifosovsky Institute for Emergency Medicine, Moscow, Russia. A total of 33 patients of thermal injury were enrolled in the study. All patients had thermal burns of II-III degree with total body surface area (TBSA) 22–75% (Frank index over 30 units). Screening D-dimer assays in blood plasma were performed on all 33 patients on day 1, 3, 10, 20 and 30 days after admission, taking for the reference value 0.17 (0.17–0.23) mg/L. All patients were divided into two groups: 1 group included 20 patients (not venous thromboembolic complications), the median age of which was 47 (31–65) years and 2 group—13 patients (with development venous thromboembolic complications which was diagnosed on doppler ultrasound), median age 53 (40–79) years. D-dimer level was examined on an automatic coagulometer "Sysmex CA 1500" (Japan) using reagents from «Siemens». Software «Statistica» version 10.0 was used for statistical analysis. The quantitative variables are compared between groups using Mann–Whitney test.

Results

For the 1st day in group 1, the median D-dimer was 2.09 mg/L (1.4–4.67), in the 2nd group 1.26 mg/L (0.78–2.6). The difference was found to be insignificant (p = 0.346). At day 3 in group 1, the median D-dimer was 1.07 mg/L (063–1.31), in the 2nd group 1.5 mg/L (0.96–2.5), the differences were not significant (p = 0, 059). At 10 and 20 days in group 1, the medians of D-dimer were 1.46 mg/L (1.12–1.88) and 1.36 mg/L (0.84–2.12), respectively, in group 2, 3.2 mg/L (2.17–7.53) and 3.24 mg/L (2.11–6.31), respectively, and D-dimer values for these days in group 2 were significantly higher than in group 1 (p = 0.004 and p = 0.025, respectively). To 30 days of statistically significant differences between the groups was not detected (p = 0.241).

Conclusions

In the early periods after injury, an elevated level of D-dimer cannot be used to predict the development of VTE in burn patients. The level of D-dimer may have prognostic value for the detection of VTE in the period from 10 to 20 days after the burn injury.

1.9.8. C0126 Possibiliti of the Metod of Thrombodynamics in Prognosis of the Thromboembolic Complications in Burn Patients

Borisov Valery [1], Vuimo T. A. [2], Kaplunova M. Y. [1], Kotova Y. N. [3], Chromina S. S. [1]

[1] *Sklifosovsky Emergency Medicine Institute, Department of Health in Moscow, Moscow, Russia*
[2] *Center for Theoretical Problems of Physicochemical Pharmacology RAS, Moscow, Russia*
[3] *Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia*

Background

To identify the possibilities of the method of Thrombodynamics and standard clotting tests in prognosis the progress of venous thromboembolic complications (VTE) in patients with burn injury.

Methods

The study included 31 patients with thermal injury, receiving treatment in the burn center of the Sklifosovsky Institute for Emergency Medicine in 2017. Index Frank, all patients, were above 30. We studied for patients with thrombosis (group 1) and groups without VTE (group 2). For the study of hemostasis have been used: standard clotting methods (APTT, PV, TV, fibrinogen) and test thrombodynamics (TD). Monitoring was carried out in points: 1 point–1 day; 2–3 a day; 3 point–10 ± 1 day; 4 point 20 ± 2 days; 5 point 30 ± 3 days.

Results

Patients in both groups parameters standard clotting tests as a whole were within the normal range (APTT 27 ± 3.4; PV 92 ± 8.5; TV 18 ± 4.6), the only exception was the level of fibrinogen of 4.02 + 0.5, which was moderately elevated. The dynamic parameters test TD (Vi, Vst) in both groups are in the area of moderate/significant hypercoagulable state. The ROC analysis revealed interesting differences between groups: the occurrence of VTE is possible when the starting speed ≥66.1 μm/min in point 2. For the point 3 values for the starting speed ≥59.2 μm/min., fixed speed ≥32 μm/min and density of clot ≥32,568 also with a probability of 92.3% of the will lead to the development of VTE. The density value of the clot in 4 ≥ 29,325 settings as well with a probability of 83.3% of may indicate the development of VTE. In addition observed a significant difference for Vst and Vi of growth of the clot between points 2 and 3 for the 2 groups, the downward trend in hypercoagulability. With similar values of the stationary velocity of clot growth (Vst) to assess differences between both groups was possible with the help of a specially introduced coefficient of Vst*1000/D. The ratio of the rate of growth of the clot to the density of the clot is significant difference between 1 and 2 groups at the point of observation 5, where the group with thrombosis (group 1) this parameter is greater than 2 μm/min*u.e.

Conclusions

The parameters of the test Thrombodynamics in contrast the standard clotting tests with sufficient sensitivity and specificity can predict the occurrence of thrombotic accidents.

1.9.9. C0211 Prevalence of Thrombophilic Disorders in Patients with Superficial Venous Thrombosis

Zgolli Selma, Kaabar Mohamed Yassine, Touil Soumaya, Cheikhrouhou Mariem, Dardouri Nesrine, Guermazi Sami

Charles Nicolle Hospital, Hematology Laboratory, Tunis, Tunisia

Background

Superficial vein thrombosis (SVT) is a common medical condition that may be associated with thromboembolic complications such as venous thromboembolism (VTE) and recurrent SVT. Despite the increasing awareness of the condition and its underlying pathogenesis, there are no clear-cut guidelines regarding routine thrombophilic testing of patients with SVT.

Our aim was to determine the prevalence of inherited thrombophilic defects in patients with SVT.

Methods

Subjects with SVT diagnosed with a Doppler ultrasonography, were retrospectively identified from medical records at the Hematology department of Charles Nicolle Hospital in Tunis from 1 January 2005 to 31 December 2017.

Patients with a prothrombin time lower than 70% were excluded.

Antithrombin (AT) deficiency was defined as levels <70%. Protein C (PC) and free protein S (PS) deficiencies were retained when their levels were lower than 60%, while activated protein C resistance (APCR) diagnosis was made when the results were <120 s.

All tests were performed using Diagnostica STAGO® reagent on STA compact automat.

Results

The chart review identified 49 patients with SVT. The M/F sex ratio was 1.33. Mean age was 41.7 years (18–69). The lower limb was the site of SVT in the majority of cases (90.32%).

We conducted a screening including AT, PC, free PS and APCR in 34 patients; 9 of them (26.47%) were positive for one or more of the thrombophilic disorders. APCR was detected in 14.63% of the cases (6/41) versus 5% in the general population in Tunisia, whereas the prevalences of PS, PC and

AT deficiencies were 8.33% (4/48), 4.17% (2/48) and 2.7% (1/37) respectively. One patient had concomitant APCR and PS defects whereas another one had low PS and PC levels.

Conclusions

Our study showed a high prevalence of thrombophilic disorders in patients with SVT corroborating our opinion to continue the thrombophilic screening in these patients. Nevertheless, because of the small sample size and the horizontal type of the study dismissing patients' follow-up regarding potential complications and treatments, our results are to be interpreted carefully and a more thourough investigation is to be conducted in order to assess the real benefit of thrombophilia testing in these individuals.

1.9.10. C0212 Prevalence of Thrombophilic Disorders in Patients with Retinal Venous Occlusion

Zgolli Selma, Kaabar Mohamed Yassine, Helali Intissar, Cheikhrouhou Mariem, Dardouri Nesrine, Guermazi Sami

Charles Nicolle Hospital, Hematology Laboratory, Tunis, Tunisia

Background

Retinal vein occlusion (RVO) is a major cause of vision loss. General risk factors such as hypertension, hyperlipidemia, and diabetes mellitus have been reported to predispose to RVO. However, the role of thrombophilic abnormalities in the pathogenesis of RVO remains controversial.

The aim of the present study was to assess the prevalence of thrombophilic disorders in patients with RVO.

Methods

Subjects with RVO were retrospectively identifed from medical records at the Hematology department of Charles Nicolle Hospital in Tunis during the observational time frame from 1 January 2005 to 31 December 2017.

Patients with a prothrombin time lower than 70% were excluded.

Antithrombin (AT) deficiency was defined as levels<70%. Protein C (PC) and free protein S (PS) deficiencies were retained when levels were lower than 60%, while activated protein C resistance (APCR) diagnosis was made when the results were<120 s.

All tests were performed using Diagnostica STAGO® reagent on STA compact automat.

Results

Thirty patients with RVO were identified. The M/F sex ratio was 1.5. Mean age was 45.1 years (25–84). Central retinal vein occlusion was found in 29 patients (96.66%), while branch retinal vein occlusion was observed in 1 patient (3.33%).

We conducted a screening including AT, PC, free PS and APCR in 29 patients and one patient was tested for APCR only; APCR was detected in 13.33% of the cases (4/30) versus 5% in the general population in Tunisia, whereas none of the subjects had PS, PC or AT defects.

Two of the APCR postitive patients (18.18%) were older than 45 years and the two others (11.76%) had a RVO prior to the age of 45.

Conclusions

We found a high prevalence of APC resistance among subjects with RVO while none of the patients had AT, PS or PC deficiency raising the question of the usefulness of the three latter tests in these patients.

However, due to the small sample size, our findings are to be interpreted carefully and a prospective comparative investigation should be conducted in order to determine the real value of thrombophilia testing in these individuals.

1.9.11. C0214 Comparison of Activated Partial Thromboplastin Time and Diluted Russel Viper Venom Test for Lupus Anticoagulant Diagnosis

Helali Intissar, Cheikhrouhou Mariem, Hammami Emna, Kaabar Mohamed Yassine, Dardouri Nesrine, Guermazi Sami

Charles Nicolle Hospital, Hematology Laboratory, Tunis, Tunisia

Background

Lupus Anticoagulant (LA) is a validated biological marker for antiphospholipid syndrome (APLS) along with anti-beta-2-GP1 and anti-cardiolipin antibodies screening.

The ISTH recommends for LA screening the association of two tests, activated Partial Thromboplastin Time with sensitive reagent (aPTT) and diluted Russel Viper Venom Test (dRVVT).

The aim of this study was to compare these two tests in patients with idiopathic thrombosis, pregnancy failure or autoimmune diseases.

Methods

We collected retrospectively positive results for LA detection from 2013 to 2017. Patients under heparin were excluded from the study. The LA testing was performed on STA Compact® coagulation analyzer (Stago, France). Lupus anticoagulant (LA) screening was performed using PTT-LA® reagent and dRVVT Screen®. When prolonged, we confirmed the antiphospholipid specificity using Staclot LA®, and/or dRVVT Confirm®. Statistical study was conducted using Mc Nemar test.

Results

LA was identified in 76 patients with a mean age of 41 years [2 weeks–89 years] and a sex ratio of 1.05. The percentages of thrombosis, pregnancy failure, both events and autoimmune diseases were 61.8%, 6.6%, 5.3 and 26.3% respectively. LA was detected in 64 patients by aPTT while 35 subjects were positive in DRVVT. We found LA by both techniques in 23 patients.

a-PTT had a higher sensitivity (84.2% versus 46%) than dRVVT ($p < 0.05$).

Conclusions

LA diagnosis is complex and laborious and there is no standardized test for its detection.

Although our results show a higher sensitivity of aPTT, combining both tests seems to be the best strategy for now which is consistent with current guidelines. Furthermore, ISTH recommends to control the LA positivity after 3 months in order to confirm the diagnosis. Would a similar approach change our findings?

1.9.12. C0305 Thrombophilia Assessment in Unusual Sites Venous Thrombosis

Amara Wafa, Chakroun Aya, Mahjoub Sonia, Hela Baccouche, Ben Romdhane Neila

Rabta Hospital Department of Hematology Bab Saadoun, Tunis, Tunisia

Background

Venous thrombosis (VT) in unusual sites commonly includes venous thrombosis of the upper extremities, abdominal, cerebral and retinal venous thrombosis. These rare locations require a rigorous diagnostic and therapeutic approach. This study aimed to profile thrombophilia markers in patients with thrombosis in unusual sites.

Methods

A retrospective study included patients with unusual sites thrombosis (January 2013–December 2017). Demographic data, personal risk factors and results of thrombophilia investigation were analyzed. Screening for inherited thrombophilia included tests for antithrombin activity (AT):

stachrom AT, protein C (PC) and protein S (PS) activities (respectively, Staclot PC and Staclot PS; STAGO) and the activated PC resistance test (Staclot aPCR; STAGO).

Results

243 patients were enrolled. The mean age was 42 year-old. The sex ratio was 0.56. The most frequent VT sites were: upper limbs (n = 19), cerebral (n = 107), abdominal (n = 92) and retinal (n = 14) veins. While Jugular veins, right heart and vena cava represented 8.2% (n = 20) of total sites. Combined VT sites were observed in 13 cases. An underlying disease or triggering event was reported in 27% of patients: pregnancy (n = 5), post-partum (n = 3), hemopathy (n = 12), chronic liver disease (n = 26), systemic disease (n = 3), inflammatory bowel disease (n = 6), infection (n = 5), cancer (n = 2), catheter (n = 3). Combined thrombophilia markers deficiencies were mainly related to liver failure or anticoagulation. In the abdominal sites, there were PS deficiency in 2 patients and PC deficiency in one patient. At the cerebral site, there were one case of PS deficiency, another of PC deficiency and two patients with activated PC resistance. Among primary thrombosis in upper limbs, there were one patient with PC deficiency and another carrying an activated PC resistance. No inherited thrombophilia was noted among patients with retinal thrombosis.

Conclusions

Unusual thrombosis sites are rare and usually due to a local risk factor or to an underlying disease. However, significant knowledge gaps are still in the involvement of these thrombophilia markers.

1.9.13. C0307 Evaluation of Thrombin Generation in Hematological Malignancies

Hadhri Meriem, Hela Baccouche, Chakroun Aya, Mahjoub Sonia, Manai Zeineb, Ben Romdhane Neila

Rabta Hospital Department of Hematology Bab Saadoun, Tunis, Tunisia

Background

Multiple myeloma (MM) and myeloproliferative neoplasms (MPN) are prototypes of hematologic malignancy associated with high thrombotic risk. Some studies have suggested that the thrombin generation assay may be a predictive marker of thrombosis. The aim of this study was to determine the hypercoagulable state in MM patients and MPN patients at diagnosis.

Methods

Eighteen patients with MM were included at diagnosis in a prospective study and compared to 11 matched controls according to age and sex and to 15 patients with MPN. Age, sex, cardiovascular risk factors and known history of thrombosis were investigated. Thrombin generation assay was performed on platelet-poor plasma using Calibrated Automated Thrombography with PPP reagent 5 pM (STAGO, France). Parameters of Lag time (lagt), peak thrombin concentration (peak), time to peak (ttpeak), endogenous thrombin potential (ETP) were analyzed.

Results

MM and MPN patients were similar with regards to age, gender and cardiovascular risk factors. Half of the patients were classified as having high vascular risk in both groups. Among the thrombin generation parameters, the lagt was shorter in the MM group (2.5 min) compared to the control group (2.9 min, p = 0.08) and the MPN group (3.6 min, p = 0.03). The ttpeak was significantly shorter in the MM group (4.4 min) compared to the control group (5.1 min, p = 0.007) and the MPN group (6.3 min, p = 0.005). The peak observed in the MM group (288.2 nM) was higher than that observed in the control group (241.2 nM, p = 0.06) and that observedin the MPN group (223.2 nM, p = 0.02). The velocity index was significantly higher in MM myelome than in controls (156 vs. 110 nM/min; p = 0.005).

Conclusions

Thrombin generation appears to be higher in MM compared to controls and patients with MPN. As a result, myeloma can be considered to be associated with a high thrombotic risk. Thromboprophylaxis is indicated especially since other risk factors related to the patient, the pathology and the treatment increase this thrombotic risk.

1.9.14. C0332 Evaluation of the Hemostatic System in Colorectal Cancer Patients Using Thromboelastography

Marina Poluektova [1], Dmitry Erygin [2], Eugene Roitman [2], Tatiana Mikhalskaya [1], Tatiana Panferova Panferova [1]

[1] *A.F. Tsyb Medical Radiological Research Center ñ Branch of the Federal State Budget Institution ìNational Medical Research Center of Radiologyî of the Health Ministry of the Russian Federation, Laboratory Diagnostic Department Obninsk (Kaluga Region), Obninsk, Russia, Russia*
[2] *Pirogov Russian National Research Medical University, Moscow, Russia*

Background

Thromboelastography (TEG) is mainly *used* in surgery and trauma. However, the role of this method in oncology is still poorly understood. The purpose of our study was to analyze TEG parameters and identify the most significant of them for evaluation of haemostasis in colorectal cancer patients.

Methods

Thirty-two patients with colorectal cancer (CRC) were examined. Of these patients: 4 had stage T1-T2, and 28 had stage T3-T4. The age of the patients ranged from 32 to 79 years (median 57 years). The control group (C) comprised 12 patients with cardiovascular disease. Age was comparable between all study groups. Assays were performed on a TEG-5000 device (Haemoscope Corporation, Niles, IL, USA) using stabilized citrated blood. The TEG provided information on blood coagulation dynamics, viscoelastic properties of formed thrombus and speed of its lysis (over 20 parameters). The level of fibrinogen and the *number of platelets*in the blood were determined using automated *analyzers* (Elite Pro, Beckman Coulter, Brea, CA, USA).

Results

Comparison of parameters between groups of CRC patients demonstrated that the time of clot formation was shortened by 5%, maximum rate of thrombus generation increased by 7%, time to maximum rate of thrombus generation increased by 9%. There was no statistically significant difference. Yet, the increase in the maximum amplitude by 7% ($p \leq 0.05$), the increase in the clot strength by 30% ($p \leq 0.05$), the increase in total thrombus generation by 8% ($p \leq 0.05$), the decrease in lysis (LY30) by 80% ($p \leq 0.01$), and the decrease in the calculated percentage of lysis (EPL) by 13% ($p \leq 0.01$) were statistically significant. In CRC patients, the platelet count and fibrinogen level exceeded control values by 20% and 40%, respectively ($p \leq 0.05$). The *thrombodynamic potential index* in CRC patients exceeded control values by 40%. The observed differences are suggestive of increased thrombus generation and thrombus strength, reduced lysis of thrombus as well as increased contribution of platelets and fibrinogen to haemostatic homeostasis in CRC patients. Values of the studied parameters did not depend on the stage of the disease.

Conclusions

1. The use of TEG for assessment of hemostasis has expanded our understanding of the thrombus properties and peculiarities of thrombus generation in colorectal cancer patients. It enables to evaluate *thrombotic* risks and undertake appropriate preventive *measures* against thrombotic complications regardless of the type and stage of treatment.

1.9.15. C0340 Anti-Domain I-Beta-2 Glycoprotein 1 Antibodies in Antiphospholipid Antibody Carriers: Predictive Value for the First Thrombotic Event. A Single Centre, Prospective Observational Follow-Up Study

Marta Tonello [1], Elena Mattia [1], Teresa Del Ross [1], Maria Favaro [1], Antonia Calligaro [1], Ariela Hoxha [1], Elisa Bison [2], Vittorio Pengo [2]

[1] *Reumatology Unit Department of Medicine Padua, Department of Medicine of Padua, Padua, Italy*
[2] *Cardiology Clinic, Department of Cardiac, Thoracic and Vascular Sciences, Padua, Italy*

Background

Antibodies directed against domain I of β2GlycoproteinI (anti-DI) correlate well with the more severe clinical pictures in antiphospholipid syndrome (APS) patients. However, at the best of our knowledge the significance of anti-DI antibodies in antiphospholipid antibodies (aPL) carriers has been never evaluated. This study investigates the clinical value of anti-DI antibodies in a homogeneous cohort of aPL carriers.

Methods

One hundred and five aPL carriers persistently positive for IgG anticardiolipin (aCL) and/or IgG anti-β2Glycoprotein 1 antibodies (a-β2GPI) and/or lupus anticoagulants (LAC) were selected. Anti-DI antibodies were detected at the basal time by QUANTA Flash® Beta2GPI-Domain I chemiluminescence immunoassay (INOVA Diagnostics, San Diego, CA, USA).

Results

Anti-DI antibodies were found in 44 aPL carriers (41.9%). Triple aPL positivity (LAC plus IgG aβ2GPI plus IgG aCL antibodies) was significantly associated to anti-DI positive carriers ($p = 0.0001$), During the follow up period, ten aPL carriers (9.5%) developed the first thrombotic event so becoming APS patients. The cumulative incidence rate of thrombotic events during the follow-up significantly prevailed in anti-DI-positive aPL carriers with respect to anti-DI negative ones ($p = 0.031$). Anti-DI antibodies, triple aPL positivity, thromboembolic risk factors and autoimmune disorders significantly prevailed in carriers becoming APS with respect aPL carriers ($p = 0.01$, $p = 0.0003$, $p = 0.001$, $p = 0.045$, respectively). Logistic regression analysis revealed anti-DI antibodies as an independent factor associated to thrombosis ($p = 0.043$, OR = 9.9, 95% CI = 1.1–91.4).

Conclusions

If our results will be confirmed by further large-scale studies, anti-DI antibodies could be considered as a new risk factor predictive of the first thrombotic event in aPL carriers

1.9.16. C0344 Comparison of Russell Viper Venomñbased and Activated Partial Thromboplastin Timeñbased Screening Assays for Resistance to Activated Protein C

Carla Monteiro Monteiro, Federico Martinez, Vitor Cunha, InÍs Moreira, Luciana GonÁalves, Manuela Carvalho, Maria Carmo Koch, Maria Carmo Koch

Centro Hospitalar Sao Joao, Serviço de Imuno-Hemoterapia, Porto, Portugal

Background

Resistance to activated protein C (APC resistance) is characterized by abnormal resistance of human plasma to the anticoagulant effects of human APC.

Most individuals with familial APC resistance have a factor V Leiden mutation making factor V/Va partially resistant to inactivation by APC. The degree of abnormality of the APC-resistance assay correlates with heterozygosity or homozygosity for the factor V Leiden mutation. But there are other clinical settings in which patients can have APC resistance, like in pregnancy, oestrogen

therapy, acquired PC or PS deficiency, presence of lupus anticoagulant and drugs that prolong coagulation times.

APC resistance assays evaluate the anticoagulant response of patient plasma after adding a standard amount of APC. When APC resistance is present, clotting time tests fail to prolong significantly after the addition of APC.

The design of the study was to compare the ProC® Ac R assay, a Russell Viper Venom-based clotting assay, with COATEST™ APC™ Resistance V assay, a functional test based on activated partial thromboplastin time.

Methods

Plasma from 29 patients were tested with the 2 different APC resistance assays according to manufacturers protocols. Protein C (PC), protein S (PS) and lupus anticoagulant were also evaluated. None of the patients was under anticoagulant therapy.

All samples were tested with and without addition of APC and the ratio between results were obtained. In ProC® Ac R assay, result is considered positive with ratio <1.8. In COATEST™ APC™ Resistance V assay, result is considered positive with ratio <0.84.

DNA sequence-based analysis for F V Leiden mutation was performed.

Results

There was no discrepancies between assays results. APC resistance was positive in both assays in 5 patients. All 5 patients were genotyped as heterozygotes for FV Leiden mutation.

PS levels below 50% of the normal range were found in 4 patients; one of them also present low levels of PC. These results did not correlated with APC resistance.

Conclusions

In contrast to other studies, in this comparison, both assays showed similar sensitivity and specificity in discriminating between wild-type factor V and heterozygotes FV Leiden mutation individuals. It would be important to increase the number of samples studied and evaluate the differences between homozygote and heterozygote FV Leiden individuals.

1.10. Genetics and Genomics in Thrombosis and Hemostasis

1.10.1. C0221 Correlation of the Debut of Clinical Symptoms in Hemophilia with Hereditary Factors of Thrombophilia

Elena Poponina [1], Elena Butina [1], Eugene Roitman [2], Olga Vyaznikova [1], Larisa Sergeeva [1], Sergey Ignatiev [1], Igor Paramonov [1]

[1] *Kirov Scientific Research Institute of Hematology and Blood Transfusion, Kirov, Russia*
[2] *RSS Clinical Hemostasiology, Office Moscow, Moscow, Russia*

Background

Hemophilia is an X-linked hemorrhagic disease associated with factor VIII deficiency (hemophilia A) or IX (hemophilia B). The clinical course of the disease may depend on mutations in genes that have a prothrombotic effect. One of the factors considered in assessing the severity of the disease is the age at which the first symptoms of bleeding appear. The aim was to find the dependence of the age of manifestation of the disease on the presence of mutations in genes predisposing to the development of thrombophilia.

Methods

Genetic analysis was performed with polymerase chain reaction in real time ("DNA-Technology", Russia) to find the polymorphism of the genes F2, F5, FGB, ITGA2, ITGB3, PAI-1 in 54

patients with severe hemophilia A and B (factor level less than 1% of the norm), of which 35 patients showed disease at the age up to 1 year, 19–1 year and older.

Results

The following frequency of occurrence of mutant alleles of thrombophilia genes was found in the group of patients whose hemorrhagic syndrome occurred at the age up to 1 year: FII (GA) was not detected; FV (GA) was not detected; FGB (GA)—in 7 patients (36.8%), FGB (AA)—1 (5.3%); ITGA2 (CT)—9 (47.4%), ITGA2 (TT)—3 (15.8%); ITGB3 (TC)—5 (26.3%), ITGB3 (CC)—1 (5.3%); PAI-1 (5G4G)—6 (31.6%), PAI-1 (4G4G)—10 (52.6%). In the group of patients whose first signs of hemophilia were diagnosed at the age of 1 year and older, the frequency of occurrence of polymorphisms was distributed as follows: FII (GA)—in 1 patient (2.9%); FV (GA)—4 (11.4%); FGB (GA)—18 (51.4%), FGB (AA)—2 (5.7%); ITGA2 (CT)—17 (48.6%), ITGA2 (TT)—6 (17.1%); ITGB3 (TC)—11 (31.4%), ITGB3 (CC)—1 (2.9%); PAI-1 (5G4G)—18 (51.4%), PAI-1 (4G4G)—15 (42.9%)

Mutations of FII and FV were detected only in patients with a later onset of disease manifestation. However, there were no significant differences between the groups ($p > 0.05$). In a detailed analysis, it was established that the first hemorrhagic manifestations appeared in carriers of mutations FII and FV later than in patients without mutations (median age was 36 months vs. 15 months ($p < 0.05$).

Conclusions

The mutations of the FII and FV genes is associated with a later debut of the symptoms of hemophilia. The relationship between the manifestation of the disease and the carrier of polymorphisms of the FGB, ITGA2, ITGB3, PAI-1 genes was not established.

1.10.2. C0235 Evaluation of Endogenous Thrombin Potential among Patients with Antithrombin Deficiency-Serbian at Deficiency Study Group Results

Mirjana Kovac [1], Gorana Mitic [2], Sanja Lalic-Cosic [3], Valentina Djordjevic [4], Branko Tomic [4], Zsuzsanna Bereczky [5]

[1] *Blood Transfusion Institution of Serbia, Beograd, Serbia*
[2] *Institute of Laboratory Medicine, Clinical Center of Vojvodina, Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia*
[3] *Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia*
[4] *Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia*
[5] *Division of Clinical Laboratory Research, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary*

Background

Inherited antithrombin (AT) deficiency is a rare autosomal dominant disorder, caused by mutation in *SERPINC1*. It is classified into two types. While the clinical picture depends on the type and the type and site of mutation, it remains unclear whether thrombotic potential is also associated with the type of mutation or not. The aim of this study was to evaluate endogenous thrombin potential (ETP) among AT deficiency carriers in relation to SERPINC1 mutations.

Methods

70 participants from 23 Serbian families with AT deficiency were included in the investigation—31 probands and 39 first degree family members. Genotyping was done usingthe Sanger fluorescent sequencing method and ETP was determined. After genotyping, participants were divided as follows: Type I deficiency (20), Type II HBS (33), Type II PE (2), and family members without mutations as the control group (15). ETP were expressed as median AUC (%) with interquartile range (IQR).

Results

Among non-carriersan ETP of 85% (16.5) was observed. Among carriers, type I vs. type II ETP values of 110% (27.0) vs. 102% (18.5; $p = 0.961$) were obtained and for asymptomatic vs. symptomatic 110% (19) vs. 115% (23; $p = 0.671$). ETP in symptomatic carriers of SERPINC1 mutations receiving long-term anticoagulant therapy showed that this treatment suppressed hemostatic activity equally regardless of deficiency type.

Conclusions

We highlight that all carriers of SERPINC1 mutations had significantly higher ETP than the non-carriers, but with no statistically significant difference with regard to the type of AT deficiency.

1.10.3. C0296 Arterial Ischemic Stroke in Toddlers: The Significance of Thrombophilic Genes & Rsquo; Polymorphisms Assessment

Olga Lvova [1], Anastasia Dron [2]

[1] *Ural Federal University, Laboratory of Brain and Neurocognitive Development, Yekaterinburg, Russia*
[2] *City Clinic Pediatric Hospital 9, Russia*

Background

Inherited thrombophilia is known as a significant risk factor for arterial ischemic stroke in children (PedAIS). Inherited thrombophilia is described to be the most frequent reason for PedAIS. But the certain combinations of single nucleotide polymorphisms (SNPs) are not investigated thoroughly especially in early life period.

Methods

Type of study: case-control. Inclusion criteria: 57 childrenwith AIS's debut under 2 y.o. (including fetal and perinatal type of PedAIS), confirmed by brain CT (MRI) scan; informed consent form. 12 single nucleotide polymorphisms (SNPs) in blood samples were identified by polymerase chain reaction: 8 for thrombophilic genes FGB:-455G>A, F2:20210G>A, F5:1691G>A, F7:10976G>A, F13:103G>T, ITGA2:807C>T, ITGB3:1565T>C, PAI-1:-675 5G>4G, and 4 for folic acid enzymes: MTHFR:677C>T, MTHFR:1298A>G, MTRR:66A>G, MTR:2756A>G. The results were compared with 117 healthy controls.

Results

Quantitative analysis showed that the carriers of 4–6 SNPs in total number of SNPs as well assome certain combinations raised the risk of the PedAIS's with early life onset (table).

Forecast value of thrombophilic SNPs in toddlers with PedAIS.

SNPs' Combinations *	PedAIS	Controls	OR	95% CI	Fisher
4 SNPin thrombophilic genes	16	6	7.22	2.59–20.12	0.000
3 SNP in folic acid enzymes genes	17	19	2.19	1.02–4.72	0.032
6 SNP in total number of genes	16	11	3.76	1.58–8.93	0.002
FGB:-455G>A+ITGA2:807C>T+PAI-1:5G-6754G+MTRR:66A>G	15	6	6.61	2.35–18.54	0.000
FGB:-455G>A+ITGB3:1565T>C+PAI-1:5G-6754G+MTHFR:1298A>G	5	2	5.53	1.00–30.46	0.039
ITGA2: 807C>T+ITGB3:1565T>C+PAI-1:-675 5G>4G+MTHFR:1298A>G	9	5	4.20	1.31–13.50	0.012

* Calculation took into account both hetero- and homozygous (not wild) alleles. We discovered more than 15 SNPs combinations that evidently increased the risk of PedAIS in toddlers (OR > 2.21, Fisher ≤ 0.05), none of them included the most investigated and fatal SNPs F2:20210G>A, F5:1691G>A.

Conclusions

Thrombophilic genes' polymorphisms must be taken into account as the important risk factor for PedAIS in early stage of life. Quantitative analysis demonstrated that the most diagnostic value had 4–6 SNPs combinations regardless of the composition of them. Carriage of SNPs combination that included genes of fibrinogen, platelets receptors, fibrinolytic system, and folic acid enzymes seemed to be the good applicants to become the certain genes-candidates combinations that predict the PedAIS risk under 2 years old.

1.10.4. C0310 Prevalence of Antithrombin Budapest 3 Mutation among Different Patients Groups; Investigation of the Age and Origin of Mutation Common in Hungary

Réka Gindele [1], Roberto Colombo [2], Zsuzsanna Szabó [3], Marianna Speker [3], Zoltán Mezei [3], László Balogh [4], Éva Katona [3], Zsuzsa Bagoly [3], Szilvia Fiatal [5], Zsuzsanna Bereczky [3]

[1] *University of Debrecen, Debrecen, Hungary*
[2] *Center for the Study of Rare Hereditary Diseases, Niguarda Ca' Granda Metropolitan Hospital, Milan, Italy*
[3] *University of Debrecen, Division of Clinical Laboratory Science, Debrecen, Hungary*
[4] *University of Debrecen, Department of Cardiology and Cardiosurgery, Debrecen, Hungary*
[5] *University of Debrecen, Department of Preventive Medicine, Debrecen, Hungary*

Background

Antithrombin (AT) is an important circulating inhibitor of blood coagulation proteases. Hereditary AT deficiency is classified as type I, type IIRS (reactive site defect), type IIHBS (heparin-binding site defect) and type IIPE (pleiotropic effect). Individuals with inherited AT deficiency have a highly increased thrombotic risk. The mutation profile of AT gene (*SERPINC1)* is heterogeneous, the most prevalent mutations are AT Cambridge II, AT Budapest 3 (ATBp3) and AT Basel. The ATBp3 mutation underlies the vast majority of AT deficiencies in the Hungarian population due to a founder effect.

Methods

Our goal was to determine the prevalence of ATBp3 mutation among different patients groups; in general Hungarian (n = 1000) and Roma population (n = 1185); in patients with venous thrombosis (n = 304), in young myocardial infarction (MI) (n = 88) and in stroke (n = 119) patients and in a clinical control group (n = 450). We aimed to investigate the age and origin of the most recent common ancestor of the ATBp3 mutation-bearing chromosomes and to give a plausible historical and demographic scenario of the founder effect. Presence of ATBp3 was investigated with a LightCycler480 instrument by using real-time PCR and melting curve analysis. Analysis of eight short tandem repeat sequences (STRs) was executed on an ABI3130 Genetic Analyzer. The decay of linkage disequilibrium (LD) over generations was modeled by DMLE+ method.

Results

The ATBp3 mutation did not occur in the general Hungarian population, in contrast, the frequency of this mutation was high, 2.8% in the general Roma population. The mutant "T" allele was associated with one single STR haplotype in ATBp3 mutation carrier Roma patients. The occurrence of ATBp3 in patients with venous thrombosis was 1.6%, in young patients with MI it was 2.3% and in stroke it was 0.8%. The ATBp3 was absent in the clinical control group. Assuming an average of 25 years per generation, the results of LD decay modeling suggests the most recent common ancestor carrying the ATBp3 mutation back to middle of the XVII century.

Conclusions

The ATBp3 rarely occurs in other populations, this is most common among Hungarian AT deficient patients. It is especially interesting that the prevalence of ATBp3 mutation in the general Roma population is so common. This knowledge draws the attention to the possibility to improve the health status of the Roma population by including the screening for ATBp3 mutation in the risk assessment for thrombotic diseases.

1.10.5. C0328 Factor V Deficiency in Norway: Genotype-Phenotype Characterization of Five Cases

Nina Iversen [1], Heidi Glosli [2], Marit Sletten [3], Marie Skogstad Le [3], Marit Hellum [3], Mari Tinholt [4], Carola E Henriksson [3]

[1] *Oslo University Hospital, Department of Medical Genetics, Oslo, Norway*
[2] *Centre for Rare Disorders, Dept of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway*
[3] *Dept of Medical Biochemistry, Oslo University Hospital, Oslo, Norway*
[4] *Dept of Medical Genetics and Dept of Haematology Oslo University Hospital, Oslo, Norway*

Background

"Mary" was the first factor V (FV) deficiency patient discovered in Norway by Owren (1943). FV deficiency is a rare autosomal recessive bleeding disorder (1:1 mill). The bleeding symptoms range from mild to severe. The objective of this studywas to identify and characterize the five Norwegian FV-deficient patients identified.

Methods

Mutation analysis of the *F5* gene was performed by Sanger sequencing of the exons and the exon/intron boundaries. FV antigen (ag) (ELISA), FV activity and thrombin generation (TG) by CAT assay were measured.

Results

In all probands the bleeding symptoms varied from asymptomatic to severe. Proband 1 and 2 were two asymptomatic adult siblings with a homozygote exon 16 mutation c.5408 A>G (His1803Arg) and FV ag of <1 and 3 IU/dL, and FV activity of 2 and 3 IU/dL, respectively. The lag time was prolonged but the peak height was normal and equal to their normozygous sister.

Proband 3 (boy 13 years), diagnosed with stroke 5 at months, had the homozygote exon 23 mutation c.6293 C>T (Pro2098Leu) which is identical to Mary's mutation. This case had FV ag/activity of 1 IU/dL and the lag time/peak height were evidently prolonged/reduced.

Proband 4 (girl 17 years) had moderate bleeding tendency with easily bruising and heavy menstrual bleedings. FV ag/activity were <1 IU/dL and the lag time/peak height were evidently prolonged/reduced. She was compound heterozygous for two missense mutations in *F5*: c.6293 C>T (Pro2098Leu) in exon 23 and the c.5408 A>G (His1803Arg) in exon 16.

Proband 5 (girl 14 years) had severe bleeding tendency with mucosal bleedings since early childhood, easily bruising and heavy menstrual bleedings. FV ag/activity were <1 IU/dL and TG were not detected after 60 min. Two heterozygous missense mutations in the *F5* gene were found; c.6293 C>T (Pro2098Leu) in exon 23 and c.5990 C>G (Tyr1997Cys) in exon 21. The second mutation in proband 5 is novel, and an inhibitor against FV has evolved after treatment with Octaplas®. NovoSeven® is successfully used to limit her bleeds. For all probands, the asymptomatic parents had FV ag of 60–98 IU/dL and FV activity of 42–59 IU/dL.

Conclusions

We identified two novel homozygous cases of the exon 16 mutation, and a novel exon 21 mutation in the most severely affected case with inhibitor evolvement. The peak height reflected the

different bleeding phenotypes in these FV cases, and may be a good evaluator for the bleeding severity.

1.10.6. C0329 Effects of Serpinc1, Proc, Pros1 and Epcr Polymorphisms on the Plasma Levels of Natural Anticoagulants in Healthy Individuals and on the Risk of Venous Thromboembolism and Myocardial Infarction

Tunde Miklós [1], Gábor Balla [1], László Balogh [2], Zoltán Boda [3], Zsuzsanna Szabó [1], Éva Molnár [1], Réka Gindele [1], Éva Katona [1], Zsuzsanna Bereczky [4]

[1] *University of Debrecen, Division of Clinical Laboratory Science, Debrecen, Hungary*
[2] *University of Debrecen, Department of Cardiology and Cardiosurgery, Debrecen, Hungary*
[3] *University of Debrecen, Department of Internal Medicine, Debrecen, Hungary*
[4] *University of Debrecen, Faculty of Medicine, Division of Clinical Laboratory Science, Department of Laboratory Medicine, Debrecen, Hajdu-Bihar, Hungary*

Background

Antithrombin (AT), protein C (PC) and protein S (PS) are natural anticoagulants and EPCR plays a role in PC activation. There are several polymorphisms (SNPs) that may influence their plasma levels. So far, controversial data have been published regarding their effects that is, at least in part, caused by gene-gene, gene-environment interactions in different populations.

Our aim was to investigate the effects of 12 SNPs (PROC rs1799809, rs1799808, rs1799810, rs2069928, rs1401296, PROCR rs867186, rs6088735, rs8119351, SERPINC1 rs222758, rs121909548, PROS1 rs8178649 and rs121918472) on the plasma levels of AT, PC and PS in healthy individuals and on the risk of venous thromboembolism (VTE) and myocardial infarction (MI).

Methods

A multiplex PCR-primer extension assay was developed to investigate the SNPs simultaneously in 366 healthy volunteers (median age 36; range 18–85; ratio of females 58.1%), in 144 VTE (median age 40; range 19–49; ratio of females 47.4%) and in 78 MI (median age 36; range 24–40; ratio of females 23.1%). AT activity was measured in heparin-cofactor (hc-AT) and progressive (p-AT) FXa-based assays, PC activity and free PS concentration were measured by chromogenic assay and latex-immunoturbidimetry, respectively.

Results

AT Cambridge (rs121909548) was absent in our population. In healthy volunteers mean hc-AT and p-AT activities were 97% (±8.9) és 106% (±10.5), respectively and rs2227589 was without effect on AT. Mean free PS concentration was 105 ± 20.7 and as it was expected, PS Heerlen (rs121918472) decreased it markedly (105 vs. 72%, $p = 0.045$), while rs8178649 was without effect. Mean PC activity was 115% (±24.9) and among PROC promoter SNPs rs1799809 and rs1799810 decreased, while rs1799808 increased it significantly even after adjustments. PROCR rs867186 and rs8119351 significantly increased, rs6088735 decreased PC activity. Taken the combined effects of PROC and PROCR SNPs into consideration the lowest and highest PC levels showed more than 30% difference ($p < 0.001$). The rs1401296 increased the risk of VTE by 2.5-fold ($p = 0.009$) and in the contrary, rs867186 was protective against VTE in FV Leiden negative patients (OR 0.24, $p = 0.026$) and against MI (OR 0.13, $p = 0.040$).

Conclusions

PC levels are highly influenced by genetic factors. Our observations suggest that PC and polymorphisms that influences its level may play a role not only in venous but also in arterial thrombosis, which is worthy of further investigations. (OTKA-K 116228)

1.10.7. C0348 Pediatric Arterial Ischemic Stroke: Prediction of Disability on Genes Polymorphisms with the Help of the Logistic Regression

Olga Lvova, Alexander Sergeev, Anna Rakhmatova, Vadim Gusev

Ural Federal University, Laboratory of Brain and Neurocognitive Development, Yekaterinburg, Russia

Background

Disability due to mental delay or motor deficiency is one of the undesirable outcomes after pediatric arterial ischemic stroke (PedAIS), which is poorly investigated and badly predicted. Statistical methods are able to identifying the certain modified and not modified marks in the debut of the disease, which could evidently forecast the outcome. Thrombophilic genes polymorphisms are known as the significant risk factor for PedAIS and considered to play the important role in it outcome.

Methods

The following personal and medical data of 75 patients with PedAIS has been processed: 8 independent variables: sex (Sex01), the carriage of single nucleotide polymorphisms in 7 genes (F5:1691G>A, ITGA2:807C>T, PAI-1:-675 5G>4G, MTRR:66A>G, MTHFR:1298A>C, AGT:521C>T, AGTR1:1166A>C). The sex was coded as 0 (girl) and 1 (boy). The number of genetic polymorphisms were coded as 0 (polymorphisms absent in both alleles), 1 (one of the alleles has polymorphism) and 2 (both alleles are represented by polymorphisms). Dependent variables: disability for neurological indicators—0 (no disability), 1 (disability). "Disability" was assessed after at last 2 years after PedAIS and interpreted as the state that is required constant external support and replacement of irreversibly lost functions of the nervous system. The method of logistic regression was used for constructing the predictive formula.

Results

Predictive formula was developed: Z = 2.08 + 0.517*(Sex01)–27.4*(F5:1691G>A)–0.426*(ITGA2:807C>T)–0.391*(PAI-1:-675 5G>4G)–0.883*(MTRR:66A>G) + 0.476*(MTHFR:1298A>C)–0.742*(AGT:521C>T)—0.996*(AGTR1:1166A>C). If the summation obtained a positive (greater than zero) result, disability outcome was predicted, negative (less than zero)–absence of disability. Sensitivity and specificity for the training set rules amounted to 0.71 and 0.62, accordingly.

Conclusions

Genes' polymorphisms that can affect the coagulation system, vascular walls condition and homocysteine level showed their informative importance for predicting adverse outcome after PedAIS. There are no certain genes which inevitably lead to disability after PedAIS, but we consider that evaluating the condition of procoagulant and prothrombotic spectrum genes seems to become such genes-candidates combinations to forecast.

1.11. Hemostasis and Inflammation

1.11.1. C0073 the Role of Monocyte Chemoattractant Proteins in the Pathogenesis of Immune Thrombocytopenia

Hasan Goze, Elif Umit, Ahmet Muzaffer Dem

Trakya University Faculty of Medicine Department of Hematology, Turkey

Background

Immune thrombocytopenia (ITP) is the most common acquired autoimmune hemorrhagic disorder with antibody-mediated thrombocyte destruction. The inflammatory process has been on

spotlight to clear the pathogenesis as well as therapeutic pathyway. Chemokines are polypeptide molecules that control leukocyte motility and trafficking through the control of leukocyte functions and transmembrane receptor activations.

Methods

84 patients with ITP and 84 healthy subjects with similar age and gender were enrolled in the study. Exclusion criteria were the presence of sequelae of ITP, the presence of chronic ITP, and the presence of high levels of ESR and CRP at the time of admission. From the blood samples taken from patients and controls, the target chemokines CCL1, CCL3, CCL4 and CCL16 levels were assessed by ELISA method.

Results

The mean age of the patients was 47.31 (22–87) and the male/female ratio was 0.31 (20/64). While 61 patients had major or minor hemorrhage, 23 patients were asymptomatic. Life-threatening severe bleeding was observed in only 6 patients. Mean platelet count in the patient group was 19.310/mm^3 (1000–92.000) and mean MPV was 10.75 fL (6.7–36.0).

In the patient group, mean CCL1 level was 388.21 ng/mL, CCL3 level 830.2289, CCL4 level 48.0619 and CCL16 level 536.9624 ng/mL, while in the control group, CCL1 level was 332.21 ng/mL, CCL3 54 ng/mL, CCL4 level 35.46 ng/mL and CCL16 level 482.02 ng/mL.

As the parameters were nonequally distributed, ANOVA anaylsis was performed and CCL4 levels were significantly higher in the patient group with a high corelation coefficient (−0.23) (p = 0.000).

	Mean (ng/mL)	
Patient (n = 84)	CCL1	388.21
	CCL3	830.22
	CCL4	48.06
	CCL16	536.96
Control (n = 84)	CCL1	332.21
	CCL3	755.54
	CCL4	35.46
	CCL16	482.02

Conclusions

Monocyte chemoattractant protein, CCL4 was significantly high in patients with ITP. The importance of targeting chemoattractants in B cell neoplasms may lead the concept of adapting these immune regulatory drugs such as bruton kinase inhibitors and phosphoinositol 3 inhibitors into the management of ITP. Our findings need to be supported with larger studies.

1.11.2. C0236 System of Hemostasis in Elderly Patients WITH Chronic Obstructive Pulmonary Disease, Permanently Living in Residential Social Service Institution

Sagynali Mamatov Murzaevit [1], Mira Arstanbekova [2], Asel Sadykbek kyzy [2], Evgeny Roitman [2], Bazira Kanat Kyzy [2], Tolkynbek Baimyratov [2]

[1] *Kyrgyz State Medical Academy Named after I. K. Akhunbaev, Bishkek, Kyrgyzstan*

[2] *Federal Scientific and Clinical Center for Pediatric Hematology, Oncology and Immunology Named after D. Rogachev, Ministry of Health of the Russian, Federation, Russia*

Background

MamatovS.M. [1], ArstanbekovaM.A. [1], RoitmanE.V. [2], BaimuratovT.T. [1]

(Kyrgyz State Medical Academy named after I.K. Akhunbaev, Department of Hospital Therapy, and profpathology with hematology teaching course[1], Kyrgyzstan, Bishkek)
(Federal Scientific and Clinical Center for Pediatric Hematology, Oncology and Immunology named after D. Rogachev, Ministry of Health of the Russian Federation [2] Russia)

Methods

In conditions of residential social service institution, the assessment of main indicators of the hemostatic system were evaluated in 25 elderly patients with COPD and 26 practically healthy elderly persons (control). The system of hemostasis assessed by the conventional method according to the coagulogram: autocoagulation test, prothrombin complex, thrombin time, fibrinogen, fibrinogen degradation products, ethanol test, fibrinase, euglobulin fibrinolysis. The research carried out during the period of exacerbation of COPD, which had confirmed by the data of a physical and traditional laboratory and instrumental examination.

Results

In the blood of elderly practically healthy people, the fibrinogen concentration was in average 3.22 ± 0.04 g/L, whereas in elderly people with COPD was found significant increase to 8.41 ± 0.12 g/L. It was also found that in elderly patients, in comparative with healthy persons ($p < 0.05$) a higher fibrinase concentration in the blood is significant (105.7 ± 0.17 s and 89.1 ± 0.13 s, respectively). Increased fibrinogenesis in COPD is due to activation of the contact factors of blood coagulation, which is confirmed by the shortening of thrombin time in elderly patients with COPD (up to 8.23 ± 0.03 s). The autocoagulation test in elderly people with COPD, as compared with healthy elderly persons, is also shortened, which indicates hypercoagulability. The fibrinolytic activity of the euglobulin fraction of blood was significantly inhibited, which averaged 331 ± 3.36 min. against 294 ± 2.91 min in healthy elderly persons.

Conclusions

1. The results obtained allow us to assume that the depression of euglobulin fibrinolysis unambiguously increases with age.
2. In elderly people, the period of exacerbation of COPD occurs with high coagulant and low fibrinolytic activity.
3. This research revealed some features in alteration of the hemostasis system in elderly patients with COPD, which can contribute to form a pneumosclerosis and chronic DIC-syndrome.

1.11.3. C0254 the Levels of Circulating Microparticles Are Inversely Correlated with Biomarkers of Thrombosis in Patients with Acute Coronary Syndromes

Zoi Pallantza [1], Efthimia Zacharia [2], Nikolaos Papageorgiou [2], Evaggelia Andronopoulou [3], Olga Zoupouli [3], Denis Gubini [3], Maria Liossi [3], Katerina Tsiligianni [3], Georgia Papacharalampous [3], Georgios Mallios [3], Iosif Darouis [3], Maria Karagrigoriou [3], Panagiota Karampela [3], Sophia Papagianni [1], Dimitrios Tousoulis [2]

[1] *Hippokration General Hospital of Athens, Hematology Department Athens, Athens, Greece*
[2] *Department of Cardiology, University of Athens, Hippocratio Hospital, Athens, Greece*
[3] *Hematology Department, Hippocratio Hospital, Athens, Greece*

Background

A number of preclinical studies have shown that circulating microparticles (MPs) are implicated with an exacerbation of thrombogenesis and inflammation. However, their potential association with biomarkers of coagulation in patients with acute coronary syndromes (ACS) has not been elucidated yet.

Methods

112 patients with ACS were enrolled in the present study (44 ST, 35 NST, 33 UA). Blood samples were obtained from peripheral veins within 12–24 h from hospital admission. 16 patients with stable CAD and 17 healthy subjects served as controls. Circulating endothelial (CD144+)-EMPs, red blood cell- ($CD253^+$)-RMPs and platelet-derived (CD41+)-PMPs and their annexin-V binding capacity ($phosphatidylserine^+$-PS^+) were determined by flow cytometry. The levels of fibrinogen, d-dimers, aPTT and INR were assessed by appropriate methods.

Results

In patients with ST: A negative correlation was noted between the levels of fibrinogen and PS-PMPs ($p = 0.038$) and between the levels of D-dimers and total PS+MPs ($p = 0.035$). INR was also inversely correlated with the levels of total PS+MPs ($p = 0.12$) and PS+EMPs ($p = 0.031$). In patients with NST: Negative correlations were noted between the levels of fibrinogen and total PS+MPs ($p = 0.034$), EMPs ($p = 0.017$), RMPs ($p = 0.018$) and PMPs ($p = 0.017$) and their subtypes: PS+EMPs, PS-EMPs, PS+RMPs, PS-RMPs, PS+PMPs, PS-PMPs ($p < 0.036$ for all). In patients with UA: Negative correlations were noted between the levels of d-dimers and total EMPs ($p = 0.011$), PS-EMPs ($p = 0.007$), total RMPs ($p = 0.046$), PS-RMPs ($p = 0.048$), and PS-PMPs ($p = 0.044$).

Conclusions

We have shown that in patients with ACS, the levels of circulating MPs are inversely associated with the levels of biomarkers of thrombosis, such as fibrinogen and d-dimers. This could be either due to a sequestration of MPs in sites of atherothrombosis or due to an actual anticoagulant effect of the first. Further studies are warranted to determine the pathophysiological pathway of the noted associations.

1.11.4. C0299 the Microthrombosis and Hypercytokinemia Markers as the Component of Systemic Inflammatory Response in Acute Massive Hemorrhage Complicated Pregnancy and Childbirth

Anatoly Brazhnikov [1], Olga Lvova [2], Vladimir Rudnov [1], Eugene Gusev [3], Natalia Zotova [3]

[1] *Ural State Medical University, Yekaterinburg, Russia*
[2] *Ural Federal University, Laboratory of Brain and Neurocognitive Development, Yekaterinburg, Russia*
[3] *Ural Branch of the Russian Academy of Science, Russia*

Background

Blood loss during pregnancy and childbirth may result in the development of systemic inflammatory response (SIRS) with the mutual activation of its mediators and hemostasis factors. We studied the microthrombosis and hypercytokinemia markers of SIRS in acute stage of bleeding which complicated pregnancy and childbirth in women.

Methods

39 pregnant and women in labor (age 29.1 ± 1.1 y.o.) with blood loss more than 10% of blood volume were enrolled. We assessed the SIRS severity by the Reactivity Level (RL), which takes into account blood level of the interleukin 6, 8, 10, 10^{-12}/mL; Tumor necrosis factor α, 10^{-12}/mL; C-reactive protein, mg/dL (Institute of Immunology and PhysiologyUral Branch Russian Academy of Science). If RL achieves 0–2 points–SIRS risk is doubtful, 3–5 points–SIRS risks is suspected to be high. Coagulopathy was evaluated according to the Clinical and Laboratory Criteria for Disseminated Intravascular (DIC scale, ISTH-2001).

Three groups were performed: "no shock group"—blood loss without clinical signs of hemorrhagic shock ($n = 13$, 26.8 ± 1.7 y.o.); "shock group"–bleeding accompanied with hemorrhagic shock symptoms ($n = 26$, 30.3 ± 1.3 y.o.); controls—women after uncomplicated delivery ($n = 36$, 29.3

± 1.3 y.o.). All blood samples for laboratory data was taken within 0–12 h after bleeding (or delivery in controls) and signing the informed consent forms.

Results

Such laboratory phenomena of SIRS as hypercytokinemia and microthrombosis have been found in both "shock" and "no shock" groups, regardless of the presence of clinical symptoms of shock. Intensity of SIRS by RL was found as 3–5 points in the majority members in "shock group" (76.9%, $n = 20$), while "no shock group" reached RL only under 2 points (84.6%, $n = 11$).

DIC value in "no shock group" members achieved 2.92 ± 1.04 vs. 5.04 ± 1.71 in "shock group" (U, $p < 0.05$) and 0.0 ± 0.00 in controls (U, $p < 0.05$).

Conclusions

Acute massive blood loss (more than 10% of blood volume) accompanied with complicated pregnancy and childbirth may trigger the microthrombosis and hypercytokinemia reactions cascades. The higher points according to DIC and LR scales which were presented in "shock group" might be associated with the most severity of SIRS and considered to be the important risk factor of life-threatening complications.

1.12. Heparins and Heparin Induced Thrombocytopenia

C0253 Heparins Significantly Affect Procoagulant and Proadhesive Properties of Acute Promyelocytic Leukemia (Apl) Cells

Alfonso Vignoli, Marina Marchetti, Anna Falanga

Hospital "Papa Giovanni XXIII", Department of Immunohematology and Transfusion Medicine & Thrombosis and Hemostasis Center, Bergamo, Italy

Background

Early deaths due to the severe thrombohemorrhagic coagulopathy remain an important cause of treatment failure in APL. Several leukemic cell-dependent mechanisms are involved in APL coagulopathy. Among these, leukemic cell interaction with EC promotes localized clotting activation and thrombus formation. Preventing APL cell-EC interactions may represent an approach for hampering excess clotting activation and microthrombi deposition. Experimental evidences suggest that heparins have the capability to affect tumor cell/EC interactions. Aims of this study were to: (1) evaluate the effects of the LMWH dalteparin and enoxaparin and unfractionated heparin on EC expression of procoagulant tissue factor (TF) and its inhibitor TFPI induced by APL NB4 cell line; and (2) determine whether the same heparins affect NB4 cell adhesion to EC.

Methods

Human microvascular EC (HMEC-1) were incubated with NB4 conditioned media (CM), or standard IL-1β, in the presence of increasing concentrations of heparins (0.01–1 IU/mL): then, EC TF procoagulant activity and antigen, and TFPI antigen were evaluated. For adhesion experiments, HMEC-1 were incubated with heparins in the presence or absence of IL-1ß and thereafter NB4 cell adhesion to EC monolayer was analyzed. The effect of heparins on EC surface adhesion molecules (ICAM-1, VCAM-1, E-selectin) expression was also tested.

Results

Both NB4-CM and IL-1β significantly increased TF expression by EC. Heparins dose-dependently inhibited the activated EC TF expression, while concomitantly increased the release of TFPI. The analysis of NB4-CM soluble mediators content showed significant amounts of VEGF and smaller quantities of other cytokines. All heparins significantly ($p < 0.05$) counteracted IL-1β-induced

NB4 cell adhesion to EC monolayers. In this system, dalteparin was the most effective, inhibiting by 80% NB4 cell adhesion. Moreover, heparins did not to significantly affect the IL-1ß-increased expression of EC adhesion molecules.

Conclusions

This study shows that APL cells can induce the EC prothrombotic phenotype, likely mediated by cytokine release. In the range of clinically relevant doses, heparins can counteract the leukemic-associated prothrombotic stimulus as well as leukemic blast cell adhesion to EC. Our findings demonstrate that heparins, particularly LMWH, can affect in multiple ways the mechanisms of APL-associated coagulopathy and might be good candidates to test for thromboprophylaxis in high-risk patients.

1.13. Platelets and Megakaryocytes

1.13.1. C0034 Regulatory Roles of Phospholipase D1 and 2 in Human and Mouse Platelets

Ray-Jade Chen [1], Kuan Hung Lin [2], Wan-Jung Lu [3]

[1] *Taipei Medical University Hospital, Taipei, Taiwan*
[2] *Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan*
[3] *Taipei Medical University Hospital, Department of Medical Research, Taipei, Taiwan*

Background

Phospholipase D (PLD) 1 and PLD2 are involved in many biological processes. In mice, PLD1 reportedly plays a more crucial role in regulating platelet activity; however, the effect of PLD on human platelet activation remains unclear. Thus, this study investigated whether PLD is involved in platelet activation and thrombus formation in humans.

Methods

In the present study, platelet aggregation, western blotting, flow cytometry, confocal microscopy, clot retraction, PFA-100, and mouse models of pulmonary thrombosis and middle cerebral artery occlusion/reperfusion were used to evaluate the role of PLD on platelet function.

Results

Our data revealed that pharmacological inhibition of PLD1 or PLD2 effectively inhibited human platelet aggregation, granule release, Akt and MAPK activation, platelet adhesion, spreading, and subsequent colt retraction and platelet plug formation. These findings indicate that both PLD1 and PLD2 are essential for human platelet activation. However, these results obtained for human platelets were different from those previously obtained for mouse platelets. To confirm these discrepancies, two in vivo studies were performed and revealed that only PLD1, but not PLD2, inhibition, alleviated ADP-induced acute pulmonary thrombosis and middle cerebral artery occlusion/reperfusion-induced brain injury in mice.

Conclusions

This study for the first time demonstrated that both PLD1 and PLD2 are involved in platelet activation and thrombus formation in humans and that PLD plays differential roles on platelet function in humans and mice. In addition, our findings indicate that targeting PLD may provide a safe and alternative therapeutic approach to preventing thromboembolic disorders.

1.13.2. C0045 Embelin Attenuates Collagen-Induced Platelet Activation through the Inhibition of Akt and Mapk Pathways

Li-Ting Huang [1], Wan-Jung Lu [2], Kuan-Hung Lin [3]

[1] *Taipei Medical University, Taipei, Taiwan*
[2] *Taipei Medical University Hospital, Taipei, Taiwan*
[3] *Shin-Kong Wu Ho-Su Memorial Hospital, Central Laboratory, Taipei, Taiwan*

Background

Platelet activation plays an important role in cardiovascular diseases, such as stroke and atherosclerosis. Embelin, the main active component of *Embelia ribes*, possess multiple biological activities, including antitumor, anti-oxidation and anti-inflammation, and has been used in the Indian system of medicine. However, whether the role of embelin on platelet activation remains unclear. Thus, this study will aim to investigate the detailed mechanism of embelin in platelet activation and thrombus formation.

Methods

To investigate the anti-platelet effects of embelin, the following experiments were performed. (1) Platelet aggregation were detected by aggregometer; (2) ATP release and (3) calcium mobilization were observed by microplate reader; (4) P-selectin secretion and (5) glycoprotein IIbIIIa (GPIIbIIIa) activation were determined by flow cytometry, and (6) protein phosphorylation were analyzed by western blotting.

Results

Our results revealed that embelin (75–100 μM) inhibited platelet aggregation induced by collagen (1 μg/mL). Embelin inhibited collagen-induced ATP release and P-selectin secretion, indicating that embelin could inhibit platelet granule release. Embelin also reduced calcium mobilization and GPIIbIIIa activation. In addition, embelin could inhibit the phosphorylation of Akt, Erk, p38, and JNK. These findings indicate that embelin can effectively inhibit collagen-induced platelet activation.

Conclusions

We for the first time demonstrated that embelin can attenuate collagen-induced platelet activation, in part, through the inhibition of Akt and MAPK pathway. In addition, our findings also indicate that embelin may offer a therapeutic potential for treating cardiovascular diseases.

1.13.3. C0159 the Role of Reactive Species Production in Assessment of Thrombotic Risk in Chronic Myeloproliferative Neoplasms Patients

Viola Maria Popov [1], Mihaela Georgeta Moisescu [2], Tudor Savopol [2], Christien Matei Oktaviani [2], Bogdan Matei [2], Meilin Omer [3], Felicia Lidia Mihai [3], Oana Patrinoiu [3], Mihaela Andreescu [3], Ion Dumitru [4], Ana Maria Vladareanu [4], Horia Bumbea [4]

[1] *Colentina Clinical Hospital, Hematology Bucharest, Bucharest, Romania*
[2] *Biophysics and Biotechnology Department UMF Carol Davila, Bucharest, Romania*
[3] *Hematology Colentina Clinical Hospital, Bucharest, Romania*
[4] *University Emergency Hospital Haematology Department, Bucharest, Romania*

Background

Patients with myeloproliferative neoplasm (MPNs) could present thrombotic complications. The presence of JAK mutation increases the risk of thrombosis. Patients with MPN and high allele burden expression (>75%) have a higher risk of thrombosis. Receptors that define the status of activated platelets, P selectin, thrombospondin and CD36 are better expressed in MPN patients with thrombotic complications. Numerous studies have shown a high oxidative status in patients with chronic myeloproliferative neoplasms, a situation that correlates with a higher thrombotic risk.

Methods

This retrospective study included 52 patients with MPNs as well as 9 controls. The group of MPNs patients included 8 patients with chronic myeloid leukaemia (CML) essential thrombocythemia (ET) and polycythemia vera (PV) 31 patients; idiopathic myelofibrosis (MF) 13 patients. We examined the flow cytometry markers of platelet adhesion (CD42a, CD42b), aggregation (CD41, CD61) and CD36.Production of reactive species (ROS) was examined using fluorescence method with DCFDA and was assessed by aria under curve (AUC) in serial measurements during 900 s.

Results

The AUC was significantly higher in MPN patients–MF group: median value 10,725,857,276.25 (min 59,387,560, max 12,872,545,955) compared with PV and ET: median value 1,001,564,080 (min 804,299,757, max 12,872,545,955), CML: median value 474,787,770 (min 76,875,400, max 11,144,380,150) or control group: median value 447,617,785 (min 43,330,060, max 9,029,350,460); p = 0.02. Patients with JAK 2 mutation have a higher level of ROS production (median value 636,616,565) than patients without any mutations JAK2 or CALR (median value 310,035,057), p = 0.04. The high allele burden expression was associated with high ROS production but without statistical significance. The expression of CD41 receptor was lower in MPNs group (min 28.58, max 100.75) compared with controls group (min 43.58, max 89.46), p = 0.02. We did not obtain statistical difference between expressions of CD61, CD42a, CD42b and CD 36 and no correlations with ROS production, although MPN patients have higher level of CD 36 expression without statistical significance.

Conclusions

Production of ROS was higher in MF patients and those patients who have JAK2 mutation present. The expression of CD 36 is higher in MPNs patients but was not correlated with ROS production. The direct association of ROS production with thrombotic risk was not identified but has to be verified in higher group of patients.

1.13.4. C0174 Alteration of Platelets in Healthy People in the Process of Short-Term High-Altitude Adaptation

Sagynali Mamatov Murzaevit [1], Aida Nartaeva [2], Evgene Roitman [3], Alik Makhmanurov [2]

[1] *Bishkek, Kyrgyzstan*
[2] *Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan*
[3] *Federal Scientific and Clinical Center for Pediatric Hematology, Oncology and Immunology Named after D. Rogachev, Russia*

Background

Mamatov S. M. [1], Nartaeva A. K. [1], Roitman E. V. [2], Makhmanurov A. A. [1]
(Kyrgyz State Medical Academy named after I.K. Akhunbaev, Kyrgyzstan [1])
(Federal Scientific and Clinical Center for Pediatric Hematology, Oncology and Immunology named after D. Rogachev, Ministry of Health of the Russian Federation [2])

Methods

Material and methods of research. The study included 25 volunteers—students of the Kyrgyz State Medical Academy after the name of I.K. Akhunbaev during the passage of internship in high-mountainous base, the Too-Ashu Pass, 3200 meters above sea level. All examined were male at the age of 20–22 years and practically healthy. The study was carried out on an automated hematological analyzer UniCel® DxH™ 800 ("Beckman Coulter"). Terms of research: background—foothills Bishkek city, 3rd, 20th and 40th day of adaptation on the Too-Ashu pass.

Results

Results of the study. In the foothills, the number of platelets ranged from 190.2 till 480.5 × 10^9/L, in average 252.4 ± 5.31 × 10^9/L, which corresponds to the normal indices of the foothill areas inhabitants. A study of the morphological composition showed that young forms (with a diameter of 5–5.5 μm) amounted to 3.1 ± 0.02%, mature (1.5–3 μm)—86.6 ± 0.02%, old (0.5–15 μm)—4.4 ± 0.07%, macroforms (less than 5 μm)—3.6 ± 0.08% and irritation forms—2.3 ± 0.01%. During the first days of stay in the mountains, the platelets count increases significantly (291.1 ± 9.02 × 10^9/L), and a significant increase was obtained on the 20th day of stay in the highlands, when their number was 359.1 ± 11.72 × 10^9/L. By the end of staying in the mountains, the number of platelets decreased relatively (312.4 ± 7.22 × 10^9/L), but the same time remains exceeded background data. The study of the morphological composition of platelets showed that in the first days and on the 20th day of staying in the mountains, there is a qualitative rejuvenation of platelets. Thus, in these terms of study, the number of young platelets (6.2 ± 0.05%) and irritation forms (7.1 ± 0.04%) increases reliably.

Conclusions

1. Short-term high-mountain adaptation of healthy people causes an increase the number of platelets, the number of which increases reliably by the 20th day of stay in the mountains.

2. Increasing the number of platelets occurs due to realization of the reserves of thrombocytopoiesis, which is confirmed by increase of number of immature platelets.

1.13.5. C0175 the Effectiveness of Using High-Altitude Climatic Therapy in Children with Idiopathic Thrombocytopenic Purpura

Sagynali Mamatov Murzaevit [1], Aizhamal Esengeldi k. [2], Evgeny Roitman [3], Alik Makhmanurov [4], Aida Nartaeva [4]

[1] *Bishkek, Kyrgyzstan*
[2] *Kyrgyz State Medical Academy, Kyrgyzstan*
[3] *Federal Scientific and Clinical Center for Pediatric Hematology, Oncology and Immunology Named after D. Rogachev, Ministry of Health of the Russian Federation, Russia*
[4] *Kyrgyz State Medical Academy, Kyrgyzstan*

Background

Esengeldi k. Aizhamal [1], Mamatov S. M. [1], Roitman E. V. [2], Mahmanurov A. A. [1], Nartaeva A. K. [1]
(Kyrgyz State Medical Academy named after I.K. Akhunbaev, Kyrgyz Republic [1])
(Federal Scientific and Clinical Center for Pediatric Hematology, Oncology and Immunology named after D. Rogachev, Ministry of Health of the Russian Federation [2])

Methods

The aim of our study was to study the effectiveness of high-altitude climatic therapy in children with idiopathic thrombocytopenic purpura.

Material and methods of investigation. We analyzed the clinical and laboratory studies of hemopoiesis in 34 patients with ITP who underwent mountain climatic treatment at the Too-Ashu pass (3200 m above sea level), among which 18 (53%) were girls and 16 (47%) were boys, 5 to 16 years. The majority (65%) were children aged 10 to 16 years. Duration of treatment in a high-mountainous base is 40 days.

Results

Results of the study. In total 34 children who underwent high-altitude climatic therapy, 3 had complete, 18 had partial remission, and 8–temporarily improved clinical and hematological indicators. There was no positive response to treatment of 4, but these children took prednisolone for a long time (from 4 to 6 years). The positive effect of high-altitude climatic therapy was more effective

in children without previous splenectomy, regardless of whether the operation was accompanied by a temporary improvement in clinical and hematological parameters or did not have a positive effect, as well as in children with less prescription of the disease.

Conclusions

1. High-mountain climate therapy causes a significant increase of the number of platelets in most children with idiopathic thrombocytopenic purpura.
2. Further research is necessary for full assessment of the effectiveness of high-mountain climate therapy and its use in the future in children with idiopathic thrombocytopenic purpura.

1.13.6. C0303 Levels of Thrombopoietin in the Acute Phase of Myocardial Infarction: Do They Modify the Effectiveness of Antiplatelet Agents on Platelet Reactivity?

María Teresa Santos, Ana Latorre, Juana Vallés, Isabel Madrid, Maria Paz Fuset, María Ferré, María Ángeles Dasí, Antonio Moscardó

Health Research Institute La Fe, Valencia, Spain

Background

Thrombopoietin (TPO) is known to regulate platelet production, but it can also act as a "primer" of platelet reactivity induced by other agonists. Scarce data are available concerning the effects of TPO on platelet function in patients with acute ST-segment elevation myocardial infarction (STEMI) treated with aspirin and clopidogrel.

Aims: To study TPO levels and platelet function in STEMI patients treated with aspirin plus clopidogrel.

Methods

We studied 129 STEMI patients (mean age 63.7 ± SEM 1.2 years; 103 men). All were treated with aspirin and clopidogrel from the onset of the acute event. Platelet function was evaluated within 48 h of the onset. The tests included (1) collagen-induceded TXA2 synthesis and recruitment (proaggregatory activity of the cell-free releaseates) in whole blood; light transmission aggregometry induced by arachidonic-acid (AA, 1 mM), collagen (1 μg/mL), ADP (20 μM), U46619 1 μM and TRAP 15 μM; VASP phosphorylation by flow cytometry and the occlusion times in the PFA-100 system with collagen/epinephrine and collagen/ADP cartridges. TPO was evaluated by commercial ELISA**.**

Results

We distributed the patients into TPO quartiles (Q) and considered low TPO the 1st and 2nd Q (range [16.02–64.09] $n = 62$) and high TPO the 3rd and 4th Q (range [65.6–267.85] ng/mL $n = 67$). The patients with high vs. low TPO levels had a significant increase in aspirin-sensitive platelet function markers: AA-induced aggregation (%) [16.95 ± 2.82 vs. 28.93 ± 3.60, $p = 0.011$], collagen-induced TXA2 synthesis (ng/mL) [11.31 ± 3.49 vs. 27.72 ± 4.49, $p = 0.006$], recruitment (mm) [32.31 ± 3.70 vs. 51.61 ± 4.77, $p = 0.002$] and collagen-induced aggregation (%) [27.45 ± 2.84 vs. 37.28 ± 37.28 ± 0.022]. In contrast, markers of the clopidogrel effect such as ADP-induced aggregation or VASP phosphorylation were not influenced by the TPO levels. No differences were found related to TPO levels in U46619- or TRAP-induced platelet aggregation or PFA-100. Interestingly, in patients with high TPO and high platelet number a 5-fold increase of residual TXA2 synthesis was observed.

Conclusions

Patients with elevated TPO had a markedly reduced effect of aspirin, while no influence of TPO on the clopidogrel effect was detected. Data suggest that elevated TPO is a determinant of aspirin resistance in STEMI patients.

[1]. Santos MT et al. J Thromb Haemost 2008;6: 615–61. FIS13/00016. ACIF/2016/465. INVICTUS+ (RD16/0019/0008).

1.13.7. C0317 Community-Adcquired Pneumonia (Cap) and Platelet Function. Involvement in Cardiovascular Complications Associated with Cap

Ana Latorre, María Teresa Santos, Juana Vallés, Rosario Menéndez, Raúl Mèndez, Antonio Moscardó

Health Research Institute La Fe Spain, Valencia, Spain

Background

Community-acquired pneumonia (CAP) is the world's leading cause of death related to infection. An increase in cardiovascular events and death, even in the long term (>1 year after CAP), has been recently described (1.2). The link between these processes could be inflammation induced by CAP which could lead to platelet activation and extracellular neutrophil trap formation (NETs), thus increasing cardiovascular risk. However, this connection has been poorly studied. AIM: to sequentially analyze (day 1, 5 and 30 after hospital admission) in patients with CAP, markers of platelet activation and NETs formation, as well as their ability to predict the occurrence of cardiovascular events in the short and long term.

Methods

58 patients with CAP were included in the prospective study. P-selectin exposure, TLR4 expression, and platelet-leukocyte and platelet-monocyte heterotypic aggregates were evaluated by flow cytometry. In a retrospective study, 80 patients (40 with cardiovascular complications at one year and 40 without complications) were included to measure circulating markers of NETs: free DNA and citrullinated histone 3 (citH3) in plasma (3). In the latter, patients with cardiovascular complication previous to CAP were excluded.

Results

Of the 58 patients included, 9 suffered cardiovascular complications during the first 30 days. Patients with these complications showed significantly higher values of CD61, TLR4 and CD62 at admission. CD62 and CD61 remained high at day 5, while TLR4 was reduced to the level of subjects without complications. Unexpectedly, the platelet-leukocyte and platelet-monocyte aggregates were reduced in patients with complications. In the retrospective series of 80 patients we found that DNA and citH3 were significantly elevated at admission in those patients who had suffered cardiovascular complications during the year following CAP.

Conclusions

Our results indicate that in CAP there is an increase in markers of platelet activation and NETs, which is associated with an increased risk of cardiovascular complications. These results suggest the importance of implementing antiplatelet therapy in patients with CAP, especially in those with elevated platelet activation markers or NETs.

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1.13.8. C0336 Thrombocytosis in Pelvic Cancer Patients: From Laboratory Indicators to Clinical Practice

Marina Poluektova [1], Eugene Roitman [2], Svetlana Glebova [1], Ekaterina Bykova [3], Lyudmila Krikunova [1], Dmitry Erygin [1], Leonid Zhavoronkov [1]

[1] *A.F. Tsyb Medical Radiological Research Center ñ Branch of the Federal State Budget Institution ìNational Medical Research Center of Radiologyî of the Health Ministry of the Russian Federation, Laboratory Diagnostic Department Obninsk, Obninsk, Russia,*
[2] *Pirogov Russian National Research Medical University, Moscow, Russia*
[3] *Institute of Atomic Energy ñ Branch of the Federal State Autonomous Educational Institution of Higher Professional Education ìNational Nuclear Research University MEPhI", Medical Faculty, Obninsk, Russia*

Background

According to modern scientific achievements in molecular biology and immunology, platelets play an important role not only in the development of thrombotic complications (in cancer patients 3–5%), but also contribute to disease progression, recurrence and metastatic tumor because of special relationships with tumor cells. The purpose of our study was to evaluate the diagnostic and prognostic significance of thrombocytosis in patients with pelvic cancer characterized as *highly aggressive*.

Methods

Hematologic and hemostasiological laboratory indicators of 200 pelvic cancer patients, who received combination therapy between 2015 and 2017, were retrospectively analyzed. Of these patients, 100 had rectal cancer (50 men and 50 women), 50 had uterine cancer and 50 had cervical cancer (CC). Depending on platelet count, the patients were divided into three risk groups: low, moderate and high. In the high-risk group, platelet count exceeded 400 × 10^9/L.

Results

In the rectal cancer *group (RCG),* 42% of female *patients* and 40% of male *patients* were at*high risk*. *In the CC group, high-risk* factors were seen in 50% and in the uterine cancer group–only in 8% of patients. Therewas a *correlation*between thrombocytosis and clinical stages III–IV of disease and age over 50 years. Histological type of tumors in high-risk patients corresponded to adenocarcinoma of medium and high degree of malignancy. Non-*keratinizing squamous cell carcinoma appeared to prevail* in CC patients. The greatest number of patients with *metasta*ses (67%) was noted in the *high-risk RCG* (women). Disease progression (metastasis, local spread and recurrence) was observed in almost all patients with CC in the high-risk group. These patients had the highest platelet count (PC): median 560 × 10^9/L (400 × 10^9/L, 1005 × 10^9/L). *There* was a statistically *significant difference* in *PC*between the groups ($p < 0.01$). In patients with pretreatment hemorrhagic complications (bleeding from rectal, uterine and cervical tumors), thrombocytosis occurred very rarely and as a rule, a more favourable disease course was observed after surgical tumor removal.

Conclusions

Thus, the presence of thrombocytosis in pelvic cancer patients can serve as an objective criterion for the risk of a complicated tumor process and should be taken into account when choosing a program to treat and prevent complications caused by paraneoplastic thrombocytosis and increasing the adhesive properties of platelets in oncology.

1.14. Pregnancy and Thrombosis

1.14.1. C0053 Investigation of the Relationship between Platelet Functions and Adipocytokines and Antiangiogenic Factors in Preeclamptic Pregnancies

Turgut Ulutin [1], Gulsel Ayaz [1], Cigdem Bayram Gurel [1], Hakan Ekmekci [2], Zeynep Gungor [2], Abdullah Tuten [3], Sait Toprak [2], Oktay Caliskan [2], Huseyin Sonmez [2], Riza Madazli [3], Orkide Donma [2], Mine Kucur [2], Ozlem Ekmekci [2]

[1] *Department of Medical Biology, Cerrapasa Medical Faculty, Istanbul University, Istanbul, Turkey*

[2] *Department of Biochemistry, Cerrapasa Medical Faculty, Istanbul University, Istanbul, Turkey*
[3] *Department of Gynecology and Obstetrics, Cerrapasa Medical Faculty, Istanbul University, Istanbul, Turkey*

Background

Preeclampsia is a pregnancy-specific syndrome characterized by clinically elevated blood pressure, edema and proteinuria and can cause fetal morbidity and mortality. The causes of preeclamptic pregnancy syndrome are multifactorial and the etiology is not fully understood. In our study, we aimed to investigate the relationship between adipocytokines and antiangiogenic factors and platelet function in preeclamptic pregnancies.

Methods

This case-control study consisted of 52 preeclamptic pregnancies and 27 healthy pregnant women with uncomplicated pregnancies in a total of 79 individuals. The levels of ghrelin, leptin, adiponectin, TGFβ1, vWF, sFlt-1, VEGF, endoglin, PIGF, HIF-1 and P-selectin in serum and plasma samples of preeclamptic and healthy pregnancies were determined by ELISA and ADP and collagen.

Results

The results of our study suggest that increased levels of vWF and endoglin may be a consequence of endothelial dysfunction. High leptin levels in preeclamptic pregnancies did not correlate significantly with platelet aggregation. Our findings also show that impaired angiogenesis for preeclampsia may lead to endothelial dysfunction, but not to platelet aggregation. These results need to be confirmed by a larger number of case-control studies.

Conclusions

We observed that endoglin, leptin and vWF levels increased significantly in preeclamptic pregnancies compared to healthy pregnancies ($p < 0.001$). However, we found that PIGF, P-selectin ($p < 0.001$) and collagen ($p < 0.05$) levels decreased significantly in preeclamptic pregnancies when compared to healthy pregnancies. We also found that endoglin levels in preeclampsia were associated with sFlt-1 (anti-angiogenic protein) levels.

1.14.2. C0149 Direct Oral Anticoagulants and Pregnancy: First Cases

Olga Dzhenina [1], Vadim Bogachev [2]

[1] *First Phlebological Centre, Moscow, Russia*
[2] *Russian National Research Medical University Named after N.I. Pirogov, Moscow, Russia*

Background

Direct oral anticoagulants (DOAC) have been widely used for a treatment of venous thrombosis patients including of reproductive aged women. For DOAC in the present time doesn't detected an absolutesafety for using in a period of gestation.

Methods

In 2017 we registered three cases of taking DOAC during pregnancy.

Results

Patient N. 28 y.o. Ds: Iliofemoral thrombosis. In the hospital a patient was taken Heparin, after her treatment had been replaced on Dabigatran Etexilate. Appraisal of the reproductive anamnesis, and an examination of a gynecologist wasn't performed. On discharge the patient told that she didn't have menstruation an expected period within 12–14 days and 4–5 weeks pregnancy was confirmed

by ultrasound diagnostics. This pregnancy was saved and DOAC had been replaced on Nadroparin Calcium. Series of ultrasound diagnostics didn't confirmed fetal abnormalities. An infant was born without complication.

Patient B. 31 y.o. Ds: popliteal vein thrombosis. Pregnancy and pathological abnormalities of pelvic organs were not revealed. However, a reproductive plans of the patient wasn't assessed and woman wasn't warned about contraception in a period of taking DOAC. After three months of DVT the patient was diagnosed 3–4 weeks pregnancy. The patient refused to interrupt that pregnancy. DOAC was replaced on Enoxaparin Sodium. Series of ultrasound diagnostics didn't confirmed a pathology of fetus. An infant was born without complication.

Patient M. 34 y.o. Ds: Iliofemoral thrombosis, 11–12 weeks pregnancy. In the hospital a patient was taking a treatment injections of Heparin. Despite of normal development pregnancy after discharge the patient received a recommendation to take Rivaroxaban. In a period of 14 weeks pregnancy, the women had misbirth. Fetal hemorrhagic syndrome and fetal abnormalities had been not seen during of autopsy. Obstetric causes of abortion isn't determined.

Conclusions

Currently there are not any data excluding or confirming feto- and embryotoxicity, and teratogenicity of DOAC to human embryo. The application of these anticoagulants in women of reproductive age should exclude pregnancy and to inform them about contraception. Planning extensive clinical research for safe taking DOAC among pregnant women with DVT is difficult and it is expediently to form common base of similar clinical cases for further integrative assessment of the potential impact of DOAC for a development of embryo.

1.14.3. C0354 Effect of Adjusted Doses of Heparin and Switch Therapy on Pregnancy Outcome in Primary Antiphospholipid Syndrome. A Prospective Cohort Management Study

Ariela Hoxha [1], Maria Favaro [1], Antonia Calligaro [1], Teresa Del Ross [1], Alessandra Teresa Ruffatti [2], Chiara Infantolino [2], Marta Tonello [1], Elena Mattia [1], Amelia Ruffatti [1]

[1] *Rheumatology Unit, Department of Medicine-DIMED, University of Padua, Padova, Italy*
[2] *Obstetrics and Gynecology Unit, University-Hospital of Padua, Padova, Italy*

Background

Most investigators currently advocate treating otherwise healthy pregnant patients affected with obstetric APS with prophylactic heparin plus low dose aspirin (LDA). Whereas, women with a history of thrombosis are usually treated with therapeutic heparin doses and LDA. Providing that appropriate treatment is prescribed, 70–80% of APS women now concludes in birth births.

We design this prospective cohort study to evaluate the efficacy and safety of different treatment strategy in pregnant APS patients

Methods

One hundred twenty-seven consecutive pregnancies occurring between 1999–2016 in 96 APS patients, median age 36 years (range 25–47) were followed-up. Eighty-seven (68.5%) were treated with prophylactic low molecular weight heparin (LMWH)+LDA [group I], 40 (31.5%) with therapeutic LMWH+LDA (group II). Adjusted LMWH doses, increasing through pregnancies following the fetal/maternal body weight gain, were used. Primary outcome was considered live birth; secondary outcomes were maternal, fetal and/or neonatal complications.

Results

There was no significant difference in live birth rate between group I (95.4%) and group II (87.5%). There was a significant higher prevalence of maternal complications in group II than in group I ($p = 0.0005$), while no difference was found regarding fetal complications. The infants in group

II had a significantly lower gestational age and birth weight ($p = 0.0001$ and $p = 0.0005$, respectively), compared to group I. Moreover, they presented a significant higher rate of neonatal complications ($p = 0.01$) due to prematurity. A higher rate of pregnancy failure was experienced in group II ($p = 0.0003$). Pregnancy failure was significantly associated with the presence of thrombosis and pregnancy morbidity and with triple antiphospholipid antibodies (aPL) positivity ($p = 0.0005$ and $p < 0.0001$, respectively). Single aPL positivity and pregnancy morbidity alone were significantly associated with a favourable pregnancy outcome ($p = 0.003$ and $p = 0.0002$, respectively). Six patients in group II switched to higher risk protocol therapy (therapeutic LMWH+LDA+plasma exchange+intravenous immunoglobulins) and two patients in group I to group II; all concluded with live birth. No side effect was observed in any groups.

Conclusions

Overall, using adjusted LMWH doses and switch from one grade of therapy to the upper one, when a pregnancy complication came out, lead to a high rate of live birth in APS patients.

1.15. Surgery: Hemostasis and Thrombosis

1.15.1. C0055 Aortic No-Touch Off-Pump Coronary Artery Bypass Grafting Is Associated with Decreased Levels of the A-Subunit of Coagulation Factor XIII: Pilot Study

Ewa Zekanowska [1], Artur Slomka [1], Aleksandra Piekus [2], Mariusz Kowalewski [2], Wojciech Pawliszak [2], Lech Anisimowicz [2]

[1] *Department of Pathophysiology, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland*
[2] *Department of Cardiac Surgery, Dr Antoni Jurasz Memorial University Hospital in Bydgoszcz, Bydgoszcz, Poland*

Background

Factor XIII-A is a transglutaminase that stabilizes the fibrin clot. However, the role of FXIII-A in patients undergoing off-pump coronary artery bypass (OPCAB) surgery is still unclear. The objective of this study was to determine whether the type of surgical technique (touch vs. no-touch OPCAB) has an influence on FXIII-A levels.

Methods

We included 30 male patients (mean age, 62 ± 7 years) scheduled for elective first-time OPCAB surgery. Subjects were divided into two groups, touch ($n = 18$) vs. no-touch ($n = 12$), based on surgical procedure. Plasma levels of FXIII-A were measured before surgery and one week after surgery using enzyme-linked immunosorbent assay.

Results

Patients from both groups were similar in term of age, BMI, LVEF, blood pressure, renal function, CBC, comorbidities, pre- and postoperative drug use, and postprocedural hospital stay. Firstly, there were no differences in levels of FXIII-A before surgery and one week after surgery between two groups ($p > 0.05$). More interestingly, aortic no-touch technique was associated with significantly lower levels of FXIII-A one week after surgery compared to the levels before surgery ($p = 0.008$). This change was not observed in patients from the touch group ($p > 0.05$). The results are summarized in Table 1.

Table 1. Plasma FXIII-A levels (%) in OPCAB patients stratified according to type of surgical procedure (values are median and interquartile range).

Touch (*n* = 18)		**No-Touch (*n* = 12)**	
Before surgery	One week after surgery	Before surgery	One week after surgery
97.14 (69.83–108.56)	82.21 (66.15–105.79)	106.89 (82.37–114.87)	75.84 (66.89–99.49)

Conclusions

The data underline that no-touch OPCAB surgery results in reduced FXIII-A levels. Future studies are needed to verify our observations.

1.15.2. C0087 Hydrodynamic Research of the Topalov Torsion Method for Reconstructive Surgery of Small Traumatic Arterial Defects

Kalina Casadiego [1], Iovtcho Boianov Topalov [2]

[1] *Ullern High School-Oslo, Oslo, Norway*
[2] *University Multi-profile Hospital for Active Treatment, Heart and Brain, Pleven, Bulgaria*

Background

The author conducts hydrodynamic studies with synthetic vascular prostheses (silicone tubes) to corroborate the Topalov method for reconstructive surgery of small traumatic arterial defects with 90° torsion of two arterial ends cut.

In order to verify the effectiveness of the operating method the hydrodynamic studies were conducted using an educational simulator for vascular sutures of Ethicon and with the help of silicone tubes, connected to the simulator, experimental analogs of damaged arteries were formed.

Methods

Two types of silicon tube analogs were made. The first type of oblique, 45° cut through tubes that were torsioned 90° in the opposite direction. The two torsioned ends of the tubes were sewn together with a continuous vascular suture with a 4/0 traumatic needle. The second type is a silicon tube cut crosswise, stitched end to end with two-end vascular suture (non-torsioned).

Two prepared solutions were passed through the torsioned and non-torsioned silicone tubes: Solution No. 1—Physiological serum and Solution No. 2—Cow milk. The temperature of the solutions during the experiment was 20 °C and the flow pressure was 150 mmHg. Then, with the help of a chronometer, the flow time of 250 mL of each solution through the prepared silicone tubes were determined.

Results

The measurements show that the fluency of the solutions through the torsioned silicone tube is similar to that of the non-torsioned tube with a minimum time difference of 9.50 s for solution No. 1 and 11.0 s for solution No. 2.

Conclusions

The hydrodynamic studies demonstrated the efficacy of the investigated method of reconstructive arterial surgery with 90° torsion of two arterial ends cut.

1.15.3. C0177 Congenital Thrombophilia Discourages the Success of Standard Vte Prevention in Wounded Soldiers

Konstantin Nikolaev [1], Sergey Kapustin [2], Eugene Roitman [3], Vladislav Zubritskij [4], Aleksej Koltovich [4], Ilja Zolobov [1]

[1] *Main Clinical Hospital of Russian National Guard, Military Medical Academy, Surgery, Balashicha, Russia*
[2] *Russian Scientific Research Institute of Hematology and Blood Transfusion of the Federal Medical and Biological Agency, St. Petersburg, Russia*
[3] *Pirogov Russian National Research Medical University, Moscow, Russia*
[4] *Main Clinical Hospital of the Russian Interior Ministry, Institute of Medical and Social Technology ÇMGUPPë, Moscow, Russia*

Background

Soldiers with heavy injuries are at high risk of VTE.

Aim: To evaluate the importance of congenital thrombophilia for VTE prevention in combat casualties.

Methods

The results of treatment of 48 wounded with combat injuries (men; mean age 29.3 ± 5.5 years) & conducted a study of congenital thrombophilia were analyzed. Mine-blast injuries have 35 (72.9%), bullet–13 (27.1%) patients.

All the wounded were at high VTE risk that & had standard VTE prevention. There were no cases of bleeding caused by anticoagulation. Fifteen patients (31.3%) performs DVT (Group I), and no DVT was found in Group II (n = 33; 68.7%). Allelic polymorphism of genes: Factors I, II, V, XII, PAI-1, HPA-1, HPA-2, P2Y12, GpIa C677T (MTHFR) were tested. Statistical analysis was used with χ^2 test to assess the reliability between the values, Fisher's exact test (two-tailed) to assess the strength of the relationship factors studied–criteria ϕ (phi) and Cramer's V.

Results

All examined soldiers had not blood disorders, vascular disease and previous DVT episodes, a testing on thrombophilia was not conducted. Mutations were detected in 44 (91.7%) wounded. It was found that the thrombophilia of Prt G20210-A (MN), HPA-2 (AB) and Fibrinogen G/A-455 (MUT) was significantly more frequent in the wounded with DVT ($p < 0.05$). The strength of the relationship (ϕ) was $0.4 \leq 0.6$ for Prt G20210-A (MN), Fibrinogen G/A-455 (MUT) and $0.2 \leq 0.4$–for HPA-2 (AB).

Conclusions

Some hereditary thrombophilia are not DVT risk factor, and the effect of several genes polymorphism combinations on the DVT risk will be the subject in further research. Considering the high frequency of DVT in combat casualties with congenital thrombophilia, standard prevention seems insufficiently effective that requires to increase the anticoagulant doses together with the involving other prevention methods.

1.16. Disseminated Intravascular Coagulation

1.16.1. C0172 Sepsis and Disseminated Intravascular Coagulation (DIC) in Intensive Care Unit. A 4-Year Single-Centre Retrospective Cohort Study

Giacomo Zoppellaro [1], Eugenia Zoppellaro [1], Marco Meggiolaro [2], Gentian Denas [3], Seena Padayattil Jose [3], Vittorio Pengo [3]

[1] *Anestesia e Terapia Intensiva, Ospedale Caí Foncello, Treviso, Italy*
[2] *Anestesia e Rianimazione, Azienda Ospedaliera Padova, Padova, Italy*
[3] *Department of Cardiac, Thoracic and Vascular Sciences, Padova, Italy*

Background

Disseminated Intravascular Coagulation (DIC) is a severe, acquired syndrome that originates in the microvasculature and may complicate several diseases. The most common cause of DIC in ntensive care unit (ICU) is sepsis, however little is known about the prevalence of DIC in this setting, how is managed and its impact on prognosis.

Methods

This is a retrospective study on patients admitted for severe sepsis (i.e., infection associated with hypotension or organ dysfunction) or septic shock (i.e., infection associated with both conditions) at the Padua ICU from January 2013 to December 2016. Data regarding reason for admittance, Sequential Organ Failure Assessment (SOFA) score, past medical history, complications during hospital stay and death were recorded for each patient. For all enrolled patients, medical records were hand-searched for: laboratory tests of the first 48 h from admittance to compute ISTH score (Figure 1); blood transfusions; use of coagulation-related drugs (low-molecular weight heparins-LMWH- prophylaxis, protein C and anti-thrombin concentrates; pro-thrombin complex concentrates; fresh frozen plasma).

Results

148 cases of severe sepsis and septic shock were included in the analysis. Of these 39 (26%) had a diagnosis of DIC based on ISTH criteria. Age, gender and other comorbidities were not statistically different. DIC patients had a significantly higher in-hospital mortality (56% vs. 38%, $p < 0.05$) with a trend towards an increase in bleeding and thrombotic complications (20% vs. 14%, $p = 0.32$). At regression analysis, DIC was the only risk factor associated with in-hospital mortality (HR: 3.22, CI 95% 1.86–5.58, $p < 0.05$). LMWH prophylaxis was less used in CID patients (45% vs. 77%, $p < 0.01$), while anti-thrombin concentrate and fresh frozen plasma were more frequently administered (47% vs. 28%, $p < 0.05$ and 74% vs. 35%, $p < 0.01$, respectively). The use of LMWH prophylaxis was more frequent in discharged DIC patients than in DIC patients who died during hospital stay (65% vs. 29%, $p < 0.05$).

Conclusions

DIC is a difficult diagnosis that severely impact on patient prognosis and is more frequent than expected, being present in more than a quarter of patients admitted to ICU for severe sepsis or septic shock. The absence of LMWH prophylaxis appeared to negatively impact on DIC patient prognosis and therefore LMWH should be always administered when not contraindicated (i.e., severe anemia, active bleeding).

1.16.2. C0234 Do People in Bahia de Banderas, Nayarit, Mexico, Know What It Is and the Importance of Disseminated Intra Vascular Coagulation?

Yair Antonio Pliego Núñez

Centro Universitario Pliego de la Costa, Jalisco, Mexico

Background

Disseminated intravascular coagulation is a frequent pathology that occurs as a secondary phenomenon to several diseases, among which are serious infections, neoplasms and obstetric catastrophes. It is characterized by a diffuse and simultaneous activation of the endogenous systems of coagulation and fibrinolysis. The deposit of small thrombi in the circulation eventually leads to multiple organ dysfunction and in some cases to death. Treatment includes specific control of the underlying cause that favors its appearance, support with blood products in patients with bleeding manifestations and therapeutic anticoagulation in patients with major thrombosis. Given the importance of this pathological entity, it was decided to do a thorough investigation, to know if in

Bahia de Banderas, Nayarit, México the population knows about the issue of Disseminated intravascular coagulation, or if they know the risk factors or the phenomena that characterize it.

Methods

Methods of quantitative analysis and techniques that come from various disciplines such as statistics and sociology were used to know and record the perceptions and knowledge of the population on the subject. The sample used for the selection was 100 people, random, stratified, by conglomerates and, in general, the primary sampling units were selected with probability proportional to their population.

Results

Results obtained: 8% of respondents know what is causing Disseminated intravascular coagulation, 2% of the people interviewed know the symptoms of Disseminated intravascular coagulation, 80% of respondents are interested in knowing that Disseminated intravascular coagulation is, 60% of the interviewees would like district to a talk about Disseminated intravascular coagulation, 1% of the interviewed population does not know in treatment of Disseminated intravascular coagulation.

Conclusions

As the results of the surveys showed, in Bahia de Banderas, Nayarit, México people know us, about disseminated intravascular coagulation, neither know its causes or treatment. With these results we realize that you need to make this information reach your hands, and know it, as it is the basis of other important diseases. The prevention of any of these events is a very large health savings.

1.17. Fibrinogen and Other Coagulation Factors

1.17.1. C0089 Identification of Fibrinogen Novel Mutations in Patients with Fibrinogen Defects

Giovanni Favuzzi [1], Elena Chinni [1], Giovanni Tiscia [1], Patrizia Vergura [1], Filomena Cappucci [1], Gennaro Vecchione [1], Rossana Bagna [2], Claudia Izzi [3], Domenica Rizzi [4], Valerio De Stefano [5], Elvira Grandone [1]

[1] *Atherosclerosis and Thrombosis Unit, I.R.C.C.S. "Casa Sollievo della Sofferenza", San Giovanni, Italy*
[2] *Neonatology and Neonatal Intensive Care Unit, University Hospital, Cittá della Salute e della Scienza, Turin, Italy*
[3] *Department of Obstetrics and Gynecology, University of Brescia, Brescia, Italy*
[4] *Department of Pediatric and Neonatal pathology, Hospital Marche Nord, Pesaro, Italy*
[5] *Institute of Hematology, Catholic University, Roma, Italy*

Background

Congenital hypo-/dys-fibrinogenemia are defects defined by mutations in fibrinogen alpha [*FGA*], beta [*FGB*], or gamma chain [*FGG*] genes. Carriers may bleed when exposed to trauma (hypo-, a-) or have thromboembolic complications (dys-), but they can be also asymptomatic and go undiagnosed. We describe 10 subjects observed between 2011 and 2016.

Methods

Functional fibrinogen was measured by Clauss method (reference value: 160–400 mg/dL), antigen by radial immunodiffusion (NOR Partigen Fibrinogen) (reference value: 1.82–3.39 g/L). After DNA extraction and PCR, direct sequencing was performed accorrding to standard protocols. Deleterious/damaging effect of missense mutations was predicted using tools SIFT (Sorting Intolerant from Tolerant, http://sift.bii.a-star.edu.sg/), and Polyphen-2 (Polymorphism Phenotyping v2, http://genetics.bwh.harvard.edu/pph2/). Mutations were classified as deleterious or damaging when SIFT was <0.05 and/or Polyphen-2 was close to 1.

Results

We studied 1 afibrinogenemic patient (p.Arg178* homozygote) with bleeding and thrombotic events, 3 hypo/dysfibrinogenemic patients (p.Thr47Ileu combined with IVS7+1G>T; p.Cys95Ser; p.Arg196Cys all in heterozygosis) referred for bleeding or thrombotic episodes (deep vein thrombosis in pregnancy, pregnancy loss, respectively) and 6 hypofibrinogenemic patients (p.Glu41Lys; p.Gly191Val; p.Gly288Ser; p.His333Arg; p.Asp342Glu and pp. 343–344 duplication; p.Asp356Val; all in heterozygosis) 4 of them were symptomatic (bleeding after major surgery, cutaneous hematoma after fall, post-partum hemorrhage, heavy menstrual periods). Overall, 4 novel mutations were found, all in hypofibrinogenemic patients. The p.Glu41Lys (SIFT score 0, Polyphen-2 score 0.986) was identified within the *FGA* in a woman with bleeding after major orthopedic surgery. The remaining 3 novel mutations were identified within the *FGG:* p.Gly191Val (SIFT score 0.02, Polyphen-2 score 1) in an asymptomatic woman; p.His333Arg (SIFT score 0, Polyphen-2 score 1) in a woman experiencing a postpartum hemorrhage; p.Asp342Glu (SIFT score 0.23, Polyphen-2 score 0.931) combined with duplication of asparagine-343 and aspartate-344 was found in a 7-years-old child who suffered from hematoma occurring after fall.

Conclusions

We identified 4 novel mutations in hypofibrinogenemic patients. All but one are in symptomatic patients and are predicted to be deleterious. Our findings contribute to shed light on the genotype-phenotype relation in congenital fibrinogen disorders.

1.17.2. C0226 Hemostasis State, Adipokines and Left Ventricular Mass Index in Young Adults Withdarterial Hypertension and Abdominal Obesity

Vasilii Chulkov, Veronika Sumerkina, Vladislav Chulkov, Sergei Sinitsin, Natalya Vereina

South Ural State Medical University, Ural, Russia

Background

The study of mechanisms of target organ damage in young adults with arterial hypertension (AH) and abdominal obesity (AO) before the development of the cardiovascular complications can improve the understanding of the pathophysiological relationships.

Methods

The study aimed to scrutinize associations between hemostasis state, adipokines and left ventricular mass index in adults 18–44 years with arterial hypertension and abdominal obesity.

Cross-sectional study. The study included 251 patients, 124 men and 127 women. All patients were divided into four groups: gr.1—with AH (n 35), gr.2—with AO (n 76), gr.3—with AH and AO (n 60), gr.4–the control gr. (n 80). We measured coagulations tests, serum adiponectin and leptin levels. Left ventricular mass index (LVMI) was estimated by transthoracic echocardiography. Data are presented as M ± SD and Me (Q25–Q75). Multivariable linear regression (MLR) was used.

Results

The most significant hemostasis differences were detected in fibrinogen levels in all groups vs. the control gr. Plasma levels of PAI-1 (ng/mL) were higher in gr.3–460.3 [292.8–631.1] and gr.1–465.7 [215.5–587.4] vs. gr.2 384.4 [272.2–558.5] and the controls—286.2 [221.8–396.7], p3–1.4 < 0.05. The plasma TFPI levels were significantly increased in gr.3–123.5 [91.7–150.1] and gp.1–126.1 [107.6–129.8] vs. gr.2–73.4 [40.1–97.6] and the control gr.–93.2 [45.4–136.9], p3–2.4 < 0.05. The leptin concentration (ng/mL) was higher in gr.3–41.9 [10.1–70.5] and gr.2–30.2 [15.0–50.7] vs. gr.1–12.6 [5.0–18.9] and the controls—9.5 [4.1–15.6], p2.3–1.4 < 0.05. Plasma levels of adiponectin were lower among patients in all groups vs. the controls. Patients in gr.3 had higher LVMI (g/m^2)—110.5 ± 17.5 vs. gr. 1—98.1 ± 13.1, gr. 2–95.0 ± 16.8, the controls—83.1 ± 15.2, p3–1.2.4 < 0.05]. According to MLR (n = 251;

$R^2 = 0.69$, $p < 0.001$), the prediction equation is: Y = 0.33 × waist circumference (sm) × 0.42 × systolic blood pressure + 0.15 × adiponectin (ng/mL) + 0.01 × PAI-1 (ng/mL).

Conclusions

In young adults with arterial hypertension and abdominal obesity the most significant differences were revealed in fibrinogen, PAI-1, TFPI serum concentrations and adipokine imbalance. Waist circumference, adiponectin, systolic blood pressure, PAI-1 and adiponectin concentrations are independently associated with left ventricular mass index.

1.17.3. C0237 Lupus Anticoagulant (LA) and Vascular Endothelial Dysfunction in Diabetic Retinopathy Patients

Tatyana Shelkovnikova Vasilyevna [1], Juno Katsadze [2], Gregory Vavin [3]

[1] *Kemerovo Regional Clinical Ophthalmologic Hospital, State Autonomous Public Health Institution of the Kemerovo Region, Kemerovo, Russia*
[2] *Federal Russian Institute of Hematology and Transfusion, St. Petersburg, Russia*
[3] *The Kemerovo State Medical University, Kemerovo, Russia*

Background

The number of patients with diabetic retinopathy and diabetic macular edema (DME) is increasing, especially among the able-bodied population of Russia. Risk factors for diabetic retinopathy (DR) are imbalances in the hemostasis system, endotheliosis, inflammation, cytokine imbalance and the presence of lupus coagulant (LA) in the body.

1. The study examined the dependence of various parameters of hemostasis in patients with DR and DME with LA.

Methods

A total of 75 patients (150 eyes) of DR and DME were examined (mean age 52 ± 10 years). Group 1-patients with NPDR—37 people, 2 group—with PPDR—38 people. The LA trial was performed using the methods: activated partial thromboplastin time (APTT), dilute protrombin time (dPT), and dilute Rassell's viper venom time (DRVVT). VEGF—by the method of linked immunofermenet assay (ELISA).

Results

In patients with diabetes—2 type with clinical forms of DR found significant deviations from the norm of parameters of hemostasis and with endotheliosis: vWf, fVIII, PC, VEGF, SFMK. An increase in the activity of the components of the procoagulant and vascular-platelet link of hemostasis and the appearance of LA, indicates the presence of thrombophilia in patients with diabetes—2 type. In patients with NPDR and PPDR with LA, the thrombore resistance of the endothelium is significantly reduced in comparison with the clinical groups of patients without LA before treatment: SFMK is increased by 1.25 times; fibrinogen 1.04; thrombin time is truncated 0.84 times; ncreased by 10.2%, factor VIII by 40.8%, activity of the VEGF increases by 33.6%; PS decreased by 12.3%, the thickness of the retina was increased by 29.5% in patients with NPDR. In patients with PPDR and LA, vWf was increased by 17.2%; f VIII by 58.8%; VEGF by 18.3%, the PC decreased by 18%, the thickness of the retina increased −32.4%.

Conclusions

In patients with PPDR, the severity of hemorrhagic syndrome is accompanied by an increase in the thrombinemia (SFMK, fibrinogen, thrombin time). LA aggravates endothelial dysfunction in the microcirculatory bed of the retina, increases thrombogenesis, which is clinically manifested by pronounced retinal thrombohemorrhagic syndrome and high cystic persistent DME in 17.3%. To

clarify the diagnosis and choose adequate therapy for DME, it is recommended to study the procoagulants and physiological anticoagulants of the hemostasis system, the presence of lupus anticoagulant, the vascular growth factor in the plasma and the patient's serum.

1.18. Fibrinolysis and Thrombolysis

1.18.1. C0155 How the Microenvironment Influences on Plasminogen Activity in Women with Some Disorders

Eugene Roitman [1], Irina Kolesnikova [2], Alla Shabalina [3], Marine Tanashyan [3], Andrey Momot [4]

[1] *RSS Clinical Hemostasiology, Office Moscow, Moscow, Russia*
[2] *Pirogov Russian National Research Medical University, Moscow, Russia*
[3] *Research Center of Neurology, Moscow, Russia*
[4] *Altay Branch of NMR of Hematology, Barnaul, Russia*

Background

In addition to known direct pathways for activation and inhibition, fibrinolytic activity is influenced by surrounding processes. We studied distinct and interacting roles of such a microenvironment for resulting plasminogen activity.

Methods

The study included women with some myeloproliferative neoplasms (MPNs n = 57), with chronic cerebrovascular diseases (CCVD; n = 88) and with CCVD comorbided with Ph-negative myeloproliferative neoplasms (n = 76), with acute ischemic stroke (AIS; n = 62) and within 12 months after AIS (n = 44), and pregnant women with preeclampsia (n = 23).

Plasminogen activity (PLG) assayed with original kit for ACL Elite Pro (Instrumentation Laboratory, USA). Microenvironment was considered to clotting factors, tissue factor (TF), VWF, coagulation inhibitors, angiogenesis markers, cell adhesion molecules, and cytokines including TNF.

Results

Higher PLG identified in preeclampsia (Median 150%), the lowest in MPNs (Median to 75.85%), other patients had PLG within normal range. PC was revealed as expected independent predictor for PLG in all groups but its regulatory contribution has varied.

In MPNs the residual regulation had almost 90% and consisted of sVEGF-R1 balanced with sVEGF-R2, and additionally Age, IL-10 and sVCAM. In CCVD, the ensemble consisting of fV oppositing with fVII, fVIII and ADP platelet aggregation took over 84.0% in control; in CCVD comorbided with MPNs teh residual regulation in 67.5% was determined by primarily endothelium-leukocyte-platelet interactions (sVCAM, VWF, ADAMTS-13 and TNF). In AIS the role of cellular interactions has supplemented fVII and TNF compounded with sVEGF-R2, whereas within 12 months after AIS the PLG adjusted control has fV and IL-6. Preeclampsia showed other picture where PLG in 83.3% was under the compound regulation of ATIII with oppositing thrombomodulin.

Conclusions

Systematic approach has revealed both qualitatively and quantitatively the role of microenvironment for plasminogen. Identified ensembles of influencing processes seems to be caused pathogenesis of considered disorders. The study has deepens our knowledge on the regulation of fibrinolysis by revealing the causes of its hypo- or hyper responsibilities.

1.18.2. C0163 Microenvironmental Upregulation/Downregulation of Fibrinolysis in Women with Some Disorders

Eugene Roitman [1], Alla Shabalina [2], Andrey Momot [3], Marine Tanashyan [2], Irina Kolesnikova [4]

[1] *RSS Clinical Hemostasiology, Office Moscow, Moscow, Russia*
[2] *Research Center of Neurology, Moscow, Russia*
[3] *Altay Branch of NMR of Hematology, Barnaul, Russia*
[4] *Pirogov Russian National Research Medical University, Moscow, Russia*

Background

It is known that basic processes, such as fibrinolysis, becomes characteristic for a disease. Fine adjust setting is done via the microenvironment. We studied what microenvironment factors involved in the tPA regulation in women with some disorders.

Methods

The study included women with some myeloproliferative neoplasms (MPNs; n = 57; Group 1), with chronic cerebrovascular diseases (CCVD; n = 88; Group 2) and with CCVD comorbided with Ph-negative MPNs (n = 76; Group 3), with acute ischemic stroke (n = 62; Group 4) and within 12 months after AIS (n = 44; Group 5), and pregnant women with preeclampsia (n = 23; Group 6).

Levels of 98 biomarkers were measured, and those microenvironment was considered to clotting factors, tissue factor (TF), VWF, coagulation inhibitors, angiogenesis markers, cell adhesion molecules, and cytokines including TNF. Age, total protein, calcium and creatinine were taken into account as well. Markers of thrombin directly or its complexes or its generation were a priori excluded from consideration.

Results

tPA was highest in Group 2 and lowest in Group 4 (Median 3.10 ng/mL vs. 1.89 ng/mL, respectively). In Group 3 t-PA (Median 2.90 ng/mL) had closely to its level in Group 2 that in Group 1 (Median 1.95 ng/mL).

Multivariate models indicated that tPA is governed by the ensemble consisting of sVEGF-R1 (strongly; 70.8% of cumulative power) with the oppositing sVEGF-R2, and Thrombospondin, TF, fVII, fV and VWF in Group 1. In Group 3 the regulatory power in 47.8% belonged to TF, the residual regulation was performed with fVII and creatinine. In Group 4 the management of tPA was made up of fVII, creatinine and Calcium (jointly 93.1% of cumulative power), and sICAM1 as a residual. For other groups reliable models have not been identified.

Conclusions

The resulting model showed the expected relationship with markers belonging to vascular wall. In Group 1 the upregulation seems to be mediated through the induction of prourokinase activation. In Groups 3 and 4, the management looked more "coagulation", but it is important that the management contained markers of renal function and water balance. All findings reflect the pathogenesis of considered disorders.

The lack of models for other groups allows us to make two assumptions: (1) either tPA (but not uPA) does not have so significant role for fibrinolysis in such patients; (2) or microenvironment effects are masked by more potent regulator (perhaps thrombin-mediated).

1.18.3. C0322 Incorporation of Alpha-2-Plasmin Inhibitor into Fibrin Clots and Its Association with the Clinical Outcome of Acute Ischemic Stroke Patients Receiving Thrombolytic Therapy

Barbara Baráth [1], Zsuzsa Bagoly [2], István Szegedi [3], Rita Kálmándi [2], László Csiba [3], Éva Katona [2]

[1] *University of Debrecen, Division of Clinical Laboratory Sciences, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen Debrecen, Hajd-Bihar, Hungary*
[2] *Division of Clinical Laboratory Sciences, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Hajd-Bihar, Hungary*

[3] *MTA-DE Cerebrovascular and Neurodegenerative Research Group, Department of Neurology, Faculty of Medicine, University of Debrecen, Hajd-Bihar, Hungary*

Background

The cross-linking of alpha-2-plasmin inhibitor (A2PI) to fibrin by activated factor XIII (FXIII) is essential for the inhibition of fibrinolysis. Little is known about the factors modifying the incorporation of A2PI into the fibrin clot and whether the extent of incorporation has any clinical consequences in the outcome of thrombotic disorders.

Methods

A2PI activity/antigen, FXIII activity/antigen and fibrinogen levels were measured from the plasma samples of 88 individuals (62 acute ischemic stroke (AIS) patients, all within 4.5 h of their symptom onset before thrombolysis treatment and 26 age-matched healthy controls). After clotting the plasma samples by the addition of thrombin and Ca^{2+}, A2PI antigen levels were measured from the serum and the extent of a2PI incorporation into fibrin clots was calculated upon the difference between plasma and serum values. The extent of A2PI incorporation was compared between patients and controls and the modifying effect of FXIII levels was also studied. In the patient group results were correlated with stroke severity and thrombolysis outcome. Severity of stroke was determined using the National Institutes of Health Stroke Scale. Patient outcomes were registered at 7 days post-lysis (good outcome, no change/poor outcome, death, therapy-associated intracranial hemorrhage) based on the change in NIHSS and the results of imaging and clinical data.

Results

In the whole cohort FXIII levels significantly correlated with the amount of A2PI incorporation into fibrin clots (r = 0.431, $p = 0.001$). In controls and in patients with good outcomes incorporated A2PI did not differ significantly (49.2 ± 4.2% vs. 47.4 ± 6.7%, $p = 1.000$). In patients suffering post-lysis intracranial hemorrhage, the extent of A2PI incorporation was significantly lower (38.1 ± 13.8%) as compared to controls and to those with good outcomes ($p = 0.004$ and $p = 0.028$, respectively).

Conclusions

Increased FXIII levels result in elevated incorporation of A2PI into fibrin clots. In stroke patients the extent of A2PI incorporation seems to have an effect on the outcome of therapy, particularly on presence of thrombolysis-associated intracranial hemorrhage.

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1.18.4. C0338 ALPHA-2 Plasmin Inhibitor Activity and Antigen Levels and p.Arg6Trp Polymorphism in Patients with Venous Thromboembolism

Éva Katona [1], Réka Bogáti [2], Tunde Miklós [2], Réka Gindele [2], Marianna Speker [2], Viktória Fedoriska [2], Adrienn Teráz-Orosz [2], Zoltán Mezei [2], Zsuzsanna Bereczky [2]

[1] *University of Debrecen, Division of Clinical Laboratory Science, Department of Laboratory Medicine, Faculty of Medicine Debrecen, Hajd-Bihar, Hungary*
[2] *Division of Clinical Laboratory Science, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Hajd-Bihar, Hungary*

Background

Alpha-2 plasmin inhibitor (A2PI) is the primary inhibitor of plasmin. In the circulation A2PI undergoes proteolytic cleavages, which significantly influences its activities. About 70% of circulating full length A2-PI (Met-A2PI) is cleaved by antiplasmin cleaving enzyme (APCE) at the N-terminus resulting in a 12 amino acids shortened form (Asn-A2PI). Asn-A2PI is cross-linked more effectively to fibrin by activated factor XIII, resulting in a slower lysis rate of plasma clots; thereby the ratio of

N-terminal isoforms may influence the fibrinolytic resistance of the clot. The p.Arg6Trp polymorphism affects the rate of this cleavage as APCE cleaves Met-A2PI(Arg6) 8-fold faster than Met-A2PI(Trp6).

In this case-control study we investigated the association of A2PI p.Arg6Trp polymorphism and A2PI activity and antigen levels with the risk of venous thromboembolism (VTE).

Methods

218 VTE patients and equal number of age and sex matched healthy controls (C) were enrolled in the study. A2PI activity was determined by Berichrom ANTIPLASMIN assay, total A2PI antigen levels were determined by a sandwich type ELISA, A2PI Arg6Trp genotype was determined by RT-PCR using LightCycler® 480.

Results

Genotype distribution was consistent with the Hardy-Weinberg distribution in both study groups. The minor allele frequency did not differ significantly between HC and VTE (0.21 and 0.20 respectively; $p = 0.841$). Possession of the Trp allele did not influence the risk of VTE (OR: 0.895, 95% CI: 0.606–1.321). A2PI activity (129 ± 1.7% vs. 115 ± 2.0%, $p < 0.001$) and total A2PI antigen levels (72.8 ± 9.2 mg/L vs. 64.6 ± 9.7 mg/L $p < 0.001$) were significantly elevated in VTE compared to HC. The correlation of A2PI activity and antigen levels was stronger in patients ($r = 0.773$, $p < 0.001$) than in controls ($r = 0.454$, $p < 0.001$). Elevated A2PI activity and antigen levels (above 128% and 70.8 mg/L, respectively) increased the risk of VTE (OR: 1.750, 95% CI: 1.158–2.645, $p < 0.001$ and OR: 4.301, 95% CI: 2.848–6.495, $p < 0.001$), which remained significant after adjustment to other cardiovascular risk factors.

Conclusions

In our study, the A2PI p.Arg6Trp polymorphism had no effect on the risk of VTE, however A2PI levels in the upper quartile resulted in a significant risk enhancement.

1.19. Lupus Anticoagulant/Phospholipid Dependent Antibodies

1.19.1. C0102 Lower Platelet Aggregation and Activation in High-Risk Patients with Antiphospholipid Syndrome

Elena Pontara, Alessandra Banzato, Baroni Giulia, Maria Grazia Cattini, Elisa Bison, Vittorio Pengo

Cardiology Clinic Thrombosis Center, Department of Cardiac Thoracic and Vascular Sciences, University of Padova, Padova, Italy

Background

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the association of thrombosis and/or pregnancy morbidity with the presence of antiphospholipid antibodies (aPLs). β2GPI is the main antigen and anti-β2GPI are directly associated with an increased risk for thrombosis. Platelet activation in APS patients during the quiescent phase of disease is rather controversial.

Methods

The aim of our study was to analyze platelet aggregation on whole blood and platelet activation (expression of P-selectin on the surface of platelets) in high-risk APS patients (triple positive). Platelet aggregation was expressed by AUC (area under curve) with a multiple electrode aggregometer after stimulation with ADP and TRAP. Platelet activation was analyzed by means of flow cytometry through the P-Selectin expression on the surface of platelets before and after stimulation with TRAP.

Finally we evaluated the activation of normal platelets incubated with anti-β2GPI antibodies by aggregometry.

Results

We studied 7 patients during the quiescent phase of the disease and 8 normal controls. None had antiplatelet therapy at time of testing and all had a normal platelet count (mean platelet count was 198 × 10^9/L in patients and 231 × 10^9/L in controls, respectively). Platelet aggregation of patients was slightly lower than that in normal controls both with ADP (42% vs. 65%) and TRAP (70% vs. 83%). Likewise, aggregation of normal platelets incubated with affinity purified IgG anti-β2GPI antibodies was lower than normal controls both with ADP (40% vs. 53%) and TRAP (63% vs. 76%). Similar results have been obtained with the flow cytometer as APS patients platelet activation was lower than normal controls both before (0.73% vs. 1.54%) and after stimulation with TRAP (27.72% vs. 33.77%).

Conclusions

In high-risk APS patients platelets show a slightly lower aggregation and activation compared to platelets of healthy subjects. We hypothesize that the link β2-Ig anti β2 may somehow interfere with the activation of platelets by various stimulating agents.

1.19.2. C0120 Anti-beta2-GPI Antibodies Induce Tissue Factor Expression in Platelets

Antonella Capozzi [1], Valeria Manganelli [1], Gloria Riitano [1], Serena Recalchi [1], Simona Truglia [2], Agostina Longo [1], Tina Garofalo [1], Roberta Misasi [1], Fabrizio Conti [2], Maurizio Sorice [3]

[1] *Dept Experimental Medicine-Sapienza University of Rome, Rome, Italy*
[2] *Dipartimento di Medicina Interna e Speciality Mediche, Sapienza University of Rome, Rome, Italy*
[3] *Sapienza University Rome, Experimental Medicine, Rome, Italy*

Background

Antiphospholipid syndrome (APS) is characterized by arterial and/or venous thromboses and habitual abortion. It is well known that in these patients thrombosis may be the result of a hypercoagulable state related to anti-β2-glycoprotein I (β2-GPI) antibodies. Moreover, platelets may play a role in thrombotic manifestations by binding of anti-β2-GPI antibodies. Recent evidence showed that platelets may express Tissue Factor (TF), the major initiator of the clotting cascade, on their surface. We analyzed whether anti-β2-GPI antibodies may trigger a signal transduction pathway leading to TF expression in human platelets.

Methods

Platelets from healthy donors were incubated with affinity purified anti-β2-GPI antibodies for 10 min, 45 min and 4 h. Cell lysates were analyzed for phospho-IRAK, phospho-p65 NF-kB and TF by Western blot.

Results

IRAK phosphorylation was observed as early as 10 min of anti-β2-GPI treatment, with consequent NF-kB activation, whereas TF expression, detectable at 45 min, was significantly increased after 4 h of anti-β2-GPI treatment. Virtually no activation was observed following treatment with control IgG.

Conclusions

In previous studies we demonstrated that anti-β2-GPI antibodies may activate a signaling pathway in human monocytes, leading to a proinflammatory and procoagulant phenotype, characterized by the release of TNFα and TF. The present work demonstrates that anti-β2-GPI

antibodies are also able to trigger a signal transduction pathway on human platelets, which involves IRAK phosphorylation and NF-kB activation, followed by TF expression.

These findings support the view that platelets play an important role in the pathogenesis of APS, with consequent release of different procoagulant mediators, including TF.

1.19.3. C0147 Rivaroxaban and False-Positive Lupus Anticoagulant

Olga Dzhenina [1], Vadim Bogachev [2], Tatiana Kirsanova [3]

[1] *First Phlebological Centre, Moscow, Russia*
[2] *Russian National Research Medical University Named after N. I. Pirogov, Moscow, Russia*
[3] *National Medical Research Centre of Obstetrics, Gynecology and Perinatology Named after V. I. Kulakov, Russia*

Background

Deep vein thrombosis (DVT) is often a manifestation of antiphospholipid syndrome (APS). The results of the laboratory examination in such cases can be critical in the choice of tactics of antithrombotic therapy.

Methods

We report 15 patients with false-positive lupus anticoagulant during rivaroxaban therapy. This study included 8 men and 7 women with DVT. The age of patients was less than 40 years. In 11 cases, a trigger of DVT was identified: trauma, long air travel for men and pregnancy, early postpartum period, use of combined oral contraceptives for women. The thrombosis was unprovoked in other cases.

Results

APS screening determined the presence of lupus anticoagulant (LA) and the level of antiphospholipid antibodies. Anti-cardiolipin, anti-β2glycoprotein-I antibodies were negative in all patients. The presence of LA was determined by the normalized ratio L1/L2. The results of this test were increased from 1.43 to 1.63 c.u (reference range ≤1.2 c.u.). In 10 weeks, nine of the patients during rivaroxaban therapy underwent repeated APS screening which showed again normal antiphospholipid antibody levels and moderately positive LA. We refrained from holding a second screening in other five patients receiving rivaroxaban.

Treatment with rivaroxaban was completed in fourteen of the patients at six months after the DVT episode. Re-definition of LA was carried out 1–3 weeks after the last use of rivaroxaban. The normalized ratio L1/L2 was negative in all these patients.

One woman replaced rivaroxaban to enoxaparin sodium, as she planned the pregnancy. The control ratio L1/L2 was conducted twice: during therapy with low molecular weight heparin therapy, and after completion of anticoagulation. Both re-screenings showed negative LA.

Conclusions

By our opinion, it is advisable to refrain from the definition of LA by the ratio L1/L2 during therapy with rivaroxaban and other direct oral anticoagulants. For laboratory confirmation of APS appropriate temporary transition to other types of anticoagulants, or at least should be carried out blood sampling for analysis strictly before taking the next dose of rivaroxaban.

1.19.4. C0227 Lupus Anticoagulant-Hipoprothrombinemia Syndrome in a Patient with Liver Cirrhosis

Maria Nieves Alonso Escobar [1], Maria Belen Moreno [1], Celia Crespo [1], Elena Hernandez [1], Antonio Corbacho[2], Rosario Rincon [1], Elena Delgado [2], Juan Camilo Restrepo [2]

[1] *Hospital Infanta Cristina, Hematology, Badajoz, Spain*

[2] *Banco de Sangre Extremadura, Badajoz, Spain*

Background

Lupus anticoagulant-hypoprothrombinemia syndrome (LA-HPS) is a rare acquired disorder caused by prothrombin antibodies, associated with systemic lupus erythematosus (SLE), viral infections, drugs, also described in healthy individual. The clinical manifestation of LA-HPS varies greatlyin severity and severe life-threatening bleeding are described added to thrombosis. Steroids are the recommended preoperative treatment, without clear protocols. Normal screening coagulation tests are described after them. Immunoglobulins and immunosuppressants can be used

Methods

Clinical case description

Results

We present a 64-year-old woman with enolic liver cirrhosis, portal hypertension, Type 2 Diabetes Mellitus, without hemorrhagic symptoms. Due to lower limb ischemia(diabetes related) surgery, the coagulation screening showed a prolonged activated partial thromboplastin time (aPTT) and next to normal prothrombin time (PT), both present 7 years ago, normal fibrinogen level and low platelet count (42.000/mm^3). Platelet function analyzer was not evaluable for baseline thrombocytopenia. Evaluation of the clotting factorsrevealed decreased levels of factor II 27%, FVII93%FX79%, FV 99%. The FXII66%, FIX97%, FVIII256% F XI 52% were analyzed in 1:8 diluted sample to rule out analytical interference of suspected LA. VWF Ag 356%. Lupus anticoagulant (LA) was demonstrated by the Dilute Russell's Viper Venom Test (DRVVT) and SCT (silica clotting time). Positive low title Anticardiolipin antibodies IgG, IgM and positive antiBeta 2 glycoprotein I IgM were detected. Antiprothrombin antibodies IgG, IgM were confirmed. The day and the day after of the surgical intervention two doses of 1 mg/kg methylprednisolone was administered without significant bleeding during or after the procedure. We were authorized for inmunoglobulins treatment but did not used them. We started antithrombotic prophilaxis with enoxaparin 20 mg/24 h first and then 40 mg/24 h plus aspirin 100 mg. 8 months later the same corticosteroid treatment was administered for urothelial papillar bladder cancer surgery with the same result.

Conclusions

LA-HPS is a rare disorder but must be suspected when APTT is prolonged including cirrhosis patients like ours. Bleedings are described in these patients but can be asyntomatic. Isolated doses of Corticosteroid therapy can be successful, whereas fresh frozen plasma or prothrombin complex concentrates should be avoided, moreover in cirrhosis patient.

1.19.5. C0258 Thrombotic Complications in Children with Primary Immune Thrombocytopenic (IPT) and the Relation with Systemic Lupus Erythematosus (SLE)

Rocío Zapata Bautista, Susana Ramírez García

Juan Ramón Jiménez Hospital, Haematology Huelva, Huelva, Spain

Background

IPT is the most common thrombocytopenia in childhood. It is the first manifestation of SLE in 5–12%. The incidence of thrombosis in patients with SLE or SAntiphospholipid syndrome (APS) is 3–4%. 40% of patients with SLE have antiphospholipid antibodies (aPL), but less than 50% will develop thrombosis. The lupus anticoagulant (LA) is considered the most potent predictor of thrombosis development, significantly increasing the risk with the triple positivity of aPL.

Methods

To evaluate the incidence of thrombosis in children diagnosed with IPT and its relationship with SLE through a retrospective analysis of these patients in our center since 1983.

Results

We analyzed 35 children, 17 (48.5%) males and 18 (51.5%) females with an average age of 5 years with the characteristics presented in Table 1.

Of the 31 studies of autoimmunity performed, only initially were positive in 4 patients for anti-nuclear antibodies (ANA) and in 6 patients for aPL, confirmed at six weeks in two of them. They only presented two thrombotic events, a girl diagnosed in childhood with IPT who presented a pulmonary thromboembolism at 20 years old, with levels of aPL in the upper limit of normal, whose causal etiology was the use of oral contraceptives discarding SLE. The second one with 6 years old, presented a massive venous thrombosis of the intracranial sinus associated with ANA and aPL positives and with a possible postmortem diagnosis of SLE. In our sample, only a second children was diagnosed SLE with a previous positive autoimmunity study and associated thrombocytopenia, currently with anticoagulant treatment without presenting thrombosis.

We don't find relationship between thrombosis and the diagnosis of SLE or positivity for aPL in patients with initial diagnosis of IPT.

Table 1. Characteristics of the 35 children

N	35
Male	17/35 (48.5%)
Platelets < 5×10^{-9}/L at diagnosis	12 (41.4%)
Spring	16/35 (45.7%)
Mild bleeding	25 (86.2%)
Antecedent of autoimmune diseases (AID)	3 (8.6%)
SLE	2 (94.3%)
Thrombotic event	2 (94.3%)
Antibodies:	31/35
aPL	6 (19.3%)
ANA	4 (12.9%)
aTSH	3 (9.6%)
Serology:	24/35
Positive IgM	1/24 (4.2%)
Answer to tto:	34/35
CTC	8/34 (22.9%)
IGs	21/34 (60%)
Splenectomy	2/34 (5.7%)
New	2/34 (5.7%)
Refractoriness	1/34 (2.9%)
Evolution:	
Chronicle	5/35 (14.3%)
Mortality	1/35 (2.85%)

Conclusions

Although more studies are needed to related both entities, IPT may be the first manifestation of SLE or SAF in children, contributing the initial study of autoimmunity to early diagnosis and the prevention of thrombotic complications.

1.19.6. C0306 a Transient Acquired Lupus Anticoagulant-Hypoprothrombinaemia Syndrome in a Child

Imen Ben Ali, Hela Baccouche, Meriam Hadhri, Aya Chakroun, Zeineb Manai, Sonia Mahjoub, Neila Ben Romdhane

Rabta Hospital, Hematology Department-La Rabta Hospital, Manouba, Tunis, Tunisia

Background

Lupus anticoagulant-hypoprothrombinaemia syndrome (LAHPS) consisted of a lupus anticoagulant associated with anti prothrombin (FII) antibodies. These antibodies, unlike other prothrombotic antiphospholipid antibodies, promote bleeding. We described a 3-year-old child with ecchymotic lesions in the legs which has appeared 3 weeks previously.

Methods

Platelet poor plasma was prepared by double centrifugation of the citrated whole blood. Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), correction of PT and APTT after 1:1 mixing with normal plasma and factor clotting activities were measured using reagents from STAGO. Rosner index was calculated. Screening for Lupus anticoagulant (LA) was also investigated (STA-STACLOT and DRVVT; STAGO, France). Search of anti-cardiolipin and anti-beta2glycoprotein was performed with ELISA method.

Results

The laboratory tests demonstrated unexpected findings: platelet count = 200 10^3/mm^3, PT = 16.5 s, APTT = 64.7 s (ratio 1.85), TT = 32.4 s and fibrinogen level = 2.61 g/L. Mixing the plasma with an equal volume of normal plasma did not correct the prolonged APTT but correct the PT. Measurement of clotting factor activities revealed an isolated FII deficiency (37.5%). The other factors were normal: V = 119%, VII = 61% and X = 91%. Further investigations revealed that his parents had normal level of FII. The screening of LA was positive and was confirmed with both DRVVT confirm and STACLOT LA. Rosner index was 45.5%. In addition, anti-cardiolipin and anti-beta2glycoprotein were negative. One month later, PT, aPTT and FII level were normal and the LA screening was negative.

Conclusions

Coagulation screening tests demonstrated unexpected findings including a prolonged APTT that did not correct on a 1:1 mix (suggesting LA) and a PT that corrected on a 1:1 mix (suggesting hypoprothrombinaemia). Although it is a rare disease, it is most common in pediatric patients. This transient deficiency was probably caused by a viral infection which is more frequent than autoimmune disorders in children aged less than 10 years. It was also paucisymptomatic which could be explained by moderate FII deficiency and normal platelet count.

1.19.7. C0314 Laboratory and Clinical Characteristics of Isolated Lupus Anticoagulants

Elena Mattia [1], Marta Tonello [1], Teresa Del Ross [1], Antonia Calligaro [1], Maria Favaro [1], Patrizia Zerbinati [2], Elena Campello [2], Paolo Simioni [2], Amelia Ruffatti [1]

[1] *Rheumatology Unit, Medicine-DIMED, Padua, Italy*
[2] *Hemorrhagic and Thrombotic Disease Unit, Department of Medicine-DIMED, Italy*

Background

Lupus anticoagulants (LAC) are usually associated to other antiphospholipid (aPL) antibodies. Isolated LAC is an uncommon finding with controversial clinical significance. Aim of this study was to evaluate the laboratory characteristics of isolated LAC and clinical features of isolated LAC-positive patients

Methods

The study populationwas made up of 180 LAC-positive patients: 44 had isolated LAC (the study group) and 136 had LAC associated to other aPL antibodies (the control group). Diluted Russell's viper venom time (dRVVT), silica clotting time (SCT), and LAC sensitive partial thromboplastin time (PTT-LAC) assays were used to detect LAC.

Results

Using the three clotting assays for testing the 44 patients with isolated LAC, SCT showed isolated LAC in 41/44 (93.2%) patients, dRVVT in 30/44 (68.2%) and PTT-LAC in 20/44 (45.5%). The Z-test for proportions showed that the sensitivity of the SCT assay in detecting isolated LAC was significantly higher than those of the dRVVT ($p = 0.0023$) and PTT-LAC ($p = 0.0001$) assays. PTT-LAC test had the highest specificity in detecting APS in patients with isolated LAC with respect SCT ($p = 0.0001$) and dRVVT ($p = 0.012$) methods. APS and its thrombotic involvement alone or associated to pregnancy morbidity significantly prevailed in patients with LAC associated to other aPL. Instead, the absence of APS was significantly found in patients with isolated LAC.

Conclusions

Our data suggest that finding a positivity for isolated LAC should take into account the detection methods and clinic characteristics of the patient in order to attribute the correct significance to its presence.

1.20. Perinatal and Pediatric Hemostasis

C0275 Predictive Capabilities of the Machine Learning Methods for the Pediatric Arterial Ischemic Strokes Outcomes Based on Thrombophilic and Folic Acid Enzymes Genes Polymorphisms

Alexander Sergeev [1], Olga Lvova [2], Anna Rakhmatova [1]

[1] *Ural Federal University, Yekaterinburg, Russia*
[2] *Ural Federal University, Laboratory of Brain and Neurocognitive Development, Yekaterinburg, Russia*

Background

Machine learning methods which assess indicators of the disease and personal data allow identifying the evident and predictable marks of it debut, course and outcome options. Pediatric Arterial Ischemic Stroke (PedAIS) is rare and severe disorder, which leads to motor and mental delay, epilepsy, etc. At the same time, the approaches to forecast it outcomes amongst children are not investigated thoroughly, predictors of bad prognosis remain unknown.

Methods

The following personal and medical data of 162 patients with PedAIS (confirmed by brain CT/MRI scan) was processed: 14 independent variables: sex, age, single nucleotide polymorphisms in 8 thrombophilic genes (FGB:-455G>A, F2:20210G>A, F5:1691G>A, F7:10976G>A, F13:103G>T, ITGA2:807C>T, ITGB3:1565T>C, PAI-1:-675 5G>4G) and in 4 folic acid enzymes genes (MTHFR:677C>T, MTHFR:1298A>C, MTRR:66A>G, MTR:2756A>G). The sex was coded as 0 (girl) and 1 (boy). The number of genetic polymorphisms were coded as 0 (polymorphisms absent in both alleles), 1 (one of the alleles has polymorphism) and 2 (both alleles are represented by polymorphisms).

Dependent variables: disability for neurological indicators—0 (no disability), 1 (disability). "Disability" was assessed after at last 2 years after PedAIS and interpreted as the state that is required constant external support and replacement of irreversibly lost functions of the nervous system.

The sample (162 records) was randomly divided into a training subsample (112 records) and a test subsample (50 records). To construct the forecast, we used 3 methods: Decision Tree, Random

Forest and Multilayer Perceptron. The number of trees (57) in the Random Forest and the architecture of the Multilayer Perceptron (MLP-38-12-2 with the activation function "Softmax" (STATISTICA 12)) were chosen based on minimizing classification errors on the test subsample.

Results

Trained models showed the following results on the test subsample. Decision Tree: sensitivity = 0.52, specificity = 0.37. Random Forest: sensitivity = 0.74, specificity = 0.59. Multilayer Perceptron: sensitivity = 0.61, specificity = 0.74.

Conclusions

The Decision Tree showed unacceptable forecast results. The Random Forest and the Multilayer Perceptron had a generally comparable predictive ability. However, Random Forest proved to be a more sensitive method, and Multilayer Perceptron—more specific. Combining these two methods will improve the accuracy of the forecast.

1.21. Women's Health Issues

1.21.1. C0105 Management and Outcome of Pregnancy in Women with Cobalamin C Defects

Michela Villani [1], Gennaro Vecchione [1], Angelica Leccese [2], Rosa Santacroce [2], Pasquale Martinelli [3], Giuseppe Maria Maruotti [3], Lucia Fischetti [1], Gaetano Corso [2], Maurizio Margaglione [2], Elvira Grandone [1]

[1] *IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy*
[2] *University of Foggia, Foggia, Italy*
[3] *University of Naples "Federico II", Naples, Italy*

Background

Cobalamin C (CblC) defects are inherited autosomal recessive disorders of vitamin B12 metabolism, with an unknown true prevalence. Although combined methylmalonic acidemia and homocystinuria are typical findings of CblC disease, clinical manifestations as well as the onset of clinical signs and symptoms are quite heterogeneous. In women with CblC defect, the appropriate clinical management of pregnancy remains to be established, with very few cases reported in the current literature.

Methods

We describe the case of a successful management of pregnancy in a 34 years-old Caucasian woman from Southern Italy with homocystinuria and methylmalonic aciduria due to CblC defect. She was referred to our Unit because of a 20th week pregnancy loss of a morphologically normal intrauterine growth restricted foetus. Then she performed a thrombophilia screening, that showed 100 μmol/L of plasma homocysteine (tHcy). At that time she was on folic acid (calcium folinate, 15 mg/day). An accurate clinical history was collected together with laboratory data.

Results

This woman was delivered at term and was in apparently good health until 20 years, when she showed a normocitic anemia (Hb 8.2 g/L), elevated inflammatory markers (ESR 55), and an impaired renal function (1.9 mg/dL serological creatinin). Urinalysis revealed proteinuria (150 mg/dL) and micro-hematuria. At that time she was found to be moderately hypertensive. Neurological examination was normal. A renal biopsy revealed thrombotic microangiopathy with predominant lesions in the glomerulus and minimal lesions in the arterioles. Whole Exome Sequencing showed a compound heterozygosity for p. Tyr130His and p. Tyr222Stop in the MMACHC gene (Methylmalonic Aciduria type C and Homocystinuria; OMIM * 609831). Plasma concentration of methylmalonic acid was 1.09 μmol/L (reference value: 0–0.7). Hydroxocobalamin, 2 mg/week i.m.

injection totally normalized tHcy plasma levels and restored anemia and renal function. Pregnancy was then started and low-molecular weight heparin at prophylactic doses (enoxaparin 4000 IU/day) prescribed in addition to hydroxocobalamin until 4 weeks post-partum. After an uneventful pregnancy, a male baby weighing 2420 gr (Apgar 1' 8, 10' 9) was delivered at 39 weeks.

Conclusions

Women with late-onset CblC defect can have a good pregnancy outcome, if adequately treated. The presented case emphasizes the importance of awareness and appropriate management of rare metabolic diseases during pregnancy.

1.21.2. C0106 Reproductive Outcome in Women with Recurrent Failures after Spontaneous or Assisted Conception: Study Design and Preliminary Data from the Ottilia and First Registries

Michela Villani [1], Domenico Baldini [2], Pasquale Totaro [3], Giovanni Larciprete [4], Mirjana Kovac [5], Domenico Carone [6], Serena Maria Passamonti [7], Eleonora Tamborini Permunian [8], Tiziana Bartolotti [9], Andrea Lojacono [10], Rossella Cacciola [11], Giuliano Lo Pinto [12], Eugenio Bucherini [13], Valerio De Stefano [14], Corrado Lodigiani [15], Elvira Grandone [1]

1 *IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy*
2 *Centro di Fecondazione Medicalmente Assistita MoMÚ Fertilife, Bisceglie, Italy*
3 *Centro PMA ìCasa di Cura Santa Mariaî, Bari, Italy*
4 *Fatebenefratelli Isola Tiberina Hospital, Rome, Italy*
5 *Blood Transfusion Institute of Serbia, Belgrade, Serbia*
6 *Center of Reproduction and Andrology (CREA), Taranto, Italy*
7 *Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy*
8 *Insubria University, Varese, Italy*
9 *Centro PMA ìARTeBIOSî, Lugo, Italy*
10 *ASST Spedali Civili and University of Brescia, Brescia, Italy*
11 *University of Catania, Catania, Italy*
12 *Galliera Hospital, Genova, Italy*
13 *Civic Hospital of Faenza, Faenza, Italy*
14 *Catholic University, Rome, Italy*
15 *Humanitas Research Hospital and Humanitas University, Rozzano, Italy*

Background

Spontaneous pregnancy loss and implantation failure after assisted reproductive technologies (ART) are very common occurrences. Available research findings on predisposing factors and possible benefits of antithrombotic treatments are inconclusive.

Methods

OTTILIA (ClinicalTrials.gov: NCT 02385461) and FIRST (ClinicalTrials.gov: NCT 02685800) registries are two prospective, multicenter, observational studies to evaluate pregnancy or ART outcome according to their clinical management and characteristics of women. Consecutive 1) pregnant women with recurrent pregnancy loss (≥3 or 2 in the presence of at least 1 normal fetal karyotype) or at least 1 intrauterine foetal death (a loss after 20 weeks of a morphologically normal fetus), and 2) women undergoing ART after ≥2 implantation failures/losses of clinical pregnancies after ART are respectively eligible. At enrolment, clinical information and index- pregnancy/ART cycle details are obtained from all women by a specially trained staff. Data are collected by means of questionnaires and recorded in a web-based database with a centralized data management. Follow-up data are collected during the three trimesters of pregnancy and in the puerperium period (6 weeks after delivery), at the time of hospital stay, routine clinical follow-up visits or telephone interviews. For statistical analysis, stratification according to sub-groups of subjects will be taken into account on the basis of propensity to receive or not the treatment. Potential confounding factors will be identified

and after the evaluation of possible relationship between single variables by univariate analysis, logistic regression analysis will be performed to estimate the independence of associations identified.

Results

To date, 184 (211 pregnancies) and 230 women (median age: 36 and 37, range: 20–47 and 24–49 years) have been enrolled in OTTILIA and FIRST registers, respectively. An antithrombotic treatment was prescribed in 141 pregnancies and 26 ART cycles. Outcome is available in 198 pregnancies (5 were lost to follow-up, 8 are ongoing) and 216 ART cycles (14 are ongoing).

Conclusions

Although no definitive conclusion can be drawn, we are confident that these registries will improve knowledge on mechanisms involved in reproductive failures in the 'real word' of women trying to get pregnant and/or to carry a pregnancy to term and support future clinical decisions.

1.21.3. C0141 ADP-Aggregation Varies by Platelet Microenvironment in Women with Myeloproliferative Neoplasms

Eugene Roitman [1], Alla Shabalina [2], Marine Tanashyan [2], Irina Kolesnikova [3]

[1] *RSS Clinical Hemostasiology, Office Moscow, Moscow, Russia*
[2] *Research Center of Neurology, Moscow, Russia*
[3] *Pirogov Russian National Research Medical University, Moscow, Russia*

Background

A real interplay exists between cancer and platelets due to their involvement in cancer progression and in cancer-associated thrombosis. Apart platelet count and microparticles, the platelet responsiveness is very important to the last. From other side, bioactive microenvironment may appreciably to vary platelet response.

Methods

ADP-induced aggregation (%) was examined in 57 women with myeloproliferative neoplasms in remission (MPNs; mean age 36 years; Group I) and in 76 women with chronic cerebrovascular diseases (CCVD) comorbided with MPNs in remission (mean age 65 years; Group II). Microenvironment was considered to clotting factors, tissue factor (TF), VWF, regulating coagulation inhibitors, angiogenesis markers, cell adhesion molecules, and cytokines including TNF. Total protein, calcium and creatine were taken into account as well.

Results

In Group I the ADP aggregation was significantly lower than in Group II (15.5 vs. 24.5; $p = 0.049$). Other differences were that Group I showed a significantly higher VWF together with reduced ADAMTS-13, higher values for sICAM, VEGF-A, sVEGF-R1, sVEGF-R2, Thrombospondin and less inflammatory response by TNF and IL-6. All women had normal creatinine but women with MPNs performed higher values in compare to Group II. Significant mean force correlations of ADP-aggregation were found positively with PC, TF, sVCAM, and TNF and negatively with sVEGF-R1 and sVEGF-R2 in Group I whereas only negatively with Age in the Group II.

Considering the microenvironment as a matrix of multidimensional interplays, the model analysis showed in Group I for ADP-aggregation managing trigger consists of Protein C and VEGF-A as a opposing (68.8% of cumulative power) together with sVCAM (22.9% in residual power). In Group II managing trigger consisted of PC jointly with fVII and creatinine and VEGF-A and sVCAM (87.5% of cumulative power), and Protein S with sVEGF-R1 as a residual.

Conclusions

Activation of platelets is explained through the composition of mechanisms requiring platelet ApoER2 receptors with VEGF as a vascular protective factor in the presense of high leukocyte-platelet aggregation followed by Josso loop. FVII and renal function in trigger composition reflect the specifics of CCVD pathophysiology. Whereas the same components are composited in the managing triggers for both groups that demonstrates leadership influence of myeloproliferative process of one as well in comorbidity on the platelet responce to ADP.

1.21.4. C0142 the Platelet Microenvironment Affecting Collagen-Induced Aggregation in Women with Myeloproliferative Neoplasms

Eugene Roitman [1], Marine Tanashyan [2], Alla Shabalina [2], Irina Kolesnikova [3]

[1] *RSS Clinical Hemostasiology, Office Moscow, Moscow, Russia*
[2] *Research Center of Neurology, Moscow, Russia*
[3] *Pirogov Russian National Research Medical University, Moscow, Russia*

Background

The platelet responsiveness is undergoing the influence of pathogenesis features of disorders. We has determined distinct and interacting roles of platelet microenvironment in collagen-induced aggregation.

Methods

Collagen-induced aggregation with laser transmission aggregometry was tested in 57 women with myeloproliferative neoplasms (MPNs; mean age 36 years; Group I) and in 76 women with chronic cerebrovascular diseases (CCVD) comorbided with MPNs (mean age 65 years; Group II). Microenvironment was considered to clotting factors, tissue factor (TF), VWF, regulating coagulation inhibitors, angiogenesis markers, cell adhesion molecules, and cytokines including TNF. Total protein, calcium and creatine were taken into account as well.

Results

Patients in Group I had totally lower median cell counts and creatinine clearance than Group II. In the comparison the Group I showed higher fibrinogen with supressed fibrinolysis, and higher VWF associated with low ADAMTS-13, and higer thrombomodulin (650 ng/mL vs. 360 ng/mL in Group II; $p < 0.001$), and higher VEGF-A opposited with higher thrombospondin, and higher IL-10.

No differences were found in clotting factors, TF, PS and PC. Collagen-induced aggregation had the same between groups (Median 40.65%; STD 55.00 in Group I vs. Median 24.00%; STD 12.51 in Group II; $p = 0.153$).

Collagen-induced aggregation has presented correlations with PC, PS, TF in Group I, and no correlations were determined in Group II.

Data exploration analysis resulted for collagen-induced aggregation the managing trigger includes PC with paradoxically oppositing thrombomodulin that jointly performed in 53.2 of cumulative power in Group I. Residual power in 46.8% had the composition of fXII, TF, sICAM and (VEGF-A+sVEGF-R2). In Group II 65.2% of controlled power belonged to PC balanced with PS with TNF and thrombospondin. Residual management was a concert of sVCAM, sICAM, VWF, fV, fXII and sVEGFR2.

Conclusions

Thus PC only is common component of both controlled triggers. This finding presumes distinct roles of platelet microenvironment in collagen-induced aggregation in women with MPNs compared in women with CCVD comorbied with MPNs. In first case great value belongs to residual control that has managed by endothelium-leukocyte-platelet interactions with TF participation. In second

case there are added proinflamatory with antiangiogenic effects adjusted with clotting factors and endothelial dysfunction level.

1.21.5. C0341 New Insights on Calcium Signaling and Platelet Function Following Estrogen Receptors Stimulation

Monica Battiston [1], Keith Neeves [2], Denise De Zanet [3], Elisabetta Lombardi [1], Francesco Agostini [1], Alessandro Da Ponte [1], Cristina Durante [1], Luigi De Marco [1], Mario Mazzucato [1]

[1] *CRO IRCCS National Cancer Institute, Stem Cell Unit, Aviano, Italy*
[2] *Chemical and Biological Engineering Department, Colorado School of Mines, Colorado, USA*
[3] *Polytechnic Department of Engineering and Architecture, University of Udine, Aviano, Italy*

Background

Oral estrogen treatment in men and women is a risk factor for venous thrombosis (VT): platelets (PLTs) responses, mediated through estrogen receptors (ERs), may be involved in this process. PLTs express beta-ERs (ERβ) on their membranes but alpha-type ERs (ERα), associated with mitochondria, have also been identified. Different ERs expression could influence the procoagulant activity of PLTs not only through functional mechanisms that require changes in PLT energy (for example expression of surface receptors that influence adhesion, granular secretion, generation of free radicals derived from oxygen) but also above all signal mechanisms, in particular the modulation of calcium ions [Ca^{2+}] or nitric oxide release

Methods

We performed confocal dynamic *real time* experiments by perfusing blood samples of healthy donors at different shear rates (250–1500 s^{-1}) to analyze platelets [Ca^{2+}] dynamics, adhesion and thrombus formation on type I collagen substrate in different conditions. We labeled PLTs with different calcium probes: FLUO 3-AM (8 μM, for cytosolic [Ca^{2+}] detection) and RHOD 2-AM (5 μM, for mitochondrial [Ca^{2+}] detection). We incubated PLTs with or without selective ERs agonists: 10 μM PPT (2,3-Bis(4-hydroxyphenyl)propionitriel) for ERα and 10 μM DPN (1,3,5-Tris(4-hydroxyphenyl)-4-propyl-1Hpyrazole) for ERβ. In some experiments we incubated PLTs with 10 nM 17β-estradiol (E2), the natural endogenous hormone.

Results

We observed a close relationship between mitochondrial and cytosolic [Ca^{2+}] changes. We demonstrated that, acting on the ERα receptors with the agonist PPT, the cytosolic calcium variations were comparable to those of the control, while 17β-estradiol, which act on ERβ (the most expressed isoform), significantly increased platelet activation, measured both in terms of cytosolic and mitochondrial [Ca^{2+}] and thrombus formation. On the contrary, experiments performed with the addition of DPN, a different ERβ selective agonist, showed reduced cytosolic [Ca^{2+}] oscillations, mitochondria calcium uptake and a marked decrease in platelet thrombus volumes measured on type I collagen.

Conclusions

Our results demonstratethat estrogen receptors (ERs) play an important role on platelet activation, in close relation with mitochondrial calcium uptake, under flow conditions. Our studies provide further information to help unravel the mechanisms involved in platelet activation driven by non genomic ERs engagement.

2. Oral Presentations

2.1. Venous Thromboembolism I

2.1.1. C0173 Predicting Recurrence after Unprovoked Venous Thromboembolism: Retrospective Validation of the Damoves Score

Ana Isabel Franco Moreno [1], Marìa Josè Garcìa Navarro [2], Cristina Lucìa De Ancos Aracil [3], Alejandra Gimeno García [4], Carmen Montero Hernández [4], Ana Villa Martìnez [4], VÌctor Piedrafita Mateo [4], Judith Ortiz Sánchez [4], Irene Carmen Sanz Acevedo [4], Josè Manuel Ruiz Giardìn [3]

[1] *Torrejon University Hospital, Internal Medicine, Madrid, Spain*
[2] *Torrejon University Hospital, Madrid, Spain*
[3] *Fuenlabrada University Hospital, Madrid, Spain*
[4] *Torrejon University Hospital, Madrid, Spain*

Background

In patients with unprovoked venous thromboembolism (VTE), the optimal duration of anticoagulation (AC) is anchored on estimating the risk of disease recurrence. In Eur J Intern Med (2015), we presented our results of the original DAMOVES score, which was derived in 398 patients with a first unprovoked VTE. Based on 7 parameters: age, sex, body mass index (BMI), D-dimer level during AC, factor VIII coagulant activity, genetic thrombophilia and varicose veins, we developed a nomogram for prediction of recurrence in an individual patient with VTE. The aim of this study was to externally validate this nomogram in patients with unprovoked VTE.

Methods

A retrospective review was performed on a cohort of patients with unprovoked symptomatic VTE from department of Internal Medicine of Torrejón University Hospital between August 2012 and October 2015. For the sake of this analysis, only patients with unprovoked VTE and who had completed at least 3 months of AC were included. We determined the proportion of patients classified as low- vs. higher-risk of VTE recurrence according to DAMOVES score (for this purpose, based on a consensus that an annual VTE recurrence rate below 5% was an acceptable risk; according to the nomogram, a score less than 11.5 points was considered a low recurrence risk). The Receiver Operating Characteristic (AUC) reflects the ability of the model to discriminate between patients with low- vs. higher-risk of VTE recurrence. In all statistical analyses, a p-value < 0.05 was considered significant

Results

A total of 121 patients with unprovoked VTE were included for the analysis. The median follow-up was 18 months after discontinuation the AC therapy. The proportion of VTE recurrence was 6.61% (8/121). In all patients, VTE recurred spontaneously. When applying, the cut-off point from the nomogram, 35 (28.92%) out of 121 subjects were categorized as having a low-risk of recurrent VTE, and 86 (71.07%) as having a high-risk. Within these two categories, the observed prevalence of recurrent VTE was 2.85% (1 out of 35 subjects) in the low-risk category, and 20% (7 out of 86) in the high-risk category. The AUC of the nomogram in the external validation cohort was 0.83 ([95% confidence interval, 0.743–0.810], p-value < 0.001). The model showed good calibration. The Hosmer-Lemeshow test showed consistent results (p-value = 0.125)

Conclusions

DAMOVES score may be suitable for identifying patients with unprovoked VTE who are at low risk of VTE recurrence

2.2. Atherosclerosis

2.2.1. C0063 an International Collaboration between Sweden and France to Assess the Risk Factors of Thrombosis in Immune Thrombocytopenia Adults

Charlotta Ekstrand [1], BÈrangËre Baricault [2], Marie Linder [3], Margaux Lafaurie [2], Laurent Sailler [4], Maryse Lapeyre-Mestre [2], Helle Kieler [3], Shahram Bahmanyar [3], Guillaume Moulis [4]

[1] *Karolinska Institutet, Department of Medicine, Stockholm, Sweden*
[2] *University of Toulouse, Toulouse, France*
[3] *Karolinska Institutet, Sweden*
[4] *University Hospital of Toulouse and University of Toulouse, Toulouse, France*

Background

Immune thrombocytopenia (ITP) is a rare autoimmune disease leading to thrombocytopenia and spontaneous bleeding. Previous studies have shown that ITP patients have an increased risk of venous and arterial thrombosis as compared with the general population. This is potentially due to hyperactive, prothrombotic platelet release from the bone marrow. However, the risk factors for thrombosis in ITP remain not well known. The aim of this study was to assess the incidence and to identify possible risk factors for thrombosis in France and Sweden in ITP adults.

Methods

France and Sweden have national health databases with coverage of more than 98% of the population, recording of in- and out-patient hospital diagnoses, procedures and drug dispensing data, both databases have been previously validated. ITP patients were identified by the D69.3 code of the international classification of diseases, version 10 between 2009 and 2015 in France, 2009 and 2016 in Sweden. Only incident primary ITP adults were included. First arterial and venous thrombosis after ITP diagnosis were identified by in-hospital diagnosis codes. Follow-up started at ITP diagnosis, and ended at first thrombosis, death, splenectomy or end of follow-up, whichever occurred first. Association between thrombosis and factors such as comorbidities, exposure to drugs, age and sex were estimated using Cox proportional hazard models.

Results

The Swedish cohort included 2490 patients and the French cohort 7219. The incidence of venous thrombosis was 6.50 (95% CI: 5.00–8.40) and 6.99 (95% CI: 5.90–8.20) per 1000 person-years in Sweden and France, respectively. The incidence of arterial thrombosis was 14.70 (95% CI: 12.40–17.50) and 15.42 (95% CI: 13.83–17.20). Mean age at ITP diagnosis was 59 and 58 years, respectively. Other risk factors for thrombosis were similar in both countries. Preliminary results show an increased risk with: history of thrombosis, increasing age, corticosteroids and male sex (only arterial). Complete analysis is ongoing.

Conclusions

The epidemiology of thrombosis in ITP and risk factors for thrombosis in ITP is similar in France and Sweden.

2.2.2. C0309 Otogenic Lateral Sinus Thrombosis in Children: Are There Prognostic and Predictor Factors? Experience of 25 Cases and a Proposal of a Management Protocol

Silvia Foligno [1], Alessandro Scorpecci [2], Michela Massoud [1], Sara Giannantonio [2], Paola Zangari [3], Giovina Di Felice [4], Antonio Minozzi [4], Pasquale Marsella [1], Matteo Luciani [1]

[1] *Department of Hematology Oncology and Transfusion Medicine, Bambino Ges Children's Hospital, IRCCS, Rome, Italy*
[2] *Department of Audiology and Otosurgery Unit, Bambino Ges Pediatric Hospital, Italy*
[3] *Department of Immmuninfection Diseases, Bambino Ges Childrenís Hospital, Rome, Italy*
[4] *Department of Laboratories, Bambino Ges Children's Hospital, IRCCS, Rome, Italy*

Background

Otogenic lateral sinus thrombosis (OLST) is a rare but potentially fatal disease affecting the pediatric population, generally occurring as a complication of otitis media and mastoiditis. So far, no specific guidelines for OLST treatment have been published, and only guidelines and recommendations for cerebral venous thrombosis are available. Our aim is describe from our experience the prevalent clinical, laboratory and radiological features of OLST in children. We attempted to find possible clinical predictors of neuroradiological outcome. Finally, we propose a management algorithm derived from our experience.

Methods

A retrospective review was conducted of the clinical records of patients affected by OLST, treated in Bambino Gesù Children's Hospital from 2006 to 2017. The inclusion criteria were pediatric age (0–16 years) and definite OLST diagnosis confirmed by a pre- and post-contrast CT or venography-MRI (vMRI) scan. Our primary outcome measure was early (1–2 months) and late (6 months) sinus recanalization assessed by means of neuroimaging.

Results

25 patients (8 females, 17 males, mean age at diagnosis = 6 ± 3 years) were included. A genetic abnormality associated with thrombophilia was found in 23 (92%) patients, the most frequent conditions being heterozygous or homozygous C677T methyl-tetrahydropholate reductase and factor V Leiden mutations. At diagnosis, anticoagulant treatment with low molecular weight heparin (LMWH) was started in all patients, while surgical treatment, consisting of mastoidectomy and tympanostomy tube insertion, was performed in 16/25 (64%) subjects. Follow-up neuroimaging showed lateral sinus recanalization in 12/25 (48%) of patients 1–2 months after diagnosis and in 17/25 (68%) after 6-months. At multivariate logistic regression analysis, no significant predictor of early and late neuroradiological outcome was found.

Conclusions

All children with OLST should be screened for thrombophilia in order to identify the risk of recurrences, to establish the discontinuation of anticoagulant therapy and to assess the need for future anti-thrombotic prophylaxis. However, no clinical or predisposing factors can influence the neuroradiology outcome. Notwithstanding, immediately after OLST diagnosis, anticoagulant treatment with LMWH should be started according to international guidelines. Our experience suggests that surgical treatment should not be indicated in all patients, but decided on a case-to-case basis.

2.2.3. C0281 Diagnostic Difficulties of Coronary Embolism

László Balogh [1], Péter Óvári [2]

[1] *University of Debrecen, Cardiology and Cardiac Surgery, Debrecen, Hungary*
[2] *University of Debrecen, Debrecen, Hungary*

Background

Acute myocardial infarction is caused by plaque rupture and local thrombus formation in majority of the cases, but there are some other, rare mechanisms like coronary embolism (CE), which can also lead to coronary occlusion. The prevalence is referred in the literature between 2–3% of all acute coronary syndrome (ACS) cases. There is no reliable and validated diagnostic criterion system, which can help in differential diagnosis and individualised therapy.

Methods

Our aim was to establish a score system by which one is able to give the probability of embolic origin of an ACS case. The established score system classifies ACS cases into 'sure', 'likely', 'probable' and 'unlikely' regarding coronary embolism. Scoring the case into 'probable' category means, that the case requires further evaluation (e.g., transesophageal echocardiography) to confirm or exclude the diagnosis of CE. More than 150 CE case reports were reviewed between 2005 and 2017. The factors on which the diagnosis was based on were collected and weighted into major and minor determinants.

Results

Four major and four minor criteria were established. Major criteria are: presence of embolic source, no plaque disruption by intracoronary imaging, lack of stenosis after thrombus aspiration and very distal coronary or double acute arterial occlusion. Minor criteria are lack of cardiovascular risk factors, young age (≤50 years), hypercoagulability and previous negative coronary angiography. Validation of the score system was performed on 1052 patients presented in our institution with ST elevation myocardial infarction (STEMI) and treated with primary percutaneous intervention (pPCI) between 2014 and 2016. According to our scoring 21 cases were categorised into 'likely' category and more deep investigation of these cases revealed high clinical probability as well.

Conclusions

The CE score system is applicable and suitable to differentiate embolic and non-embolic acute coronary occlusions and it can easily be used in everyday clinical practice especially in embolism suspicious cases. Thrombus aspiration has been pushed into the background in the treatment of ACS because it does not significantly influenced clinical outcomes. However, in CE cases it can help to clarify the aetiology and sometimes aspiration alone without stent implantation is an adequate therapy for complete revascularisation.

2.3. Miscellanea

2.3.1. C0048 Evaluation of the Plasmic Score for the Prediction of ADAMTS13 Activity in Patients with Thrombotic Microangiopathies

Giovanni Tiscia [1], Filomena Cappucci [2], Potito Scalzulli [2], Nicola Cascavilla [2], Cosima Battista [3], Antonio Abrescia [4], Filippo Aucella [2], Caterina Buquicchio [4], Maurizio Bregante [5], Giovanna DAndrea [6], Bruno Di Paolo [7], Giulio Giordano [5], Barbara Infante [8], Silvia Piano [5], Prudenza Ranieri [3], Livio Tullo [8], Angelo Ostuni [3], Elvira Grandone [2]

1 *Casa Sollievo della Sofferenza, Hemostasis and Thrombosis, San Govanni Rotondo, Italy*
2 *Casa Sollievo della Sofferenza, Hospital/Research Institute, Italy*
3 *Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy*
4 *Ospedale "Mons. Dimiccoli", Barletta, Italy*
5 *Ospedale "A. Cardarelli", Campobasso, Italy*
6 *Azienda Ospedaliera Universitaria Riuniti, Foggia, Italy*
7 *Ospedale "San Pio da Pietrelcina", Vasto, Italy*
8 *Azienda Ospedaliera Universitaria Riuniti, Foggia, Italy*

Background

The *PLASMIC* score was proposed to predict the likelihood of a severe ADAMTS13 deficiency in the context of Thrombotic MicroAngiopathies (TMAs), to promptly identify and properly treat acute patients with suspected Thrombotic Thrombocytopenic Purpura (TTP). We evaluated the diagnostic performance of the score in patients consecutively referred to our Unit.

Methods

From 2012 to 2017, we tested ADAMTS13 in 42 patients diagnosed with TMA. From electronic records we extracted clinical and laboratory data referred to time of blood drawn for ADAMTS13 testing: full data were available for 25 of them. The score evaluates 7 parameters (1 point each): -platelet count <30 × 10^9/L, -hemolysis variables (reticulocyte count >2.5%, undetectable haptoglobin, or indirect bilirubin >2 mg/dL), -no active cancer, -no history of cell transplant, -mean corpuscular volume (MCV) <90 fL, -INR < 1.5, and -creatinine level <2 mg/dL. Scoring system is defined low (0–4), intermediate (5), high (6–7) likelihood of ADAMTS13 <10%. Relevant clinical data, i.e., therapeutic procedures and immunosuppressive agents use, were collected. A ROC curve was generated and the Area Under Curve (AUC) was calculated to test the discrimination value.

Results

The *PLASMIC* score showed a good discrimination performance with a resulting AUC of 0.89 (95% CI 0.76–1.00; $p = 0.008$). According to the prediction model, we observed 6 patients in the low risk group, 4 and 15 in the intermediate and high-risk group, respectively. No severe deficiency was found in any case in the low-risk group, whereas a severe deficiency was found in 2 out of 4 intermediate-risk group patients and in 14 out of 15 high-risk group patients. In the low-intermediate risk group (0–5), we observed 2 short-term (i.e., within 1 week after the disease onset) deaths, both in patients with severe sepsis. All 25 patients were treated by Plasma EXchange (PEX) and steroids. Nine patients [4 with a refractory TTP and 5 with relapsed TTP (2 of 3 patients having previous episodes of TTP)] were also treated by rituximab. We identified a TTP relapse in 3 (1 with score of 5) severely-deficient patients: in 2 of them (score = 6), who were diagnosed with cancer (pancreatic cancer and myeloproliferative neoplasm), a long-term death occurred.

Conclusions

In our patients, *PLASMIC* score has a good predictive value of the pretest likelihood of a severe ADAMTS13 deficiency. Further research is needed to confirm present data.

2.3.2. C0050 Apolipoproteins C-I, -II, -III and E, Coagulation Activity and Risk of Venous Thromboembolism

Fernanda Andrade Orsi [1], Willem Lijfering [2], Frits Rosendaal [2], Suzanne Cannegieter [2]

[1] *Department of Clinical Epidemiology, Leiden University Medical Center, Department of Clinical Epidemiology, Leiden, The Netherlands*
[2] *Leiden University Medical Center, Leiden, The Netherlands*

Background

Recently, apolipoproteins (apos) C-I, C-II, C-III and E have emerged as risk factors for arterial cardiovascular disease. Whether the same holds true for venous thromboembolism (VTE) is currently unknown. However, an association between apo and VTE may be present as apo might have proinflammatory and prothrombotic properties. Here, we investigated the association of apoC-I, C-II, C-III and E with procoagulant factors, natural anticoagulantsand inflammatory markers, and further with VTE risk.

Methods

A total of 127 patients with VTE and 299 controls were randomly selected from the MEGA study. Apolipoproteins were quantified using multiple reaction monitoring mass spectrometry and theirlevels were analysed as continuous (per SD increase) and as categorical variables (tertiles). Regression models were adjusted for age, sex, statin and estrogen use, alcohol intake, body mass index, and diabetes. Mediation analyses assessed whether the association between apolipoproteins and VTE could be explained by coagulation or inflammatory markers.

Results

Increase in apoC-I, C-II, C-III and E levels were associated with increase in levels of vitamin K dependent procoagulant factors (II, VII, IX, X) and natural anticoagulants (protein C and S). Additionally, increase in apoC-III and apoE was associated with increase in levels of factor (F)VIII and von Willebrand factor (VWF). Increase in C-reactive protein (CRP) levels was observed with increasing apoE levels only. The risk of VTE was not affected by apoC-I levels. ApoC-II levels were associated with 1.25 (95% CI 0.93; 1.69) fold increased risk of VTE and no dose response relation was observed over tertile categories. ApoC-III continuous levels were associated with a 1.11 (95% CI 0.90; 1.37) fold increase in VTE risk and the upper apoC-III tertile presented a 1.26 (95% CI 0.70; 2.26) fold increased VTE risk compared with the lowest tertile. The upper apoE tertile showed a 1.85-fold (95% CI 1.0; 3.42) increased risk of VTE compared with the lowest tertile. The relative risk of VTE for the upper apoE tertile decreased 20% when adjusted for FVIII and 23% when adjusted for VWF. Other potential mediators did not materially affect risk estimates for VTE.

Conclusions

ApoC-I, C-II, C-III and E were associated with both procoagulant factors and natural anticoagulants and higher apoE levels increased the risk of VTE. The association between apoE and venous thromboembolism was partially explained through mediation via FVIII and VWF.

2.4. Venous Thromboembolism II

2.4.1. C0017 Initial Results of Oral Thrombolytic Agent Clinical Application

Pavel Madonov [1], Svetlana Mishenina [2], Dmitriy Kinsht [2], Stanislav Leontiev [3], Sergey Zotov [4], Maksim Ufimtsev [4]

[1] *Novosibirsk State Medical University, Pharmaceutical Faculty, Novosibirsk, Russia*
[2] *Novosibirsk State Medical University, Novosibirsk, Russia*
[3] *Pirogov Russian National Research Medical University, Moscow, Russia*
[4] *South Ural State Medical University, Chelyabinsk, Russia*

Background

Standard therapy for deep vein thrombosis of the lower extremities includes anticoagulants and antiaggregants. The use of thrombolytic plasminogen activators is seriously limited, as they cause dangerous complications. We have developed an oral thrombolytic based on subtilisin immobilized on polyethylene glycol—Trombovazim®, and present the main results of the study on the efficacy and safety of lower limbs deep vein thrombosis treatment with the inclusion of Trombovazim® in therapy.

Methods

A multicenter, randomized, double-blind, placebo-controlled clinical trial.

All 154 volunteers who took part in the clinical trial "VETTER-1" received only conservative standard therapy, including anticoagulants, non-steroidal anti-inflammatory drugs and phlebotrophic drugs. None of the participants underwent surgical intervention. The mode of mechanical compression was not taken into account.

All participants were divided into 2 groups—control and observation. The control group (n = 59) received a placebo, and the observation group was divided into 3 subgroups who received tested drug at a dose of 1600, 3200 and 4800 U/day. The drug effectiveness was determined by means of an objective control method—blood flow ultrasound angioscanning. Statistical treatment of the results was carried out after trial completion.

Results

Comparison of revascularization in the zone of compromised blood flow revealed a distinct dose-dependent effect: subgroups that received drug at a dose of 1600, 3200 and 4800 U/day showed a relative frequency of positive dynamics of 0.7070 (+21%, $p = 0.0535$, $n = 28$), 0.7257 (+24%, $p = 0.0188$, $n = 32$) and 0.7470 (+28%, $p = 0.0082$, $n = 35$) respectively. The study did not reveal any negative dynamics in the observation group, and recorded 3 such cases in the control group. The difference between frequency of thrombus lysis in the observation group was 0.87 versus 0.63 in the control group ($p = 0.07$). All participants who received tested drug at a dose of 4800 U/day had complete dissolution of thrombus. The safety assessment was based on the analysis of vital functions, laboratory and instrumental examination of subgroup receiving the maximum drug dosage, and did not reveal any undesirable events at all visits during trials.

Conclusions

The use of the oral thrombolytic agent at a dose of 3200 and 4800 U/day statistically significantly increases the effectiveness of the treatment. The tested drug doses does not cause hemorrhagic complications and is well tolerated by patients.

2.4.2. C0294 the Diagnosis of Isolated Subsegmental Pulmonary Embolism Is Poorly Reproducible in Symptomatic Patients

Raffaele Pesavento [1], Davide Ceccato [2], Giorgio De Conti [3], Raffaella Motta [4], Paolo Prandoni [5]

1 *University of Padua, Department of Internal Medicine, Padua, Italy*
2 *Dept.of Internal Medicine-University of Padua, Padua, Italy*
3 *U.O di Radiologia I, Azienda Ospedaliera Universitaria di Padova, Padua, Italy*
4 *Department of Radiology, University of Padua, Padua, Italy*
5 *Department of Cardiothoracic and Vascular Medicine, University of Padua, Padua, Italy*

Background

Multi-detector row spiral computed tomography (MDCT) is currently the exam of reference for the diagnosis in patients with clinical suspicion of acute pulmonary embolism (PE). Its ability to evaluate the sub-segmental pulmonary arteries increases the number of diagnoses of isolated sub-segmental pulmonary embolism (ISSPE). The prognostic value of ISSPE is still unclear and whether to offer an anticoagulant treatment in the affected patients remains controversial. Thus, a reliable and reproducible diagnosis of ISSPE is important before exposing patients to potentially dangerous anticoagulation. Very few available studies specifically evaluated the reproducibility of ISSPE diagnosis, showing contrasting results. The aim of this study was to assess the inter-observer agreement of the diagnosis of ISSPE in a patient population with clinical suspicion of PE.

Methods

We made a retrospective review of the MDCT images requested for a clinical suspicion of PE and included in the electronic archive of our two departments of Radiology. A selection of 71 MDCT scans of consecutive outpatients admitted in the ER for suspected PE was done by two senior thoracic radiologists, according to the following criteria: images in which at least one sub-segmental intraluminal filling defect was established as present without any more proximal defects and images without defects, randomly selected. The suspicion of PE was based on history, physical findings, chest radiography, blood gas findings, simplified Wells or simplified Geneva score, and D-Dimer value in patients with low clinical probability. The radiological evaluation was performed using a 64-detector row CT scanner. The selected images were randomly distributed and reviewed separately and prospectively by three senior thoracic radiologists, blind to the findings and previous reports of reading. The multi-reader kappa coefficient was calculated to assess the inter-reader agreement.

Results

A concordant diagnosis or exclusion of ISSPE was done in 10 (14.1%) and 49 patients (69.0%), respectively. A discordant diagnosis was done in 11 patients (15.5%). The inter-reader kappa coefficient was equal to 0.52 (95% CI, 0.28–0.75).

Conclusions

The inter-reader agreement for the diagnosis of symptomatic isolated sub-segmental PE was unexpectedly low and raises concerns about its accuracy and reproducibility, even using high definition MDCT scanners.

2.4.3. C0327 Impact Analysis of Prognostic Stratification for Pulmonary Embolism: The Iapp Study

Marco Donadini [1], Walter Ageno [2], Marco Cei [3], Francesco Dentali [2], Patrizia Fenu [3], Nicola Mumoli [4], Fulvio Pomero [5], Roberta Re [6], Gerardo Palmiero [7], Laura Spadafora [5], Alessandro Squizzato [2]

1 *ASST Sette Laghi, Clinical Medicine, Varese, Italy*
2 *University of Insubria, Insubria, Italy*
3 *Azienda USL6 Livorno-Presidio Ospedaliero di Cecina, Cecina, Italy*
4 *Azienda USL6 Livorno-Presidio Ospedaliero di Livorno, Livorno, Italy*
5 *Azienda Ospedaliera Santa Croce e Carle, Cuneo, Italy*
6 *Azienda Ospedaliera 'Maggiore della Carità, Novara, Italy*
7 *Azienda USL12 Viareggio-Ospedale Versilia, Viareggio, Italy*

Background

Pulmonary Embolism Severity Index (PESI) is an extensively validated prognostic score on the risk of adverse outcomes after acute pulmonary embolism (PE). However, there is no evidence that adopting PESI changes physicians behaviour, improves patients outcomes and/or reduces costs.

The aim of the study is to demonstrate that the use of PESI will help physicians to correctly identify PE patients at low-risk of adverse outcomes, thus discharging them earlier and reducing the duration of hospital stay (LOS)

Methods

The iAPP study (Impact Analysis of Prognostic Stratification for Pulmonary Embolism) is a multicenter randomized controlled trial, enrolling consecutive adult outpatients with an objective diagnosis of acute PE. Within 48 h from diagnosis, treating physicians are centrally randomized, for every patients, to stratify PE prognosis by formally calculating PESI and reporting it in the clinical records form or to routine practice. Randomization is stratified by the intented treatment choice.

The primary outcome is the median LOS. Secondary efficacy outcomes include the proportion of patients undergoing complete home-treatment, post-discharge visits to emergency department or hospital re-admissions. Safety outcomes include mortality, PE complications, hospital-acquired infections or iatrogenic complications.

To find a statistically significant difference ($p < 0.05$) between the median LOS of the two groups, with an α error of 0.05 and a statistical power of 80%, 220 patients for each group need to be enrolled.

The study was approved by the ethics committee of the participating centers.

ClinicalTrials.gov identifier NCT03002467

Results

The study is ongoing. 63 patients were enrolled from September 2016 until December 2017 at five centers. The mean age was 71.7 years (SD 12.9) and 31 patients were females. Treating physicians were randomized to use PESI for 35 patients, who presented a mean PESI score of 122.3 (SD 45.5), or to perform routine practice for 28 patients. The mean LOS was 10.6 days (SD 8.1) and it tended to be

shorter among patients from PESI group as compared to those from the routine practice group, without reaching statistically significance (9.9 days, SD 9.2, versus 11.4 days, SD 6.8, respectively, $p = 0.49$).

Conclusions

The iAPP study is expected to provide an impact analysis on the use of PESI in clinical practice, in terms of changing physicians behaviour on the duration of hospitalization. The recruitment is proceeding slower than expected.

2.4.4. C0188 Rosuvastatin Use Reduces Thrombin Generation in Patients with Venous Thromboembolism: Results from a Randomized Clinical Trial

Fernanda Andrade Orsi [1], Joseph Biedermann [2], Marieke Kruip [3], Felix van der Meer [4], Frits Rosendaal [5], Mettine Bos [4], Frank Leebeek [3], Suzanne Cannegieter [5], Willem Lijfering [5]

[1] *Department of Clinical Epidemiology, Leiden University Medical Center, Department of Clinical Epidemiology, Leiden, The Netherlands*
[2] *Star-Medical Anticoagulation Clinic, Rotterdam, The Netherlands*
[3] *Department of Hematology, Erasmus University Medical Center, The Netherlands*
[4] *Department of Internal Medicine, Section of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands*
[5] *Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands*

Background

Although the use of statins after a venous thromboembolism (VTE) is appealing to prevent recurrence, *it cannot be recommended* since the effect of statins on hemostasis is not proven. The STAtins Reduce Thrombophilia (START) trial was aimed to investigate if statin improves the coagulation profile in patients with prior VTE.

Methods

After anticoagulation withdrawal, patients with VTE were randomized to rosuvastatin 20 mg/day for 4 weeks or no intervention. Thrombin generation was assessed at baseline and at end of study by Calibrated Automated Thrombogram. The primary endpoint was the difference in change in endogenous thrombin potential (ETP) and peak between rosuvastatin users and non-users. Analyses were done by intention to treat and regression models were adjusted for age and sex.

Results

The study comprised 245 patients, 126 rosuvastatin users and 119 non-users. Mean age was 58 years, 61% were men, 49% had unprovoked VTE and 75% presented cardiovascular (CV) risk factors. In rosuvastatin users, mean ETP was 25 nM min (95% CI, −72 to 22) lower, while in non-users ETP was 97 nM min (95% CI, 41 to 154) higher at the end of the study. The mean difference in ETP change was −120 nM min (95% CI, −193 to −48) in rosuvastatin users versus non-users, which is equivalent to a treatment effect of 10% reduction in ETP. The difference in peak change was −12 (95% CI, −26 to 2) in rosuvastatin users versus non-users. Time to peak decreased in rosuvastatin users, the difference was −0.2 min (95% CI, −0.4 to 0.03). Other thrombin generation parameters did not change substantially. All these results were not materially affected when we restricted the analyses to patients who did not develop an acute infection during follow-up, and when we adjusted our findings for age and sex. Predefined subgroup analyses with regard to sex and VTE cause (provoked or unprovoked) revealed similar results as in the main analysis, while the reduction in ETP by rosuvastatin appeared more pronounced in participants with CV risk factors and with pulmonary embolism than in those without CV risk factors and with deep vein thrombosis, respectively.

Conclusions

Rosuvastatin 20 mg/day improved the coagulation state in patients with VTE by reducing thrombin generation after anticoagulation withdrawal. These findings provide clinical rationale for the conduction of randomized controlled trials to evaluate the effectiveness of rosuvastatin in decreasing the risk of recurrent VTE.

2.4.5. C0077 an Italian Registry on Risk Factors for Venous Thromboembolism in Blood Donors Clinicaltrials.Gov: NCT03282747

Elvira Grandone [1], Angelo Ostuni [2], Lazzaro di Mauro [3], Nadia Coffetti [4], Anna Turrini [5], Giobatta Cavallero [6], Patrizia Vergura [7], Filomena Cappucci [7], Antonio de Laurenzo [7], Michela Villani [7], Nicola Di Renzo [8], Alberto Tosetto [9], Maurizio Margaglione [10]

1 *Viale Padre Pio, San Giovanni Rotondo, Italy*
2 *Azienda Ospedaliero-Universitaria, Policlinico di Bari, Bari, Italy*
3 *I.R.C.C.S. Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy*
4 *A.S.S.T. Bergamo Est, Seriate, Italy*
5 *Ospedale "Sacro Cuore-Don Calabria" Negrar, Verona, Italy*
6 *"Santa Croce e Carleî Hospital, Cuneo, Italy*
7 *I.R.C.C.S. Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy*
8 *P.O. Vito Fazzi, Lecce, Italy*
9 *Ospedale S. Bortolo, Vicenza, Italy*
10 *University of Foggia, Foggia, Italy*

Background

The impact of several risk factors in the occurrence of venous thrombosis with/without pulmonary embolism, collectively called venous thromboembolism (VTE), is well known in patients who previously suffered from VTE. Little is known about their impact in healthy population.

Methods

We evaluated the incidence of risk factors for VTE in a population of Italian blood donors: BMI, blood group, previous transfusions, plaster cast, previous surgery, gross veins, history of venous thrombosis and/or use of anticoagulation drugs. The study started in 1 June 2017. Information were collected by means of a self-administered questionnaire. All analyses were performed using SPSS version 11.0. Odds ratios (ORs) for risk factors for VTE were calculated. Proportions were compared using Fisher exact test or c2-test where appropriate. Adjusted OR and 95% confidence interval (CI) were calculated using logistic regression models that controlled for potential confounding variables such as age, BMI, blood group, surgery, plaster cast, immobilization, transfusion.

Results

Until 20 November, 5506 questionnaires were collected. 4120 (75.3%) men and 1354 (24.7%) women were consecutively enrolled. Mean age (+SD) was 42.7 + 12.3 years in men, 38.4 + 13.4 years in women ($p < 0.001$), BMI was 26.05 + 4.14 in men and 24.5 + 4.93 in women ($p < 0.001$). Group 0 was observed in 48% and non-0 in 52%. With regards to smoking habits, no significant difference was observed between men and women with the exception for ex-smokers (143/1354 women vs. 786/4120 men, $p < 0.001$). A history of vein thrombosis (mostly superficial ones) was referred by 36 (0.7%) subjects, gross veins by 320/5442 (5.9%), previous surgery by 1896/5478 (34.6%). Previous transfusion was reported by 73/5019 (1.5%) individuals and 236/5268 (4.5%) had used at least once anticoagulation drugs. At univariate analysis, gross veins, bed rest/plaster cast, surgery and transfusions were associated with vein thrombosis. At logistic regression, a significantly and independent association was found between VTE and gross veins (OR: 15.8, 95% CI 7.7–32.6), plaster cast/bed rest (OR: 2.3, 95% CI 1.0–5.3) and transfusion (OR: 5.1, 95% CI 1.3–19.5).

Conclusions

To the best of our knowledge, this is the first study in a large series of blood donors aimed at investigating the distribution of risk factors for VTE. We find that gross veins, plaster cast/bed rest and previous transfusion are independent risk factors for VTE.

2.4.6. C0343 Venous Thromboembolism in Hospitalized Pediatric Patients: Generation of a Risk Model from a Single-Center Prospective Nested Case-Control Study

Giovanni Del Borrello [1], Giulia Maria Matta [2], Marta Baricco [2], Elena Giachetti [2], Chiara Maddaloni [2], Alice Viano [2], Paola Saracco [2]

[1] *Ospedale Infantile Regina Margherita, Ematologia Pediatrica Torino, Piemonte, Italy*
[2] *Ospedale Infantile Regina Margherita, Piemonte, Italy*

Background

Hospital-associated venous thromboembolism (HA-VTE) is increasingly recognized as a complication of high-level contemporary pediatric care. Much effort has been deployed over the last few years to define a risk stratification model to identify hospitalized children in need of thrombo-prophylaxis. The body of evidence so far come from retrospective studies conducted mainly in the US. The objective of this study is to derive a novel HA-VTE risk prediction rule based on observational prospective data in a tertiary care pediatric hospital in Italy.

Methods

Children and infants (>28 days old) who developed VTE during their hospitalization at Regina Margherita Children Hospital (Turin, Italy) from 1 January 2014 to 31 July 2016 were enrolled in this prospective nested case-control study. Four age- matched hospitalized control children were randomly selected for each case of HA-VTE. Univariate and multivariate analyses were used to identify independent risk factors and develop a risk-prediction model. ROC curve and AUC were derived. The model has been internally validated on three subgroups of patients: critically-ill children, non critically-ill children and patients with hematologic/oncologic diseases.

Results

40 cases of HA-VTA occurred during the study period, yielding an average incidence of 27.5 per 10,000 hospitalized children per year. A 9-point risk score was derived based on 4 statistically-significant risk factors: immobilization >72 h, trauma, systemic infection, hospitalization ≥7 days. A risk score ≥4, identified high-risk children with a sensitivity of 57.5%, specificity of 93.13% and AUC of 0.823 (95% CI 0.747–0.897). The estimated risk for HA-VTE with scores of 2–3 and 4 or more were respectively 0.23% and 2.26%. The application of the score allowed to classify correctly 85.5% of critically-ill children, 89% of non critically-ill children, 80% of patients with hematologic and oncologic diseases.

Conclusions

The application of a risk prediction model to all hospitalized children may help the clinician in the decision-making regarding thrombo-prophylaxis. A multicentre, controlled intervention trial is needed.

2.5. Platelets and Inflammation

2.5.1. C0010 Platelet Rescue by Macrophage Depletion in Obese ADAMTS13 Deficient Mice at Risk for TTP

Roger Lijnen [1], Lotte Geys [2], Elien Roose [3], Karen Vanhoorelbeke [3]

[1] *Center for Molecular and Vascular Biology, Cardiovascular Sciences Leuven (N/A), Belgium*
[2] *Center for Molecular and Vascular Biology, Leuven, Belgium*
[3] *Laboratory for Thrombosis Research, Kortrijk, Belgium*

Background

Thrombotic thrombocytopenic purpura (TTP) is caused by the absence of ADAMTS13 activity. Thrombocytopenia is presumably related to the formation of microthrombi rich in von Willebrand Factor (VWF) and platelets. Obesity may be a risk factor for TTP; it is associated with abundance of macrophages that may phagocytose platelets.

Our aim was to evaluate the role of obesity and ADAMTS13 deficiency in TTP, and to establish whether macrophages contribute to thrombocytopenia.

Methods

Lean or obese ADAMTS13 deficient (*Adamts13*$^{-/-}$) and wild-type (WT) mice were injected with 250 U/kg of recombinant human VWF (rVWF), and TTP characteristics were evaluated 24 h later. In separate experiments, macrophages were depleted in the liver and spleen of lean and obese WT or *Adamts13*$^{-/-}$ mice by injection of clodronate-liposomes, 48 h before injection of rVWF.

Results

Obese *Adamts13*$^{-/-}$ mice had a lower platelet count than their lean counterparts suggesting that they might be more susceptible to TTP development. Lean *Adamts13*$^{-/-}$ mice triggered with a threshold dose of rVWF did not develop TTP, while typical TTP symptoms developed in obese *Adamts13*$^{-/-}$ mice, including severe thrombocytopenia and higher LDH levels. Removal of hepatic and splenic macrophages by clodronate injection in obese *Adamts13*$^{-/-}$ mice, before treatment with rVWF preserved the platelet counts, measured 24 h after the trigger. In vitro experiments with cultured macrophages confirmed a VWF dose-dependent increase of platelet phagocytosis.

Conclusions

Obese *Adamts13*$^{-/-}$ mice are more susceptible to the induction of TTP-related thrombocytopenia than lean mice. Phagocytosis of platelets by macrophages contributes to thrombocytopenia after rVWF injection in this model.

2.5.2. C0276 Platelet Adhesion under Flow Condition Is Significantly Affected by Hematocrit (HCT) Levels in Polycythemia Vera (PV) Patients

Sara Gamba [1], Alfonso Vignoli [2], Paola van der Meijden [3], Marina Marchetti [2], Cinzia Giaccherini [2], Frauke Swieringa [3], Hugo ten Cate [3], Guido Finazzi [2], Alessandro Rambaldi [2], Johan Heemskerk [3], Anna Falanga [2]

[1] *Hospital, Department of Immunohematology and Transfusion Medicine & the Hemostasis and Thrombosis Center*
[2] *Hospital "Papa Giovanni XXIII", Italy*
[3] *Maastricht University, Maastricht, The Netherlands*

Background

PV is characterized by a high rate of thrombosis both at diagnosis and during follow-up. Aspirin+phlebotomy with a target HCT of 45% is currently recommended in all PV patients regardless of risk status. Recently, a novel mechanism by which elevated HCT can lead to increased thrombosis risk has been described. The red blood cells could push the platelets closer to the vessel wall, thus promoting their adhesion. Aim of our study was to characterize in PV the in vitro platelet thrombus formation capacity to collagen under flow condition at an arterial-like shear rate in relation to HCT levels.

Methods

Fifty-two PV patients (26 M/26F) were enrolled after giving informed consent. Whole blood thrombus formation was performed in a parallel plate flow-chamber for 4′ at 1000 s^{-1} shear-rate over a collagen-coated surface. Thrombi were then stained with an anti-P-selectin-FITC antibody to evaluate platelet activation, and annexinV-AlexaFluor647 to detect procoagulant phosphatidylserine (PS). Results are expressed as mean ± SEM of the % of area covered by thrombi or the % of adherent platelets positive for either P-selectin or AnnexinV.

Results

Platelet adhesion was significantly increased in PV (48.9 ± 1.6%) compared to controls (37.5 ± 1.7%, $p < 0.01$). In both PV and controls, platelets forming the inner thrombus core expressed P-selectin, while PS was expressed by some platelets at the external thrombus border. Patients' thrombi were usually larger and more complex than those formed by controls' platelets. A significant (<0.005) positive correlations was found between HCT levels and either platelet adhesion and P-selectin positive platelets. No significant correlation was found between platelet adhesion and count. On the basis of the median value of HCT of our patients' population (43.7%), subjects with an HCT value above the median had a significantly higher adhesion than the subjects with an HCT below (42 ± 1.9 vs. 51 ± 2.3%, $p < 0.05$). After a multivariate analysis adjusted for sex, age, therapy and JAK2-V617F allele burden, the HCT value was found still significantly associated with platelet coverage and p-selectin expression.

Conclusions

An elevated HCT is a relevant thrombotic risk factor in PV. Our findings support the hypothesis that this is, at least in part, due to an increased platelet adhesion to the vessel wall, likely favored by local rheological factors coming from the increased red blood cell count typical of this disease.

2.5.3. C0168 Fine Adjusting Regulation of Fibrinolysis in Women with Some Disorders

Eugene Roitman [1], Andrey Momot [2], Marine Tanashyan [3], Alla Shabalina [3]

[1] *RSS Clinical Hemostasiology, Office Moscow, Moscow, Russia*
[2] *Altay Branch of NMR of Hematology, Barnaul, Russia*
[3] *Research Center of Neurology, Moscow, Russia*

Background

We studied what microenvironment factors involved in the regulation of fibrinolysis, what are layers where they are appearing as well as how deep their effect is seen within fibrinolysis, in women with some disorders.

Methods

The study included women with some myeloproliferative neoplasms (MPNs; $n = 57$; Group 1), with chronic cerebrovascular diseases (CCVD) comorbided with Ph-negative MPNs ($n = 76$; Group 2), and with acute ischemic stroke ($n = 62$; Group 3). Basing on 98 biomarkers the microenvironment was considered coagulation, anticoagulation, platelets and vascular wall, angiogenesis and cytokines, calcium, creatinine and Age including. Thrombin or its complexes or its generation markers were excluded from consideration as a priori expected.

Conceptually, fibrinolysis was considered as three consecutive layers where the first layer is plasminogen, the second layer contains interactions between tPA and PAI-1, and the third layer is presenting in D-dimer.

Results

Multivariate models indicated that in Group 1, we found that angiogenesis markers affect the first two layers of fibrinolysis. Starting from the layer "tPA and PAI-1" platelet activation with VWF and platelet-leukocyte-endothelial adhesion has gotten first place. Their influence has been reinforced with fVII and fVIII. Protein C as regulatory anticoagulant was significant only for D-dimer. The Age showed the transit effect through all fibrinolysis.

In Group 2 platelet activation with VWF demonstrated transit regulation in fibrinolysis. Endothelial effects become important starting from the layer "tPA and PAI-1" and preserved for the layer "D-dimer". Creatinine and Age were also gained and retained their significance at the same layers. Comparing with Group 1, the Protein C appeared as a regulator for plasminogen only but then it had no value at the subsequent stages.

Protein C showed similar picture in Group 3 whereas platelet activation with VWF showed managing role only at first two layers in comparison with Group 1. Interesting finding was the pronounced involvement of calcium as a regulator for interactions between tPA and PAI-1 and as well as determining parameter for D-dimer. Besides Age proved to be significant parameter only for D-dimer.

Conclusions

Predominant microenvironmental influences become characteristic to disorder. The knowledge on the leader microenvironmental trends and markers defining them contributes the understanding of unsuccessful of standard antithrombotic prevention.

2.5.4. C0181 Apolipoprotein C-III Is a Predictor of Activated Factor VII-Antithrombin Complex Levels: A New Link between Plasma Lipids and Coagulation Pathway

Federica Tosi [1], Marcello Baroni [2], Annalisa Castagna [1], Filippo Stefanoni [1], Francesca Pizzolo [1], Antonella Bassi [3], Patrizia Pattini [1], Barbara Lunghi [2], Domenico Girelli [1], Barry Woodhams [4], Francesco Bernardi [2], Oliviero Olivieri [1], Nicola Martinelli [1]

[1] *Department of Medicine, University of Verona, Verona, Italy*
[2] *Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy*
[3] *Institute of Clinical Chemistry, University Hospital of Verona, Verona, Italy*
[4] *Haemacon Ltd., Bromley, Kent, UK*

Background

Activated factor VII-antithrombin (FVIIa-AT) complex is a potential biomarker of prothrombotic diathesis, reflecting tissue factor (TF) exposure, and has been associated with mortality in patients with coronary artery disease (CAD). Previous works indicated plasma lipids as predictors of FVIIa-AT variability.

Aims: to evaluate the relationships between FVIIa-AT plasma concentration and lipid/apolipoprotein profile.

Methods

Within the framework of the Verona Heart Study we selected 666 subjects (131 CAD-free and 535 CAD, 75.3% males, mean age 61.1 ± 10.9 years) not taking anticoagulant drugs and for whom plasma samples were available for FVIIa-AT assay and for a complete lipid profile, including apolipoprotein (Apo) A-I, B, C-III, and E. FVIIa-AT plasma levels were measured by ELISA.

Results

There were significant direct correlations of FVIIa-AT levels with total and HDL cholesterol, triglyceride, Apo A-I, Apo C-III, and Apo E. Apo C-III ($R = 0.235$, $p = 7.7 \times 10^{-10}$) showed the strongest correlation. Including all the lipid parameters in an adjusted regression model only Apo C-III was a

significant predictor of FVIIa-AT levels, explaining about 5% of FVIIa-AT variability. Such result was confirmed after adjustment for sex, age, CAD diagnosis, renal function, and lipid-lowering therapies. FVIIa-AT levels increased progressively across Apo C-III quartiles from the lowest to the highest (from 74.7 [69.6–80.2] to 99.0 [91.6–107.1] pM, $p = 5.9 \times 10^{-8}$ by ANOVA with polynomial contrasts for linear trend) and such trend was confirmed in CAD, CAD-free, males and females subgroup analyses.

The rs964184 polymorphism (tagging also APOC3 gene locus), which has been linked with cardiovascular risk and plasma lipids by genome-wide association studies, was associated not only with Apo C-III levels (CC 10.5 [10.1–10.8], CG 10.8 [10.1–11.5], and GG 13.9 [11.6–16.7] pM, $p = 0.033$) but also consistently with FVIIa-AT plasma concentration, being higher in the carriers of the risk allele G (CC 81.4 [77.7–85.4], CG 89.9 [83.0–97.4], and GG 97.7 [75.7–126.0] pM, $p = 0.018$).

Conclusions

Our results indicate a strong association between Apo C-III and FVIIa-AT levels, thereby supporting the hypothesis that Apo C-III, one of the most important actor in lipid metabolism, may influence TF-FVIIa pathway with prothrombotic effects.

2.6. Awarded Oral Presentations

2.6.1. C0229 Adalimumab-Based Regimen versus Dmards for the Treatment of Venous Thrombosis in BEH ET Syndrome

Giacomo Emmi [1], Antonio Vitale [2], Elena Silvestri [3], Maria Boddi [4], Gerardo Di Scala [3], Augusto Vaglio [5], Luca Cantarini [2], Domenico Prisco [3]

1 *University of Firenze, Department of Experimental and Clinical Medicine, Firenze, Italy*
2 *Rheumatology Siena, Tuscany, Italy*
3 *Internal Medicine Firenze, Tuscany, Italy*
4 *Vascular Unit Firenze, Tuscany, Italy*
5 *Nephrology Unit Parma, Emilia-Romagna, Italy*

Background

Since Behçet syndrome (BS) is the prototype of inflammation-induced thrombosis, immunosuppressants are recommended in place of anticoagulants for the treatment and the secondary prevention of thrombosis. In the present study, we assessed the clinical efficacy and the corticosteroid-sparing effect of adalimumab (ADA)-based treatment versus DMARDs alone in a large retrospective cohort of patients with BS-related venous thrombosis

Methods

We retrospectively collected data from 70 BS patients treated with DMARDs alone or ADA-based regimens (ADA ± DMARDs) because of recurrent venous complications. Both clinical and imaging evaluations were performed to define vascular response. We explored differences in outcomes between ADA-based regimens and DMARDs, particularly with respect to efficacy, corticosteroid-sparing role and time on treatment. We also evaluated the role of anticoagulants as concomitant therapy on the efficacy of the two treatment regimens

Results

Of the 35 patients on DMARDs, 18 (51%) received azathioprine, nine (26%) cyclosporine, five (14%) cyclophosphamide and three (9%) methotrexate. Of the 35 patients on ADA, 27 received ADA-monotherapy and 8 ADA plus DMARDs. After a mean follow-up of 25.7 ± 23.2 months, ADA-based regimens induced clinical and instrumental improvement of venous thrombosis more frequently ($p = 0.001$) and rapidly ($p < 0.0001$) than DMARDs. Moreover, the mean dose of corticosteroids administered at the last follow-up was significantly lower among patients on ADA-based regimens

than among those treated with DMARDs ($p < 0.0001$). Also, the time on treatment was significantly longer in subjects receiving ADA plus DMARDs than in those receiving DMARDs alone ($p = 0.002$). No differences were found in terms of efficacy and time on treatment between DMARDs ($p = 0.26$) or ADA-based regimens ($p = 0.31$) among subjects receiving anticoagulants and those who did not. Treatment efficacy and the time on treatment did not differ between patients who received or those who did not receive anticoagulants in either DMARD or ADA group

Conclusions

In this large retrospective study, we have shown that an ADA-based regimen is more effective and rapid in inducing the resolution of venous thrombosis in BS patients when compared to DMARDs monotherapy. This prompt effect allowed reduction of steroid exposure. Moreover, our findings support the notion that anticoagulation does not modify the efficacy on venous complications of either ADA-based regimens or DMARDs

2.6.2. C0064 Differential Effects of Dabigatran and Rivaroxaban on Fibrinolysis

Suzanne Zwaveling [1], Saartje Bloemen [2], Joke Konings [3], Hilde Kelchtermans [3], Coenraad Hemker [3], Adam Miszta [4], Bas de Laat [5]

1 *Maastricht University, Biochemistry Maastricht, Limburg, The Netherlands*
2 *Maastricht University, Maastricht, The Netherlands*
3 *Synapse Research Institute, Maastricht, The Netherlands*
4 *Department of Pathology and Laboratory Medicine, Chapel Hill, NC, United States*
5 *Synapse Research Institute, Maastricht, The Netherlands*

Background

Little is known about the effect of direct oral anticoagulants (DOACs) on fibrinolysis. Thrombin is known to counter fibrinolysis by creating a denser fibrin network and by activating factor XIII and thrombin-activatable fibrinolysis inhibitor (TAFI) in the presence of thrombomodulin (TM). DOACs may indirectly have a profibrinolytic effect by reducing thrombin. Here, we studied the effect of rivaroxaban (RIV) and dabigatran (DAB) on clot lysis.

Methods

Normal pool plasma (NPP) was measured in the presence of DAB (300 nM) and RIV (750 nM) or without any addition (control). Clot lysis of plasma with and without DOACs, initiated with 1 pM TF and 100 IU tissue-type plasminogen activator (t-PA) was measured using turbidimetry at 405 nm. To study the effect of TM and TAFI we performed the experiments in the presence and absence of 1 nM TM, 1 nM activated protein C (APC) and in TAFI-deficient plasma. The clot lysis time (CLT) was defined as the time from half maximal fibrin formation, to half maximal degradation.

Results

RIV and DAB significantly decreased the CLT (control: 31.3 min vs. DAB: 17.0 min and RIV: 14.7 min). In the presence of TM the CLT of the control was prolonged (31.3 min vs. 83.7 min). This effect was confirmed to be TAFI-dependent. The CLT was differentially affected by DAB and RIV in the presence of TM (control: 83.7 min; DAB: 82.3 min; RIV: 65.7 min). When APC was present in NPP (a control for the TAFI dependence in the presence of TM) there was no difference from NPP without APC. However, when APC was added in the presence of a DOAC there was a cumulative anticoagulant effect and hardly any clot formation. In TAFI-deficient plasma the TM effect was muted, confirming a TAFI-dependent reaction (-TM: 18.7 min. vs. +TM: 18.3 min). Also with DOACs present, the prolongation of the CLT by TM was restored (DAB-TM: 18.0 min vs. DAB+TM: 18.7 min; RIV-TM: 15.0 min vs. RIV+TM: 15.0 min).

Conclusions

Our results show that RIV and DAB, as inhibitors of thrombin, affect fibrinolysis when measured in the absence of TM. The addition of TM, which enables TAFI-dependent reactions, prolongs the CLT in the presence of both DOACs. APC enhances the anticoagulant effect of DOACs. In vivo TM and protein C can both be present in varying concentrations, depending on the location. Due to the variance in response to TM and APC, further research into the fibrinolytic effects of DOACs may be warranted.

2.6.3. C0195 State of Microcirculatory and Hemostasis Systems in Rats after Moderate Hypothermia

Natalia Lycheva Alexandrovna

ZAO (Closed Joint Stock Company) St. Peterburg Institute of Pharmacy, Toxicology, St. Petersburg, Russia

Background

Hypothermia has general impact on the organism. At the same time, the major components providing proper nourishment of tissues are microcirculatory bloodstream and hemostasis system. It has been shown that hypothermia promotes multiple organ dysfunction syndrome, which makes studying the impact of hypothermia on the state of hemostasis and microcirculatory systems an important and relevant task.

Methods

Current study was performed on 50 male Wistar rats. State of microcirculatory bloodstream in all animals was assessed with laser Doppler flowmetry. Condition of hemostasis system was studied according to routine protocols and an integrated method of examination–thromboelastography. Statistical analysis was performed using the Mann-Whitney nonparametric test in Statistica 10.0 software package.

Results

The analysis of the experimental data has revealed that moderate hypothermia has pronounced modulating influence on the microcirculatory system. Vasodilation occurred immediately after reaching this stage of hypothermia, suggesting the beginning of decompensation in the experimental animals. The highest incidence of hemodynamic pathologies, underlying multiple organ dysfunction syndrome, was observed in 5 days after the end of body temperature recovery and was marked by massive decrease in the vascular tone, intensification of hemodynamics, accompanied by the presence of thrombinemia markers in the blood stream and pronounced inhibition of fibrinolysis. Enhanced hemodynamics of the nutritional vascular bed together with the progressive prothrombotic state are a potent risk factor for thrombosis and multiple organ dysfunction syndrome. Vasospasm, occurring 2 weeks after body temperature recovery, indicates deep modulation of vasculature and preservation of high-level sympathetic input, as well as increasing rigidity of blood vessel walls. Rising fibrinogen concentrations confirm progressive inflammatory reaction.

Conclusions

Observed patterns can provide a clear picture of development and course of the pathological reactions in the bodies of the affected people and help us develop the guidelines on the administration of drugs for preventive therapy. For instance, we have determined the period of maximal severity of the prothrombotic state, during which administration of anticoagulative and antiplatelet drugs, as well as of the agents that enhance rheological properties of blood, is required. The reported study was funded by RFBR, according to the research project 16-34-60054 mol_a_dk.

2.6.4. C0144 Ticagrelor Inhibits the Platelet-Mediated Inflammatory Responses

Aikaterini N. Tsouka [1], Kenny M. Hansson [2], Alexandros D. Tselepis [3]

[1] *Atherothrombosis Research Centre/Laboratory of Biochemistry, Department of Chemistry, University of Ioannina, Ioannina, Greece*
[2] *Cardiovascular and Metabolic Diseases, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Sweden*
[3] *Atherothrombosis Research Centre/Laboratory of Biochemistry, Greece*

Background

Apart from their important role in haemostasis and thrombosis, platelets also participate in inflammatory reactions, through mechanisms that may involve the CD40 ligand (CD40L), P-selectin and cell-to-cell interactions withleukocytes. Ticagrelor is a specific reversible $P2Y_{12}$ antagonist that potently inhibits ADP-induced platelet aggregation. We investigated the possible ticagrelor effects on various platelet activation markers and on platelet-leukocyte interactions.

Methods

Whole blood of healthy volunteers was incubated with ticagrelor at various concentrations ranging from 0.25 μM to 4 μM for 5 min at 37 °C and then activated with 50 μM ADP. Platelet activation was evaluated by flow cytometry, determining the membrane expression of P-selectin and CD40L using the monoclonal antibodies, anti-CD61-PerCP, anti-CD154-FITC and anti-CD62P-PE. CD40L was expressed as the percentage of$CD61^+/CD154^+$ cells, whereas P-selectin was expressed as Mean Fluorescence Intensity. Formation of platelet-monocyte and platelet-neutrophil conjugates was determined by dual labelling withanti-CD61-PerCP and anti-CD14-FITC or anti-CD45-PE, respectively. The platelet-monocyte and platelet-neutrophil conjugates were assessed as the percentage of $CD61^+/CD14^+$ and $CD61^+/CD45^+$ particles, respectively.

Results

Ticagrelor inhibited the ADP-induced membrane expression of P-selectin and CD40L in a dose dependent manner exhibiting IC_{50} values of 0.64 μM and 1.12 μM, respectively. Furthermore, the ADP-induced formation of platelet-neutrophil and platelet-monocyte conjugates, was significantly reduced by 82% and 42%, respectively, in the presence of 4 μM of ticagrelor.

Conclusions

Ticagrelor expresses important pleiotropic antiiflammatory effects by inhibiting the membrane expression of platelet inflammatory mediators as well as the interaction of platelets with leukocytes. The clinical significance of these effects in patients treated with ticagrelor deserves further investigation.

2.6.5. C0136 Two Novel Variants of the ABCG5 Gene Cause Xanthelasmas and Macrothrombocytopenia; Review of Hematological Abnormalities Related to Sitosterolemia

Jose Maria Bastida [1], Rocio Benito [2], Kamila Janusz [2], Maria Luisa Giros [3], Jesus Maria Hernández-Sánchez [2], Maria DÌez-Campelo [4], Shally Marcellini [5], Ana Hortal [6], Susana Riesco [7], Ana Rodriguez [8], Miguel Quijada [8], Maria Luisa Lozano [9], Jose Rivera [9], Jesus Maria Hernandez-Rivas [5], Jose Ramon Gonzalez-Porras [5]

[1] *Hospital Universitario Salamanca, Hematologia Salamanca, Salamanca, Spain*
[2] *IBSAL, IBMCC, CIC, Universidad de Salamanca-CSIC, Salamanca, Spain*
[3] *Secció díErrors Congénits del Metabolisme-IBC, Servei de Bioquìmica I Genëtica Molecular Hospital Clìnic Barcelona, IDIBAPS, CIBERER, Barcelona, Spain*
[4] *Hospital Universitario Salamanca, Salamanca, Spain*
[5] *Hospital General Segovia, Segovia, Spain*
[6] *Complejo Asistencial Zamora, Zamora, Spain*
[7] *Hospital Universitario Salamanca, Salamanca, Spain*
[8] *IBSAL, IBMCC, CIC, Universidad de Salamanca-CSIC, Salamanca, Spain*

[9] *Centro Regional de Hemodonación de Murcia, Murcia, Spain*

Background

Sitosterolemia (STSL) is a rare inherited disorder caused by genetic variants in *ABCG5* and *ABCG8* genes, which predisposed to hyperabsorption and accumulation of plant sterols (PS). Increased levels of PS produce xanthomas and premature coronary atherosclerosis, and may be misdiagnosed as familial hypercholesterolemia (FH). Hematological abnormalities may occasionally be present. This clinical picture is unfamiliar to many physicians, and patients may be at high risk of misdiagnosis. Our aims wereto report two novel variants causing STSL and review the hematological abnormalities and mutational landscape of STSL.

Methods

A 46-year-old female, who showed FH-related xanthelasmas, was referred to us presenting life-long macrothrombocytopenia. Molecular analysis was performed by a 72-gene panel using high-throughput sequencing approach. Plasma PS levels were evaluated by gas-liquid chromatography (GLC). The STSL landscape was reviewed since 1974 published reports.

Results

Peripheral blood (PB) parameters showed: hemoglobin level, 13.3 g/dL; reticulocytes, 2%; platelet count, 69.8 × 10^3/mm^3, mean platelet volume, 15.5 fL. A PB smear revealed 22% stomatocytes and giant platelets. Two novel variants were detected in exons 7 (c.914C>G) and 13 (c.1890delT) of the *ABCG5*. High concentrations of sitosterol (668.2 μM, NR < 10 μM), campesterol (169.6 μM, NR < 3 μM) and β-cholestanol (30.7 μM, NR = 2.2–12.6 μM) were detected. After 4 months of ezetimibe treatment, plasma PS levels were 30% reduced and platelet count increase up to 115 × 10^3/mm^3. We identified 27 unrelated patients with hematological abnormalities related to STSL. The median age at diagnosis were 31 years old (range 2–61), most of them were Asian (59%) and females (66%). Bleeding symptoms were reported in 10 unrelated patients. Other metabolic alterations were associated to macrothrombocytopenia in 19 patients (70%). A combination of macrothrombocytopenia and stomatocytes was identified in most of theses cases (93%). Only 11 out of the 28 reported variants in *ABCG5* and 10 out of 31 in *ABCG8* are associated with macrothrombocytopenia.

Conclusions

We identified two novel variants in *ABCG5* in a syndromic macrothrombocytopenia. PB smear is extremely useful for establishing the suspicion of STSL. Definitive diagnosis of STSL by measurement of serum PS and molecular analyses prompted the use of ezetimibe therapy.

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