DIFFERENCES IN CLINICAL PRESENTATION OF PULMONARY EMBOLISM IN WOMEN AND MEN

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Keywords: pulmonary embolism, gender, D-dimer, helical computed tomography

Background: Risk of recurrence of pulmonary embolism (PE) is higher in men than in women. Differences in clinical presentation of deep vein thrombosis (DVT) have been reported between the two genders but comparative data on PE are lacking.

Objectives: To compare the clinical characteristics between women and men presenting with suspected and confirmed PE and their impact on clinical probability prediction scores and on diagnostic work-up of PE, and to assess whether differences in clinical presentation could account for the increased recurrence rate in men.

Methods: Combined data from three prospective cohort studies including a total of 3414 outpatients with suspected PE were used respectively. Prevalence of clinical characteristics, pretest probability of PE and diagnostic yield of non-invasive tests were compared between genders.

Results: The overall prevalence of PE was similar among women and men (22.3% vs 23.1%; p=0.95). The clinical probability prediction scores (both Geneva score and Wells score) performed equally well in both genders. A non invasive diagnostic work-up combining plasma D-dimer measurement and lower limb venous compression ultrasonography was more often possible in men. Finally, the proportion of PE-associated DVT was higher in men than in women (43% vs 33%; p=0.009).

Conclusions: In spite of some differences in the clinical presentation of PE between women and men, clinical probability prediction scores perform equally in both genders. A higher prevalence of PE-associated DVT in men could possibly indicate greater severity of PE episodes and partly account for the higher recurrence rate in men.

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LONG-TERM EVALUATION OF THE RISK OF RECURRENT AFTER CEREBRAL SINUS-VENOUS THROMBOSIS

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Background: The clinical course of cerebral sinus-venous thrombosis (CSVT) is largely unknown because prospective studies are lacking with a long follow-up and with the goal to assess thrombosis recurrence rate and predisposing factors for recurrence.

Methods and results: 145 patients with a first CSVT were followed-up for a median time of 6 years after discontinuation of anticoagulant treatment. End points were recurrent CSVT or other clinical manifestations of venous thromboembolism. CSVT recurred in 5 patients (3%) and other manifestations of venous thromboembolism (deep vein thrombosis of the lower limbs or pulmonary embolism) in 10 additional patients (7%), for an overall incidence of recurrences of 2.03% patients-year (95%CI 1.64-3.14) and of recurrent CSVT of 0.63% patients-year (95%CI 0.20-1.30). Nearly half of the recurrences occurred within the first year after discontinuation of anticoagulant therapy. Risk factors for recurrent venous thrombosis were male sex (adjusted hazard ratio 9.66, 95%CI 2.86-32.7) and, for thromboses other than CSVT, severe thrombophilia due to antithrombin, protein C, protein S deficiency, antiphospholipid antibodies or combined abnormalities (adjusted hazard ratio 4.71, 95%CI 1.34-16.5)

Conclusions: The risk of recurrent CSVT is low, but higher in the first year after discontinuation of anticoagulant treatment and among men. Mild thrombophilia abnormalities are not associated with recurrent CSVT, but severe thrombophilia entails an increased risk of deep vein thrombosis of the lower limbs or pulmonary embolism.

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CLINICAL PREDICTION OF VTE RECURRENCE IN PATIENTS WITH PREVIOUS UNPROVOKED VENOUS THROMBOEMBOLISM: RESULTS FROM AN INDIVIDUAL-LEVEL META-ANALYSIS

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Keywords: venous thrombosis, D-dimer, clinical prediction rule, prediction algorithm

Background/Aims: Several patient characteristics, including D-Dimer after stopping anticoagulants, gender or thrombophilia, have been associated with recurrence of VTE after a first episode of unprovoked VTE. Very few data exist about their joint effect on prediction of recurrence of venous thromboembolism. We aimed to evaluate the efficacy and safety of D-Dimer and ultrasound to establish the optimal duration of anticoagulation for venous thromboembolism. The aims of the study are: to) obtain a recurrence rate < 5% per year in the first and second year after anticoagulation is suspended according to the procedure ii) to allow the patient to stop the treatment for the first episode of venous thromboembolism, iii) anticoagulation suspension in feasible in at least 40% of all subjects included in the study.

Methods and results: In 10 additional studies, data on recurrence after treatment of the first episode of venous thromboembolism was available. Of these 123 (60%) have stopped anticoagulation and 61 had a recurrent event (4.9%). In 83 subjects anticoagulation was resumed and 1 major bleeding event was observed (1.2%). Additional data will be available in the near future.

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RESULTS OF THE D-DIMER AND ULTRASOUND IN VENOUS THROMBOEMBOLISM: PRELIMINARY DATA FROM THE DULCIS INVESTIGATORS

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Keywords: D-dimer, recurrent venous thromboembolism, oral anticoagulants

Background: The purpose of this study is to evaluate the efficacy and safety of a procedure employing the evaluation of residual vein obstruction (RVO) and D-dimer to establish the individual risk of recurrence and thus the necessity to prolong or stop anticoagulation after deep vein thrombosis (DVT) and/or pulmonary embolism (PE).

Methods: To compare the clinical characteristics between women and men presenting with suspected and confirmed PE and their impact on clinical probability prediction scores and on diagnostic work-up of PE, and to assess whether differences in clinical presentation could account for the increased recurrence rate in men.

Results: The overall prevalence of PE was similar among women and men (22.3% vs 23.1%; p=0.95). The clinical probability prediction scores (both Geneva score and Wells score) performed equally well in both genders. A non invasive diagnostic work-up combining plasma D-dimer measurement and lower limb venous compression ultrasonography was more often possible in men. Finally, the proportion of PE-associated DVT was higher in men than in women (43% vs 33%; p=0.009).

Conclusions: In spite of some differences in the clinical presentation of PE between women and men, clinical probability prediction scores perform equally in both genders. A higher prevalence of PE-associated DVT in men could possibly indicate greater severity of PE episodes and partly account for the higher recurrence rate in men.
Materials and methods: Systematically appraise the risk of recurrence for VTE provoked by different transient risk factors.

Aims: Compare the risk of recurrence after stopping anticoagulant therapy between different transient risk factors. The risk of recurrence after stopping anticoagulant therapy is lower for VTE provoked by surgery than by a non-surgical transient risk factor. Both groups have a lower risk than any transient risk factor, and 1.8 (95% CI 1.1-8.1) when compared with a non-surgical factor.

Results: In the 24 months after stopping therapy, the rate of recurrence was 3.3% per patient-year (95% CI 2.8% to 3.9%; 11 studies, 2268 patients) for any transient risk factor, 0.7% (95% CI 0.0 to 1.5%; 3 studies, 248 patients) for a surgical factor, and 4.2% (95% CI 2.8 to 5.6; 3 studies, 509 patients) for a non-surgical factors. The rate ratio for a non-surgical compared with a surgical factor was 3.0 (95% CI 1.1-8.1). The rate ratio for unprovoked thrombosis was 2.3 (95% CI 1.9 to 2.8) when compared with any transient risk factor, and 1.8 (95% CI 1.2 to 2.5) when compared with a non-surgical factor.

Conclusions: The risk of recurrence after stopping anticoagulant therapy is lower for VTE provoked by surgery than by a non-surgical transient risk factor. Both groups have a lower risk than unprovoked VTE.

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COMPARISON OF RISK PROFILE AND CLINICAL OUTCOME OF PATIENTS AFTER ACUTE PULMONARY EMBOLISM IN UNIVERSITY AND NON-UNIVERSITY HOSPITALS

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Keywords: pulmonary embolism, university hospital, clinical outcome

Background: Current knowledge on diagnostic management and treatment of patients with acute pulmonary embolism (PE) is partly derived from outcome studies including patients from university hospitals alone. It is debatable whether these data are applicable to patients in non-university hospitals.

Aims: To compare baseline characteristics and clinical outcome of patients with PE treated in university hospitals versus patients treated in non-university hospitals.

Materials and methods: Post-hoc analysis on data derived from Christopher Study, a prospective multicenter management study.

Results: A total of 399 (59%) patients with PE presented to a university hospital and 275 (41%) to a non-university teaching hospital. The characteristics of patients from the university and non-university hospitals were different with respect to female ratio (46% vs. 56%), Odds Ratio [OR] 0.65, 95% confidence interval [CI] 0.47-0.88), outpatient ratio (73% vs. 84%, OR 0.53, 95%CI 0.36-0.79), presence of immobilization (37% vs. 23%, OR 2.0, 95%CI 1.4-2.8) and the presence of active malignancy (19% vs. 12%, OR 1.6, 95%CI 1.1-2.5). Risk on venous thromboembolic recurrence (3.3% vs. 2.6% OR 1.3, 95%CI 0.50-3.9) and mortality (9.0% vs 6.9% OR 1.3, 95%CI 0.75-2.4) were higher for patients in university than in non-university hospitals. Bleedings occurred twice more often in patients from university hospitals (4.3% vs 2.2% OR 0.65, 95%CI 0.36-0.79). Time-to-event analysis was performed by Kaplan-Meier estimates with log-rank test. Post-hoc analysis on data derived from Christopher Study, a prospective multicenter management study.

Conclusions: Physicians should be aware of differences in patient characteristics and outcome between university and non-university hospitals when interpreting results from large clinical trials and applying these to their everyday medical practice.

Table

<table>
<thead>
<tr>
<th>University hospital (n=399)</th>
<th>Non-university teaching hospital (n=274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total recurrences</td>
<td>13 (3.3)</td>
</tr>
<tr>
<td>Fatal recurrent PE</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Non-fatal recurrent PE</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Non-fatal recurrent DVT</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>All bleeding complications</td>
<td>17 (4.3)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7 (1.8)</td>
</tr>
<tr>
<td>Clinically relevant bleeding</td>
<td>9 (2.3)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>36 (9.0)</td>
</tr>
</tbody>
</table>

Data are displayed as No (%).

PE = pulmonary embolism, DVT = deep vein thrombosis

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KEY ROLE OF EARLY DIAGNOSIS IN REDUCING MORTALITY IN PATIENTS WITH HEPARIN-INDUCED THROMBOCYTOPENIA (HIT): A SINGLE-CENTER EXPERIENCE WITH FONDAPARINUX AS ALTERNATIVE ANTICOAGULANT

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Keywords: fondaparinux, heparin-induced thrombocytopenia, thrombosis

Background: HIT is an immune-mediated adverse reaction of heparins caused by platelet-activating anti-Factor-Xa/heparin antibodies. Fondaparinux, a selective inhibitor of factor Xa which does not react with HIT antibodies, could represent a potential alternative to manage this condition.

Methods: We treated 52 patients with strong suspect of isolated HIT (20 patients) or HIT and thrombosis, HITT (32 patients). In the HITT group, we applied therapeutic dosages of fondaparinux (7.5 mg/day) or lower, according with bleeding risk.

Results: We treated 52 patients with strong suspect of isolated HIT (20 patients) or HIT and thrombosis, HITT (32 patients). In the HITT group, we applied therapeutic dosages of fondaparinux (7.5 mg/day) or lower, according with bleeding risk.

Conclusions: Whilst DVT and PE are manifestations of the same pathology the clot confined to the calf had an almost 5-fold lower cumulative recurrence rate than PE was about 3-fold greater in patients presenting with symptomatic PE compared to those presenting with DVT alone. Patients presenting with DVT confined to the calf veins are at low risk of recurrence and of recurrence as PE.

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DOES THE CLINICAL PRESENTATION AND EXTENT OF VENOUS THROMBOSIS PREDICT LIKELIHOOD AND TYPE OF RECURRENCE? A PATIENT LEVEL META-ANALYSIS OF 2,554 UNSELECTED PATIENTS AFTER A FIRST THROMBOSIS

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Keywords: Venous Thrombosis; Pulmonary embolism; recurrence risk

Aims: To determine if the mode of presentation of a first episode of venous thromboembolism (VTE) predicts likelihood and type of recurrence.

Materials and methods: Patient-level meta-analysis of seven prospective cohort studies. Time-to-event analysis was performed by Kaplan-Meier estimates with cumulative recurrence rates reported at different years of follow up and annualized rates presented as events per 100 patient-years. Hazard ratios (HR) were calculated by Cox regression models including two- and three-level variables for clinical presentation and extent of disease and adjusting for other putative confounders (age, sex, provoked or unprovoked VTE, hormone therapy).

Results: In 869 patients presenting with symptomatic PE the cumulative rate of recurrence at 5 years was 22.0% and recurrence as PE was 10.6%. In 1,365 patients presenting with symptomatic proximal DVT without symptomatic PE the recurrence rate at 5 years was 26.4% and recurrence as PE was 3.6%. The risk of recurrence as PE was about 3-fold greater in patients presenting with symptomatic proximal DVT compared to distal DVT, even if without a statistical significance (hazard ratio 4.5, 95% CI 0.6 – 33.9). Patients with clot confined to the calf had an almost 5-fold lower cumulative recurrence rate than patients with proximal DVT without PE (hazard ratio 4.8, 95% CI 1.2-11.0).

Conclusions: Whilst DVT and PE are manifestations of the same pathology the clot confined to the calf veins are at low risk of recurrence and of recurrence as PE.

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IS ATRIAL FIBRILLATION ASSOCIATED WITH PULMONARY EMBOLISM?

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Keywords: atrial fibrillation, pulmonary embolism, new-onset dyspnea

Background: Pulmonary embolism (PE) is deemed to trigger atrial fibrillation (AF). Nevertheless, the association between PE and AF is based on weak data. We compared AF prevalence among patients with or without PE, in a cohort of patients with PE suspicion.

Methods and results: Data from two trials on PE diagnosis were analyzed. 2449 consecutive patients admitted for clinically suspected PE were included. ECG was systematically performed. PE was diagnosed in 551 (22%) patients by computed tomography. The prevalence of AF was 4.6% in patients with PE and 5.8% in patients without PE, a non-significant difference (p=0.28). After adjustment for confounding factors, AF tended to decrease PE probability (OR 0.68, CI95% 0.42-0.98, p=0.122). As AF can manifest as new-onset dyspnea, its presence could have misled to PE suspicion. Accordingly, AF significantly decreased PE probability when the suspicion of PE was based on a new-onset dyspnea (OR 0.47, p=0.010). However, when PE was suspected because of a chest pain without dyspnea, AF tended to increase the risk of PE (OR 2.42, CI95% 0.97-6.07, p=0.059).

Conclusions: Despite common belief, presence of AF does not increase PE probability when this diagnosis is suspected. When PE suspicion is based on a new-onset dyspnea, AF decreases significantly the risk of PE, probably because AF can mimic its clinical presentation. On the contrary, when PE suspicion does not emerge from a new onset dyspnea, AF tends to increase PE probability. This observation is suggestive of a true association between these two conditions.

Table: Association between PE and AF, heart failure and COPD, accounting for dyspnea presence

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>New dyspnea</th>
<th>No new dyspnea</th>
<th>Test for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2449</td>
<td>N=1756</td>
<td>N=693</td>
<td></td>
</tr>
<tr>
<td>Adjusted OR of PE in case of AF (95%CI)*</td>
<td>0.68 (0.42-1.11)</td>
<td>0.47 (0.26-0.84)</td>
<td>2.42 (0.97-6.07)</td>
<td>p=0.093</td>
</tr>
<tr>
<td>AF</td>
<td>p=0.122</td>
<td>p=0.010</td>
<td>p=0.059</td>
<td></td>
</tr>
<tr>
<td>n=133</td>
<td>n=104</td>
<td>n=29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted OR of PE in case of COPD (95%CI)*</td>
<td>0.33 (0.20-0.51)</td>
<td>0.32 (0.20-0.51)</td>
<td>1.40 (0.81-2.38)</td>
<td>p=0.099</td>
</tr>
<tr>
<td>COPD</td>
<td>p=0.001</td>
<td>p=0.001</td>
<td>p=0.515</td>
<td></td>
</tr>
<tr>
<td>n=247</td>
<td>n=217</td>
<td>n=30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted OR of PE in case of heart failure (95%CI)*</td>
<td>0.53 (0.31-0.88)</td>
<td>0.43 (0.25-0.73)</td>
<td>1.88 (0.36-8.99)</td>
<td>p=0.095</td>
</tr>
<tr>
<td>Heart failure</td>
<td>p=0.014</td>
<td>p=0.002</td>
<td>p=0.475</td>
<td></td>
</tr>
<tr>
<td>n=143</td>
<td>n=135</td>
<td>n=9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, sex and presence of AF, heart failure, COPD, stroke or cancer in the past and creatinine clearance.

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FOLLOW-UP IN PULMONARY EMBOLISM WITH CT ANGIOGRAPHY: IS IT NECESSARY?

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Keywords: follow-up, CT angiography, thromboembolism

Aims: To assess the utility of 6-months follow-up CT pulmonary angiography (CTA), for controlling interruption of anticoagulant therapy and determine evolution to chronic pulmonary embolism (PE) and/or chronic thromboembolic pulmonary hypertension

Materials and methods: From March 2001 to January 2010 we reviewed the CT angiography of patients with acute pulmonary embolism at diagnosis and after 6 months of treatment. According to findings we divided patients in two groups: total resolution (group A) and non total resolution (group B). Group B was defined as: CT signs of persistence of the clot (filling defect or complete occlusion), evolution to chronic PE (severe arterial luminal narrowing or vessel occlusion of a stenosed artery) and pulmonary hypertension -PHT-(mosaic parenchyma pattern) at the level of the central and peripheral pulmonary arteries.

Results: 605 patients were studied with CT angiography both at diagnosis and at six months of treatment. Patients were treated with anticoagulant therapy during at least 6 months. 40% of patients did not achieve complete resolution. Persistence of clot was seen in 21%. In the other 19%, progression to chronic pulmonary embolism was seen. No case of pulmonary hypertension was observed in group A, but 10% of group B patients had CT signs of pulmonary hypertension. There were no differences in clinical symptoms between group A and group B.

Conclusions: CT is a useful tool in the follow-up of thromboembolism patients, in particular those who could develop pulmonary hypertension in the future. Complete resolution of pulmonary embolism should be confirmed before stopping anticoagulant treatment.

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STATINS, FIBRATES, AND VENOUS THROMBOEMBOLISM: A META-ANALYSIS

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Keywords: statins, fibrates, venous thromboembolism

Background/Aims: Recent data suggest a possible benefit of lipid-lowering drugs, in particular statins, in preventing venous thromboembolism (VTE). The aim of this systematic review of the literature is to assess the effect of lipid-lowering drugs on VTE occurrence.

Materials and methods: MEDLINE and EMBASE databases were searched to identify studies that evaluated the effect of lipid-lowering drugs, in particular statins and fibrates, on VTE risk until April 2009. A scoring system was used to divide studies into two quality categories. Odds ratios (ORs) and 95% confidence intervals (CIs) were then calculated and pooled using a fixed and a random-effects model. Statistical heterogeneity was evaluated through the use of I2 statistics.

Results: Three randomized controlled trials (RCTs), three cohort, and eight case-control studies were included in our systematic review, for a total of 863,805 patients. Statins use significantly reduced VTE risk [OR, 0.81; 95% CI, 0.66-0.99, (CIs) were then calculated and pooled using a fixed and a random-effects model. Data on other lipid-lowering drugs were lacking.

Conclusions: This meta-analysis of available literature suggests that statins may lower the risk of VTE, whereas fibrates may increase this risk. Due to several methodological limitations, this conclusion should be considered with caution, and additional, specifically designed RCTs are warranted.

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CT ANGIOGRAPHY: IS IT NECESSARY?

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Keywords: anticoagulant treatment.

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Materials and methods: From March 2001 to January 2010 we reviewed the CT angiography of patients with acute pulmonary embolism at diagnosis and after 6 months of treatment. According to findings we divided patients in two groups: total resolution (group A) and non total resolution (group B). Group B was defined as: CT signs of persistence of the clot (filling defect or complete occlusion), evolution to chronic PE (severe arterial luminal narrowing or vessel occlusion of a stenosed artery) and pulmonary hypertension -PHT-(mosaic parenchyma pattern) at the level of the central and peripheral pulmonary arteries.

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Conclusions: CT is a useful tool in the follow-up of thromboembolism patients, in particular those who could develop pulmonary hypertension in the future. Complete resolution of pulmonary embolism should be confirmed before stopping anticoagulant treatment.

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THE PROGNOSIS OF PULMONARY EMBOLISM DEPENDS OF ITS LOCALIZATION? RESULTS FROM THE RIETE

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Keywords: pulmonary embolism, recurrences, mortality

Background: The prognosis of pulmonary embolism (PE) depends mainly on mortality and recurrences. Mortality is associated with advanced age, renal failure, cancer and long previous hospitalization. Recurrences are related with a high level of plasmatic D-dimer and persistent signs of deep venous thrombosis (DVT) in the leg ultrasound, after anticoagulation is stopped. However it’s not known if the prognosis is worst when PE affects the main pulmonary artery or a lobar branch than when affects segmental or subsegmental branches.

Aims: To know if the prognosis of PE depends on its localization and if there are risk factors related.

Methods: Retrospective study of all patients with PE included in the RIETE between January 2001 and August 2004. The following variables were analyzed: age, gender, other diseases, previous PE and/or DVT, cancer, previous immobilization, shock, clinical signs of DVT, localization (main and lobar artery group I, segmental and subsegmental branches group 2) d-dimer, respiratory failure, radiologic and electrocardiographic findings, mortality and recurrences. Statistics: descriptive, univariate and multivariate analysis. Significance was considered when p<0.05.

Results: Group 1 included 443 patients, mean age 68.5 years old, 222 male and 221 female. Group 2 included 97 patients, mean age 63.4 years old, 57 male and 40 female. The number of recurrences was small in the two groups. Fiftyfive patients (15%) of the group 1 and 5 (7%) of the group 2 died. Cancer and respiratory failure were found the only variables significantly related to mortality in both groups but we did not find differences either in mortality or in recurrences between the two groups. Variables found as significant in both groups in the univariate analysis were shown in the table. No significances were seen in the multivariate analysis.

Conclusions: With the limitations of the study - few patients in group 2 compared with those of group 1– we conclude that the prognosis of PE is independent of its localization. Cancer and respiratory failure can predict mortality but no recurrences of PE and it is also independent of its localization.

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Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (%)</th>
<th>Group 2 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>5 (0.01)</td>
<td>2 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>8 (0.01)</td>
<td>10 (0.10)</td>
<td></td>
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<tr>
<td>Other diseases</td>
<td>16 (0.03)</td>
<td>21 (0.12)</td>
<td></td>
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<tr>
<td>Abnormal Rx</td>
<td>26 (0.59)</td>
<td>22 (0.23)</td>
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</table>

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Keywords: fondaparinux, superficial-vein thrombosis, treatment

Background/Aims: The randomized CALISTO trial demonstrated that once-daily fondaparinux 2.5 mg for 45 days is effective and well tolerated in patients with symptomatic superficial-vein thrombosis (SVT) of the legs. Since this trial was performed in 17 countries, we analyzed the data according to geographic area to evaluate possible country-related differences in practice patterns.

Results: 670 patients were recruited in Western countries (group 1), 1345 in Russia and Ukraine (group 2) and 987 in other European countries and Israel (group 3). Demographic and SVT characteristics were comparable between the three groups. The qualifying SVT predominantly involved the great saphenous vein alone in all geographic areas. At inclusion, the use of graduated compression stockings and antiplatelet agents was less frequent in Western countries. During the study, recourse to ligation of the sapheno-femoral junction and use of anticoagulants, as a whole, was well balanced between the three groups of countries. However, Western countries showed a predominance of anticoagulant use over ligation, the reverse being evident in Russia and Ukraine.

Conclusions: Although demographic characteristics are similar, the clinical management of patients with SVT is country-dependent. This may be related to the absence of an evidence-based, effective and safe treatment for SVT. Once-daily fondaparinux 2.5 mg for 45 days may fulfill this need.

Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (%)</th>
<th>Group 2 (%)</th>
<th>p-value</th>
</tr>
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<tr>
<td>Gluedapolcular compression on discharge</td>
<td>74 (0.00)</td>
<td>363 (0.24)</td>
<td></td>
</tr>
<tr>
<td>Aspirin or other antiplatelet agents</td>
<td>16 (0.02)</td>
<td>7 (0.01)</td>
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Letters bestposter
Background: Little information exists on the long-term clinical outcome of venous thromboembolism (VTE) in elderly patients.

Aims: To prospectively compare the long-term clinical outcome of VTE in a cohort of elderly patients aged >75 years and in a cohort of patients aged ≤75 years enrolled in a large, multicenter registry and to identify independent predictors of clinical outcomes in the elderly.

Patients and methods: Consecutive patients with symptomatic, objectively confirmed, acute VTE were included in the MASTER registry in 25 Italian centers. Patients were followed-up for 24-months. Major clinical outcomes were death, recurrence of VTE, and major bleeding. Cox regression analysis was used to assess major determinants of outcomes.

Results: A total of 2119 patients (49.8% males) were enrolled in the study, of whom 440 (20.8%) were >75 years and 1679 (79.2%) ≤75 years. Information on mortality at 2 years was available for 2021 patients (413 >75 years and 1608 ≤75 years) and information on VTE recurrence and bleeding events was available for 1988 patients (404 >75 years and 1584 ≤75 years). The 2-year cumulative incidence of mortality was 13.1% in patients >75 years and 7.0% in patients ≤75 years, hazard ratio (HR) 1.52, 95%CI 1.09-2.13. Cancer (HR 3.44, 95%CI 1.94-6.09) was the only independent predictor of mortality in the elderly. The 2-year cumulative incidence of recurrent VTE was 6.4% in patients >75 years and 6.2% in patients ≤75 years (HR 1.05; 95% CI 0.67-1.63). The 2-year cumulative incidence of bleeding was 4.0% in patients >75 years and 2.2% in patients ≤75 years, Odds Ratio 1.84; 95% CI 0.97-3.50.

Conclusions: As expected, long term mortality rates after acute VTE are significantly higher in patients >75 years than in younger patients. Rates of recurrent thrombotic events were similar between the two groups, whereas bleeding events were nearly twice as frequent in the elderly.

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P495

VENA CAVA FILTERS: EXPERIENCE OF THE RIE REGISTRY

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Keywords: vena cava filters, venous thromboembolism, bleeding

Background/Aims: Vena cava filters (VCF) are devices used in venous thromboembolism (VTE) as second-line treatment with a weak scientific evidence for use. The objectives of this study are to analyze demographics and clinical characteristics of patients with VCF in a broad population of patients with VTE.

Material and methods: The RIETE registry is an ongoing, international, multicenter, prospective registry of consecutive patients presenting with symptomatic acute VTE confirmed by objective tests. We retrospectively analyzed the data of all patients with VTE who were treated with a FVC in the registry, and compared them with those treated with anticoagulant therapy.

Results: Among 27,424 patients included in the registry 621 were treated with a VCF. Comparing VCF group with no VCF there was an equal distribution by gender. Among VCF patients were younger (p<0.001), their comorbidities were higher and there were fewer patients with none comorbidities (p<0.001). Among VCF the bleeding rate in the month preceding the VTE was higher (20% vs 2.1%; p<0.001). The risk factors for developing VTE such as cancer, previous surgery, previous VTE or immobilization were significantly higher in VCF group (p<0.001). When analyzing the way of presentation of the VTE, DVT coexisting with PE was significantly higher in VCF patients (33% vs 16%; p<0.001). There were more cases of bilateral DVT (12% vs 4.2%; p<0.001), the majority of them were proximal (90% vs 82%; p<0.001). The implantation of a VCF took place in patients that were younger (p<0.001), had more coagulation problems, a higher rate of renal impairment (p<0.001). The bleeding risk was significantly higher in VCF group (p<0.001).

Conclusion: These results suggest that VCF are used in younger patients, but with higher comorbidities, higher risk of bleeding and poorer prognosis. Follow up studies are needed to know clinical balance between risk-benefits of these devices.

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P569

PULMONARY EMBOLISM IN CRITICALLY ILL PATIENTS: REASONS FOR SUSPICION, FREQUENCY AND OUTCOMES

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Keywords: pulmonary embolism, intensive care unit, computed tomography pulmonary angiography

Background: Pulmonary embolism (PE) is a challenging diagnosis in critically ill patients and has potentially serious complications; however, few studies have been performed in the intensive care unit (ICU).

Aims: To explore the clinical features leading to computed tomography pulmonary angiography (CTPA) to diagnose PE, to evaluate the findings of CTPA, and to compare the outcomes of patients with PE vs without PE.

Methods: Retrospective study of clinical and radiographic records of consecutive ICU patients undergoing a CTPA for suspected PE during their ICU stay at 2 hospitals in Italy. Data were collected on baseline characteristics, features leading to a suspicion of PE, CTPA findings and hospital mortality.

Results: Among 97 patients, PE was confirmed in 16 out of 103 (15.5%) CTPAs. Among 27.424 patients included in the registry 621 were treated with a VCF. Comparing VCF group with no VCF there was an equal distribution by gender. Overall, the only clinical features distinguishing patients with PE vs without PE (50% vs 33.3%, p not significant).

Conclusions: In ICU patients, PE was more frequently suspected as a cause of ICU admission than as a result of clinical events developing during the ICU stay. In the latter setting, no particular clinical features were associate with the diagnosis of PE. Further research is urgently required in this challenging field.

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P667

THE ITALIAN REGISTRY OF CHILDHOOD THROMBOSIS (REGISTRO ITALIANO TROMBOSI INFANTILE – RITI)

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Keywords: childhood, thrombosis, registry

Background: Thromboembolism (TE) in newborns and children is becoming a rapidly increasing condition burdened by mortality and high morbidity. A dramatic increase in TE (from an annual rate of 34 to one of 54 cases per 10,000 admissions) has been reported in tertiary care hospitals in US between 2001-2007. Risk factors, clinical features and prognosis are dependent on age as well as on optimal treatment strategy. However randomised controlled trials are not available and most current treatment recommendation are extrapolated by adult studies. National and international registries have been created in countries aiming at developing clinical trials to better understand and improve outcomes in children with TE. In 2008, a multi-centre research network of Italian investigators, patroonized by the main national Pediatric Scientific Associations, has developed a national prospective on-line registry of childhood TE based on a secure web database (RITI-www.trombosinfantili.it). The initiative has been supported by an Italian orlus association (ALT). The aim of this study is to get a better understanding and method to enroll most cases of childhood (birth to 18 yr) TE (including systemic venous and arterial TE and stroke) since 01/01/2007 and collect data on risk factors, yield of clinical laboratory and radiographic investigations, the tolerance, dosing, safety and failure rates of anticoagulant and thrombolytic treatments and acute and long-term patient outcome. Recurrences, perceived quality of life, number of hospital admissions and procedures for disease sequelae are included in the registry, giving information on social cost of pediatric TE.

Results: RITI has completed the pilot phase and started the final launching by March 2010. It includes more than 100 patients, confirming a different approach to TE among various pediatric centres and a poor prognosis in more than half of patients. Neoplas and adolescents are the most representative age groups. Cardiac and oncological disease and central vascular line the most frequent association with systemic TE; stroke cases are over-represented (45%) as most participating investigators during the pilot phase being pediatric neurologists; LMWH rather than UH or warfarin has been the anticoagulant drug of choice in 90%.

Conclusion: RITI will represent an opportunity for both Italian pediatricians and investigators of other registries to collaborate on multiple studies on risk factors, diagnostic investigations, optimal treatment strategy and acute and long-term outcome of childhood TE.

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P119

THE SHOCK INDEX VS. THE SIMPLIFIED PULMONARY EMBOLISM SEVERITY INDEX FOR PROGNOSIS IN PATIENTS WITH ACUTE PULMONARY EMBOLISM

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Keywords: pulmonary embolism, prognosis, survival

Aims: To assess the performance of 2 prognostic models (the Shock Index [SI] and the simplified Pulmonary Embolism Severity Index [sPESI]) in predicting short-term mortality in patients with pulmonary embolism (PE).

Methods: We compared the ability of the Shock Index (SI) and the sPESI for predicting 30-day outcomes in a cohort of 985 patients with objectively confirmed PE. Outcomes were assessed during the first month after the diagnosis of acute PE. The primary outcome of the study was all-cause mortality. The secondary outcome was objectively confirmed non fatal symptomatic recurrent VTE, or non fatal major bleeding.

Results: Overall, 113 out of 985 patients died (11.5%; 95% confidence interval [CI], 9.5% to 13.5%) during the first month of follow-up. The sPESI classified fewer patients as low risk (31% [304/985], 95% CI: 28% to 34%) compared to the SI (85% [835/985], 95% CI: 83% to 87%) (P < 0.0001). Using either prediction rule, the low-risk groups showed statistically relevant 30-day mortality difference (sPESI 2% [95% CI, 0.4-3.5] versus SI 9.8% [95% CI, 7.7-11.8]; P<0.0001), and 30-day non fatal adverse events (sPESI 4.6% [95%CI, 2.3% to 7.0%] versus SI 9.8% [95%CI, 7.7 to 11.5%]; P<0.0001).

Conclusion: The sPESI quantified the prognosis of patients with PE better than the SI. The sPESI can be used in daily clinical practice. This was especially true during the initial days of acute pulmonary embolism.

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**P20**

PROGNOSTIC IMPACT OF Calf Muscle NEAR-INFRARED SPECTROSCOPY IN PATIENTS WITH A FIRST EPISODE OF DEEP VEIN THROMBOSIS - DOES ISOLATED CALF DEEP VEIN THROMBOSIS HAVE A ROLE IN THE DEVELOPMENT OF POST-THROMBOTIC SYNDROME?

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Background: The risk factors that affect the development of post-thrombotic syndrome (PTS) are not fully recognized, and it is difficult to reliably predict which patients are likely to develop PTS in acute phase of deep vein thrombosis (DVT).

Aims: To investigate changes in calf muscle deoxygenated hemoglobin (HHb) levels after DVT, and to determine the indicative parameters reflecting the progression of PTS.

Methods: Seventy-six consecutive patients with a first episode of unilateral DVT were prospectively enrolled. Clinical manifestations were categorized according to the CEAP (Clinical, Etiologic, Anatomical, and Pathophysiologic) classification, and the patients were divided into no-PTS (C0–3Es,As,d,p,Pr,o) and PTS (C4 6Es,As,d,p,Pr,o) groups. Near-infrared spectroscopy (NIRS) was used to measure calf muscle HHb levels at 6 months after diagnosis of DVT. The calf venous blood filling index (HHbFI) was calculated on standing, and the venous ejection index and the venous retention index (HHbRI) were then obtained after exercise. All patients were followed up for more than 24 months after the diagnosis of DVT.

Results: Out of 76 patients evaluated, 20 (26.3%) had PTS. The proportion of iliofemoral DVT was significantly higher in patients who developed PTS than in patients who did not (P=0.043). The NIRS-derived HHbFI and HHbRI were significantly increased in patients who developed PTS in comparison with those who did not (P=0.04 and P=0.0001, respectively). HHbRI was significantly increased in patients with iliofemoral DVT in comparison with patients with calf DVT (P=0.041). An optimal cut-off point of 2.9 for HHbRI showed the strongest ability to predict the development of PTS, with a sensitivity of 100% and a specificity of 82.1%.

Conclusions: HHbRI as measured by NIRS is significantly increased in patients with iliofemoral DVT as compared with those with calf DVT. Furthermore, HHbRI > 2.9 is a strong predictor of the development of PTS at 6 months.

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**P350**

FREQUENCY OF ASYMPTOMATIC DEEP VEIN THROMBOSIS FOLLOWING ANKLE FRACTURES

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Keywords: deep veins, thrombosis, ankle fracture

Background: Ankle fractures are frequent; 60,000/yr in the UK. We studied the frequency of asymptomatic DVT following ankle fractures.

Aims: Our aim was to determine the frequency of asymptomatic DVT following ankle fractures.

Methods: Eligible patients were identified in the Accident & Emergency department within 30 hours of ankle fracture. The deep veins of both legs were imaged by duplex Doppler for DVT at 4 weeks.

Results: Of 39 patients recruited so far, 29 patients had Duplex imaging 4 weeks following ankle fracture; nine of these treated by open reduction.

Nine (31%) of patients had a DVT; two above knee and 7 below knee. Four (44.5%) were in the 9 patients treated surgically.

Conclusions: The frequency of DVT following ankle fracture was high at 31% and higher still in those undergoing open reduction despite prophylaxis with enoxaparin.

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**P55**

QUALITY OF LIFE IN PATIENTS WITH VASCULAR DISEASE OF THE LIVER: RESULTS OF A QUESTIONNAIRE SURVEY IN 49 PATIENTS WITH CONSOLIDATED LIVER DISEASE


For the French network for vascular disorders of the liver

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Keywords: Budd-Chiari syndrome, portal vein thrombosis

Background: Patients with vascular liver disease, Budd-Chiari syndrome (BCS) or portal vein thrombosis (PVT) are most often young active patients. Once their disease is consolidated with current therapeutics including anticoagulants, beta blockers or interventional radiology, there is no existing data concerning their psychological and functional outcomes. The frequency of asymptomatic DVT following ankle fractures.

Aims: To investigate changes in calf muscle deoxygenated hemoglobin (HHb) levels after DVT, and to determine the indicative parameters reflecting the progression of PTS.

Methods: Seventy-six consecutive patients with a first episode of unilateral DVT were prospectively enrolled. Clinical manifestations were categorized according to the CEAP (Clinical, Etiologic, Anatomical, and Pathophysiologic) classification, and the patients were divided into no-PTS (C0–3Es,As,d,p,Pr,o) and PTS (C4 6Es,As,d,p,Pr,o) groups. Near-infrared spectroscopy (NIRS) was used to measure calf muscle HHb levels at 6 months after diagnosis of DVT. The calf venous blood filling index (HHbFI) was calculated on standing, and the venous ejection index and the venous retention index (HHbRI) were then obtained after exercise. All patients were followed up for more than 24 months after the diagnosis of DVT.

Results: Out of 76 patients evaluated, 20 (26.3%) had PTS. The proportion of iliofemoral DVT was significantly higher in patients who developed PTS than in patients who did not (P=0.043). The NIRS-derived HHbFI and HHbRI were significantly increased in patients who developed PTS in comparison with those who did not (P=0.04 and P=0.0001, respectively). HHbRI was significantly increased in patients with iliofemoral DVT in comparison with patients with calf DVT (P=0.041). An optimal cut-off point of 2.9 for HHbRI showed the strongest ability to predict the development of PTS, with a sensitivity of 100% and a specificity of 82.1%.

Conclusions: HHbRI as measured by NIRS is significantly increased in patients with iliofemoral DVT as compared with those with calf DVT. Furthermore, HHbRI > 2.9 is a strong predictor of the development of PTS at 6 months.

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**P14**

ACTIVATED PARTIAL THROMBOPLASTIN TIME MONITORING IN PATIENTS RECEIVING UNFRACTIONATED HEPARIN FOR VENOUS THROMBOEMBOLISM IN RELATION TO CLINICAL OUTCOMES

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Keywords: venous thromboembolism; unfractionated heparin; subcutaneous, activated partial thromboplastin time

Background: Venous thromboembolism (VTE) is a prevalent and serious condition, which requires anticoagulation treatment for prolonged time duration. The use of unfractionated heparin administered intravenously or subcutaneously for acute management of VTE has been studied with favourable clinical results. Most physicians use activated partial thromboplastin time to monitor the treatment effect, in an effort to obtain better efficacy with less bleeding complications. Recent data, however, do not support this practice. We set to explore the medical literature for the correlation between the level of anticoagulation and the clinical outcomes.

Methods: Randomised controlled trials comparing subcutaneous unfractionated heparin to any other treatment modality in patients with venous thromboembolism were obtained and analysed statistically.

Results: 17 reports from 15 randomised controlled trials were included. Of these, eleven included anticoagulation measurements. Seven and six trials were included in our analysis for subcutaneous and intravenous modes of administration, respectively. No correlation between the anticoagulation level and the major clinical outcomes were found, except for the initial anticoagulation measurement and the total mortality at three months, but not to death related to treatment or disease progression.

Conclusions: A weight-adjusted subcutaneous unfractionated heparin without anticoagulation monitoring is feasible for patients with acute venous thromboembolism. No differences exist between intravenous and subcutaneous modes of administration with regards to the correlation between anticoagulant measures and the clinical outcomes. More research is needed to substantiate this observation.

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Results: Out of 583 patients with PE, 52% were women. Mean age was 66.48±17.5. Shock index≤1 was present in 15% (86 patients). Mean age of non-severe PE was 67.05 years and 63.23 in severe PE (p<0.05). Age distribution is showed in the table. Overweight or more existed in 70% and comorbidity in 69.67% (p<0.05). In 94%, PE was in outpatient, of which 14.53% was severe. In admitted patients (6%, 35 patients), PE was severe in 18.92% (7). Antithrombotic prophylaxis (ATP) was prescribed in 94.29% (33). Patients with ATP had, as risk factor for TED: 0.06% (2) cancer and surgery; 0.03% (1), hip surgery; 0.09% (3) non-surgical immobilization, 0.06% (2) severe acute infection. There was a total of 21 (4.1%) deaths (3.9% vs. 5.2%, p<0.05). Six deaths related with PE. In remaining died patients: 1 bleeding at 80 days, 8 infection (5 after 3 months), 1 cardiac failure at 15 days, 1 pulmonary hypertension after 7 years and 5 for neoplastic progression after 3 months.

Conclusions: 1. Mean age is 66.48 years with differences according to severity: 63.32 vs 67.05 years, p<0.05. 2. Overweight exists in 70.24% without severity differences. 3. PE was severe in 14.5% of outpatients and 19% in admitted patients. 5. Mortality was 4.1% without severity differences. Most of them were later than 3 months after PE diagnosis.

Table: Distribution by age

<table>
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<tr>
<td>&gt;80</td>
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</tbody>
</table>

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Aims: VTE is a serious preventable complication of hospitalization and considered a major cause of morbidity and mortality in hospitalized patients. Lack of studies in our Middle East region in such domain is a great problem. Knowing the exact figures about the incidence of VTE mortality and morbidity will empower the Health Care Professionals “HCP” to develop and improve the treatment and prophylaxis of VTE via continuous medical education of HCP, active dissemination and implementation of guidelines and how we adhere to them. This study is the first registry to be done in this region of the world.

The main objectives are:
1. finding out the proportion of mortality due to VTE in comparison with the total annual mortality;
2. finding out the total number of VTE events in one year;
3. determining the percentage of patients who got VTE prophylaxis among that population.

Patients: All patients diagnosed with in-hospital VTE during hospitalization within the period from 1 July 2008 till 30 June 2009 and those hospitalized with confirmed diagnosis of VTE.

Main Outcome measures: Proportion of VTE related mortality and morbidity among patients admitted to the hospital either due to lack of VTE prophylaxis or inadequate prophylaxis, inadequate dose, or duration.

Results: The one year data review reveals 238 cases of VTE (age range 46-79 years old). 57 cases out of those 238 cases died due to VTE incidence which represents a mortality of 23%. 118 cases (49.5%) had developed /occurred in the surgical ward, while the rest (120 cases, 50.5%) were in medical wards. Those 238 cases are split between 169 DVT cases (71%) and 69 PE cases (29%). Upon reviewing patients records in surgical ward cases (118 case of VTE, 49.5% of total cases) we noticed that only 51 case had received VTE prophylaxis representing 43% of total surgical ward cases. While in medical ward cases (120 case of VTE, 50.5% of total cases) we noticed that only 27 case had received VTE prophylaxis representing 22% of total medical ward cases. Even in those cases receiving prophylaxis, their prophylaxis is not matching with ACCP guidelines either in terms of duration or dosage.

Conclusion: The study shows that there is improper implementation of the international VTE Prophylaxis guidelines (more prominent in the medical ward) which could be attributed to the lack of knowledge and absence of formal policy for VTE prophylaxis. Inaccurate database documentation regarding the prevalence of PE related death in the hospital being only mentioned in discharge by CT Pulmonary Angiography. Autopsy can detect other cases, but it is not performed due to several constrains.

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Deep vein thrombosis (DVT) is one of the most common complications in post-operative patients. It is associated with considerable morbidity and mortality. Majority of patients with postoperative DVT are asymptomatic. The pulmonary embolism, which is seen in 10% of the cases with DVT, may be a fatal complication. Thus, it becomes imperative to prevent DVT rather than to diagnose and treat.

Context: Deep vein thrombosis in high risk south Asian patients undergoing major operations.

Aims: To document the risk of DVT following major operations and to evaluate the effectiveness of Nadroparin therapy in preventing postoperative DVT.

Materials and methods: Prospective randomised control study comparing effectiveness of Nadroparin therapy in preventing DVT in a cohort of 65 patients undergoing major abdominal operations.

Sixty-five patients were randomised preoperatively; Group-I received Nadroparin prophylaxis and Group-II no prophylaxis. The primary outcome DVT was assessed, seven to ten days after operation using bilateral lower limb venogram. Secondary parameters like adverse effects, intraoperative blood loss, operating time, postoperative platelet count, intraoperative blood transfusion requirements and the total duration of postoperative bed rest were also compared.

Statistical analysis used: The relative risk of DVT and secondary outcome measures among the patients receiving Nadroparin was compared to those in control group, using t-test, Chi-square test and paired samples test.

Results: There was no evidence of DVT in both the groups as documented using postoperative bilateral lower limb venogram, also there was no statistical difference among both groups in secondary parameters.

Conclusions: The incidence of DVT is very low or absent even among high risk South Asian population. More studies needed to find the physiologic basis of relative high immunity to DVT in this population. The LMWH’s did not increase the incidence of DVT, LMWH’s, venography

Keywords: DVT, LMWH’s, venography

Table 1: Risk stratification and type of surgery performed.

<table>
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<th>Group</th>
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<th>High risk</th>
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<tr>
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<td>14</td>
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<td>6</td>
</tr>
<tr>
<td>Group II (C)</td>
<td>13</td>
<td>15</td>
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</tr>
<tr>
<td>Total</td>
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<td>29</td>
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Table 2: Types of operations performed

<table>
<thead>
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<th>operation</th>
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<th>Group-II (C)</th>
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<td>8</td>
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<tr>
<td>CBD exploration</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Rectal Operation</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Exploratory laparotomy</td>
<td>14</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Oesophagectomy</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ilio-Iguinial lymph node dissection</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>31</td>
<td>65</td>
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</tbody>
</table>
VENOUS THROMBOEMBOLISM PROPHYLAXIS: A COLLABORATIVE APPROACH TO CHANGING PRACTICE

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Keywords: VTE, prevention, procedures

Background: Venous thromboembolism (VTE) risk assessment and prophylaxis prescription in hospitalised patients is frequently inadequate despite readily available, evidence-based consensus guidelines. Systematic implementation of VTE prophylaxis by a multi-disciplinary team may improve prophylaxis and thereby reduce VTE associated mortality and morbidity.

Aims: The aims of this study were to redesign the systems and processes involved in VTE prophylaxis using nurse led VTE prevention teams and to report its effect on the rate of appropriate VTE prophylaxis.

Methods: The process of VTE prophylaxis was redesigned in a tertiary level acute care hospital. Following an active education program, nurses undertook responsibility for VTE risk assessment of all admitted patients and for the initiation of mechanical prophylaxis. Where inadequate anticoagulant prophylaxis was identified, the nurses alerted medical staff to allow prompt correction. VTE prophylaxis was provided according to evidence based protocols. Senior medical staff and other key stakeholders agreed on the protocols and supported the system changes prior to program implementation. Audit of appropriate prophylaxis was conducted before the nurse led redesign and annually thereafter for four years to assess its efficacy.

Results: Audit was performed on 2063 patients. The majority of these were at risk of VTE and required prophylaxis. The rates of appropriate prophylaxis in at risk patients increased from 27% to 85% (p<0.0001) over a period of four years following the introduction of the nurse led VTE prevention teams.

Conclusions: Nurses who are upskilled in VTE risk assessment and prophylaxis and are committed to VTE risk reduction have the ability to contribute significantly to improving rates of appropriate VTE prophylaxis and reducing subsequent VTE complications. Nurses are well positioned to improve outcomes for patients at risk of VTE. The improvement in VTE prophylaxis rates is likely to reduce hospital complications. Nurses are well positioned to improve outcomes for patients at risk to improving rates of appropriate VTE prophylaxis and reducing subsequent VTE

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THROMBOSIS AND CELIAC DISEASE: REVIEW OF 5 CASES

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Keywords: celiac disease, Budd-Chiari, cerebral venous thrombosis

Background: Celiac disease (CD) is an autoimmune enteropathy and is a part of disorders recognized as being thrombogenous.

Aims: To review some case reports of venous thrombosis (VT) of unusual sites associated with a CD.

Patients and methods: Retrospective study of singular sites of VT occurred in CD and collected in internal medicine practice from January 2000 to December 2009 (individual recruitment).

Results: 5 patients are studied, 5 women, average age is 44 years (21- 65). VT is localized in abdomen (4) and brain (1). VT revealed CD in 4 times (abdominal VT). The last case of CD is associated with a CD.

Discussion: Cerebral venous thrombosis and abdominal thrombosis are unusual modes of revelation of CD and implicated to malignant degeneration, an acquired thrombophilia, an hepatocellular insufficiency and a severe malabsorption (Vit B12 deficiency).

Conclusions: Unusual sites of thrombosis in CD are rare. Maghrebine literature report series of VT in CD by many authors so it is necessary to considered this affection as an etiologic cause of VT, particularly in these areas.

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TIME-TRENDS IN TREATMENT AND CARDIOVASCULAR EVENTS IN PATIENTS WITH HEART FAILURE: A PHARMACOSURVEILLANCE STUDY

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Keywords: epidemiology, heart failure, pharmacotherapy, prognosis

Aims: Prognosis for patients with a first hospitalisation for heart failure (HF) may have improved, but data beyond 2003 are lacking. We assessed the temporal relationship of cardiovascular events and treatment in patients with a first hospitalisation for HF between 1998-2007.

Methods: Data were obtained from the PHARMO Record Linkage System, a Dutch population-based registry of pharmacy records linked with hospital discharge records. Patients were selected based on a first hospital discharge of documented HF. Two time-periods were compared: 1998-2002 and 2003-2007. We analyzed all prescribed cardiovascular medication and the occurrence of events within the first year after hospitalisation for HF. Cardiovascular events were defined as rehospitalisation for HF, myocardial infarction or stroke; ischemic events as myocardial infarction or stroke. Logistic and cox regression analysis was performed to calculate odds ratios (OR), hazard ratios (HR), and 95% confidence intervals (CI) between the two time-periods.

Results: We identified 17,921 patients (8374 between 1998-2002, 9,547 between 2003-2007). Mean age was 75±11 and 76±11 years, respectively. There was an increase in almost all prescriptions in the second period, particularly beta-blockers (Table). In the first year after hospitalisation there was no clear reduction in the risk for any cardiovascular event between the two time-periods. The incidence of ischemic events was reduced in the second time-period compared to the first.

Conclusion: This large study shows that prescription of cardiovascular medication in patients with a first hospitalisation for HF increased in recent years, while the incidence of ischemic events decreased.

Table

<table>
<thead>
<tr>
<th>Prescriptions</th>
<th>1998-2002 (%)</th>
<th>2003-2007 (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAAS-inhibitors</td>
<td>45.29 (64.1)</td>
<td>54.45 (57.0)</td>
<td>1.13 (1.06-1.20)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>3052 (36.4)</td>
<td>5333 (55.9)</td>
<td>2.21 (2.08-2.34)</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>2456 (29.3)</td>
<td>3203 (33.5)</td>
<td>1.22 (1.14-1.30)</td>
</tr>
<tr>
<td>Antiplaete agents</td>
<td>2379 (28.9)</td>
<td>3051 (32.0)</td>
<td>1.18 (1.11-1.26)</td>
</tr>
<tr>
<td>Statins</td>
<td>1397 (15.6)</td>
<td>2719 (28.5)</td>
<td>2.15 (2.00-2.32)</td>
</tr>
</tbody>
</table>

Events in the first year HR (95% CI)

- All cardiovascular events (including rehospitalisation HF): 1648 (19.7) 1791 (18.8) 0.99 (0.93-1.06)
- Ischemic events only (myocardial infarction or stroke): 228 (2.7) 183 (1.9) 0.74 (0.64-0.90)
- Pulmonary embolisms: 19 (0.2) 20 (0.2) 1.44 (0.81-2.56)

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CHEST PHYSICIANS’ KNOWLEDGE OF APPROPRIATE THROMBOPROPHYLAXIS: FINDINGS FROM THE PROMOTE STUDY

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Keywords: VTE prophylaxis, knowledge, questionnaire

Introduction: Venous thromboembolism (VTE) is a major cause of morbidity and in-hospital mortality. Several guidelines recommend thromboprophylaxis for at-risk patients, however, guideline adherence is missing worldwide. The PROMOTE (Prophylaxis-foR-vEinthromboembolism) questionnaire was designed to evaluate the knowledge of chest physicians regarding VTE prophylaxis.

Methods: The questionnaire was developed using a hierarchic method to encompass the most important issues regarding thromboprophylaxis and contained five background questions and thirteen clinical scenarios each covering one or more aspects of VTE prophylaxis. During the 4th International Congress on Pulmonary Disease, Intensive Care and Tuberculosis, the questionnaire was distributed to the chest physicians (pneumologists, thoracic surgeons, intensive-care specialists, cardiologists and internists). The 8th edition of the American College of Chest Physicians (ACCP) guidelines on antithrombotic and thrombolytic therapy were used to evaluate thromboprophylaxis appropriateness.

Results: 83 completed questionnaires were received (response rate: 37.1%). The most commonly cited VTE risk factors were: bed-ridden state (80%), surgery (68%), cancer (61.2%), obesity (52.5%), hypercoagulability (47.5%), old age (41.2%), VTE history (40%), hyperestrogenic state (36.2%), heart failure (30%), stroke (22.5%), and COPD (22.5%).

Overall appropriate response rate to the questions was 67.7% (95%CI: 64.5%-71%). Cardiologists, and surgeons had the most and the least appropriate responses (77.1%, and 62.7%, respectively). The most striking knowledge gaps were about improper low-molecular-weight heparin dosing (failure rates of 66.2% and 58.1% for two different clinical scenarios), inadequate use of non-pharmacological prophylaxis for those with contraindications to anticoagulants (failure rates of 59.6%, and 39.2% in two separate scenarios), and inadequate prophylactic measures for young patients undergoing major surgical procedures (failure rate: 52.6%).

Conclusions: Lack of proper knowledge could partly justify the huge gap between the guidelines recommendations and the current VTE prophylaxis practice. PROMOTE is the first systematically-developed questionnaire to address the VTE prophylaxis knowledge assessment amongst the chest physicians and might be a useful tool to improve VTE prophylaxis state.

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PREVENTING VENOUS THROMBOEMBOLISM – POLICIES, PROGRAMS AND PROGRESS IN AUSTRALIA

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Keywords: VTE, prevention, policies

Background: While extensive evidence exists to guide the proper prophylaxis and treatment of venous thromboembolism (VTE), several studies show that the evidence is not being followed. In a large multinational cross sectional survey of hospitalised patients identified at risk for VTE, only approximately 50% of these at risk patients were receiving appropriate prophylaxis. The burden of VTE is considerable and a recent study in Australia estimated the total cost of VTE per patient per annum including medical costs, lost productivity etc was $AS 475,150 ($US 334,000). Appropriate VTE prophylaxis and prevention delivers significant cost benefits.

Aims: To compare the policies and programs underpinning VTE prevention in Australian States and their progress in VTE prevention in hospitalised patients.

Methods: While extensive evidence exists to guide the proper prophylaxis and treatment of venous thromboembolism (VTE), several studies show that the evidence is not being followed. In a large multinational cross sectional survey of hospitalised patients identified at risk for VTE, only approximately 50% of these at risk patients were receiving appropriate prophylaxis. The burden of VTE is considerable and a recent study in Australia estimated the total cost of VTE per patient per annum including medical costs, lost productivity etc was $AS 475,150 ($US 334,000). Appropriate VTE prophylaxis and prevention delivers significant cost benefits.

Aims: To compare the policies and programs underpinning VTE prevention in Australian States and their progress in VTE prevention in hospitalised patients.

Results: Two of the largest States, New South Wales and Queensland, have robust hospital mortality. Several guidelines recommend thromboprophylaxis for at risk patients, however, guideline adherence is missing worldwide. The PROMOTE (Prophylaxis-foR-vEinthromboembolism) questionnaire was designed to evaluate the knowledge of chest physicians regarding VTE prophylaxis.

Methods: The questionnaire was developed using a hierarchic method to encompass the most important issues regarding thromboprophylaxis and contained five background questions and thirteen clinical scenarios each covering one or more aspects of VTE prophylaxis. During the 4th International Congress on Pulmonary Disease, Intensive Care and Tuberculosis, the questionnaire was distributed to the chest physicians (pneumologists, thoracic surgeons, intensive-care specialists, cardiologists and internists). The 8th edition of the American College of Chest Physicians (ACCP) guidelines on antithrombotic and thrombolytic therapy were used to evaluate thromboprophylaxis appropriateness.

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Conclusions: Lack of proper knowledge could partly justify the huge gap between the guidelines recommendations and the current VTE prophylaxis practice. PROMOTE is the first systematically-developed questionnaire to address the VTE prophylaxis knowledge assessment amongst the chest physicians and might be a useful tool to improve VTE prophylaxis state.

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AETIOLOGIES OF JUGULAR THROMBOSIS OBSERVED IN INTERNAL MEDICINE PRACTICE

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Dr Mohammad-Lamine Debaghine, Bab El Oued University Hospital Centre, Algiers City, Algeria

Keywords: jugular thrombosis, lemiere syndrome

Background: Deep vein thrombosis is frequently observed in internal medicine practice but the jugular localizations are rare and this imposes to determine imperatively their aetiology

Aims: To review the main aetiology of jugular thrombosis observed in our practice.

Patients and methods: Retrospective and descriptive study from January 2000 to December 2009 in an internal medicine center. The studied items relate to history, clinical presentation, biological and morphological additional investigations, therapeutic modalities and the following up.

Results: We brought together 13 cases, 7 women and 6 men. The average age was 49 years. These patients showed in the majority of the cases a stereotypical symptomatology made by trachelodynia with oedema filling the bottom of bag known as clavicular. The found causes were infectious pathology in 3 cases (Lemierre syndrome in two cases), neoplasia in 2 cases (lung, colon), thrombophilia in 2 cases, systemic erythemic lupus associated with a syndrome of antiphospholipids (2) and with a nephritic syndrome is identified (1), Behcet’s Disease (3) and finally 1 case stayed with no etiology in 1 year of follow-up. All the patients were treated by anticoagulant treatment associated with the treatment of the identified cause (antibiotic therapy, corticosteroids, antimalarial drugs, antineoplastic chemotherapy, immuno-suppressives drugs, etc.). The evolution was favorable (on the general and vascular plan) in all patients except for patients with neoplasia.

Conclusion: Diagnosis of the jugular thrombosis can be strongly suspected by clinical signs and confirmed secondarily by the additional examinations mostly limited to an echo vascular doppler ultrasound method and angio IRM (neck, brain).

The prognosis depends strictly on the aetiology and the precocity of the care. Even if the ‘good-hearted’ (‘benignant’) causes (in particular those of infectious origin) are curable, regrettably the thromboses which accompany neoplasias or chronic inflammatory diseases constitute events which come to darken even more the prognosis of these diseases (recurrence, extensive and propagating thrombosis, etc.).

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PERSISTENCE OF RESIDUAL THROMBUS IN PATIENTS WITH IDIOPATHIC VENOUS THROMBOSIS AND ITS RELATIONSHIP WITH OTHER RISK FACTORS FOR RECURRENT

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Keywords: thrombus residual, relapse thrombosis

Background/Aims: The persistence of venous thrombosis after a first episode of unprovoked venous thrombosis has been associated with the risk of recurrent event.

Several recent articles have examined the relationship between residual venous obstruction and D-dimer levels. The aim of this study is to analyze the relationship between the persistence of venous thrombus and the presence of thrombophilia and postphlebitic syndrome.

Methods: Prospective study: we included all patients with a first episode of idiopathic venous thrombosis, diagnosed between January 2005 and January 2008. Six months after the first episode all patients underwent compression ultrasonography, a thrombophilia study, a d-dimer level and a clinical re-evaluation searching for postphlebitic syndrome.

Results: 84 patients were analyzed, with a minimum follow-up time of six months and a maximum of two years, median of 17 months (12-24). 53.6% were men. The average age was 61.7 ± 18.4 years (range 19-91 years). After the acute phase, all patients were treated with oral anticoagulants or low-molecular-weight heparin because they do not adequately reflect the balance between procoagulant and anticoagulant clotting factors. Recently a test has become available to routinely measure the endogenous thrombin generation potential (ETP) by Dade Behring (Germany).

Aims: The comparison of ETP values and other coagulation markers between controls and patients with liver cirrhosis.

Methods: 56 samples of consecutive patients with histologically confirmed liver cirrhosis, and 30 samples of controls were investigated for PT/INR, fibrinogen, D-dimers and ETP parameters. We used the chromogenic method on the fully automated Behring Coagulation System (BCS) for the measurement of thrombin generation parameters.

Results: 6 patients had alcoholic cirrhosis, 22 HCV, 5 PBC, 7HBV, 1HBV and HDV and 13 cirrhosis of unknown origin.

Summary/Conclusions: The automated ETP test can play an important role in the evaluation of haemostatic liver function in patients with cirrhosis. A potential clinical implication of these findings is that the laboratory investigation of the coagulation function, presently performed with the PT and APTT, may be inadequate to assess the true risk of bleeding when patients with cirrhosis undergo invasive procedures such as liver biopsy and transplant surgery. Perhaps the measurement of thrombin generation might be more suitable to evaluate the hemorrhagic risk.

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THROMBIN GENERATION AND OTHER COAGULATION MARKERS IN PATIENTS WITH LIVER CIRRHOSIS

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Keywords: thrombin generation, cirrhosis

Background: The role played by coagulation defects in the occurrence of bleeding in cirrhosis is unclear. Conventional coagulation tests (PT/INR, aPTT) seem unable to predict the severity of bleeding problems in patients with liver cirrhosis, possibly because they do not adequately reflect the balance between procoagulant and anticoagulant clotting factors. Recently a test has become available to routinely measure the endogenous thrombin generation potential (ETP) by Dade Behring (Germany).

Aims: The comparison of ETP values and other coagulation markers between controls and patients with liver cirrhosis.

Methods: 56 samples of consecutive patients with histologically confirmed liver cirrhosis, and 30 samples of controls were investigated for PT/INR, fibrinogen, D-dimers and ETP parameters. We used the chromogenic method on the fully automated Behring Coagulation System (BCS) for the measurement of thrombin generation parameters.

Results: 6 patients had alcoholic cirrhosis, 22 HCV, 5 PBC, 7HBV, 1HBV and HDV and 13 cirrhosis of unknown origin.

<table>
<thead>
<tr>
<th>Controls</th>
<th>Patients</th>
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</thead>
<tbody>
<tr>
<td>mean</td>
<td>sd</td>
</tr>
<tr>
<td>Hage</td>
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<tr>
<td>INR</td>
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<tr>
<td>Fibrin/D</td>
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<tr>
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VENOUS THROMBOEMBOLISM AFTER ORTHOPAEDIC MAJOR SURGERY IN PATIENTS WITH CORRECT THROMBOPROPHYLAXIS


Hospital Povisa, Vigo, Spain

Keywords: thromboembolism, orthopaedic major surgery, thromboprophylaxis

Background: Venous thromboembolism (VTE) prophylaxis is routinely administered during the in-hospital period and after discharge in patients who undergo orthopedic major surgery (OMS). However, VTE risk may persist and the standard duration of thromboprophylaxis may not provide adequate protection.

Aims: To describe the clinical characteristics, risk factors, complications and evolution of VTE after OMS in patients with appropriate prophylaxis.

Materials and methods: A retrospective, descriptive study was carried out of the histories of patients diagnosed of VTE between January 2000 and December 2008. In all patients the thromboprophylaxis regimen was continued for 30 days and anepisodes occurred within three months after surgery.

Results: 41 patients were diagnosed of VTE (63% female; mean age 67.8 years; average stay 16.4 days). Type of surgery: hip fracture: 12; hip replacement: 10; knee replacement: 6; ankle fracture: 6; femur fracture: 3; other fractures 4. Time from surgery to VTE was 32.3 days. During in-hospital period 13 episodes occurred and 28 occurred after discharge (the prophylaxis period had finished in 17). Risk factors are present in 15 patients: previous VTE (5), venous insufficiency (4), cancer (3), stroke (4), COPD (4), BMI >30 (1), smoking (3), chronic heart failure (2), and thrombophilia (1). Screening for thrombophilia was carried out in 10 patients and was positive in 9: hyperhomocysteinemia (4), heterozygote/homozygote carrier of C677 MTHF (3/2), protein C deficiency (2) and homozygote carrier of prothrombin G20210A (1). All patients received anticoagulant treatment for at least 3 months and was permanent in 12 cases (10 with atrial fibrillation and 2 for recurrent VTE). Two patients developed major bleeding, one died for sepsis and recurrent VTE occurred in 2 cases.

Conclusions: Despite an appropriate prophylaxis some patients develop VTE after OMS because the risk is present for more time than prophylaxis is usually recommended. Screening for thrombophilia may detect unsuspected thrombophilic defects.

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LABORATORY AND IMAGING STUDIES PREDICTORS OF MORTALITY AFTER PULMONARY EMBOLISM


Department of Internal Medicine, Hospital Povisa, Vigo, Spain

Keywords: pulmonary embolism, mortality, predictors

Background/Aims: Pulmonary embolism (PE) is known to be a cause of death in patients with venous thromboembolism. The aim of this study was to analyse laboratory and imaging studies predictors of mortality after PE.

Materials and methods: A retrospective study was carried out of the histories of patients diagnosed of PE between January 2007 and December 2007.

Results: 112 patients were diagnosed of PE, with a mean age of 67 years, 46% male. Mortality rate was 12.5%, and a survival for up to 12 months 94%. Patients who did not had lower values of systolic and diastolic pressures (117/79 vs 123/73), arterial oxygenembolism saturation and arterial oxygen tension (92% and 71mmHg vs. 90% and 68mmHg), and higher D-dimer values (5620 vs 2467) and cardiac frequency (75/353 examinations (21.2%) were positive for CVC-related apposition or fibrin-sleeve. The remaining 54 for clinical suspected CVC complications involved the venous vessel wall (sub-occlusive or occlusive DVT), or fibrin-sleeve without wall involvement. US exams for generic control, the frequency of positive Doppler was significantly higher in the group of clinically suspected CVC complications (p=0.039) and the probability of US test positivity doubled when CVC complications were clinically suspected (OR 2.12, 95% CI 1.07-4.19, p=0.03). On the contrary, in the absence of clinical suspect, the probability of US test positivity halved (OR 0.47, 95% CI 2.24-0.93, p=0.02).

Conclusions: In the ultrasound monitoring of CVC-related complications, the pretest probability based on clinical suspect of complications was significantly related to the presence of thrombosis. According to our results ultrasound CVC surveillance in absence of clinical suspected complications is questioned.

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ORTHOPAEDIC MAJOR SURGERY IN PATIENTS WITH CORRECT THROMBOPROPHYLAXIS

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Keywords: inflammation, end stage renal disease, biochip array

The purpose of this study is to profile several inflammatory mediators in order to better understand their role in the underlying mechanism of vascular changes in ESRD. Plasma samples from 49 patients with ESRD were collected prior to maintenance hemodialysis sessions. A group of 56 normal individuals, both male and female, was included as control. Cerebral Artery II chips were used in the Randox® system to simultaneously measure Neuron Specific Enolase (NSE), Neutrophil Gelatinase-associated Lipocan (NGAL), Soluble Tumor Necrosis Factor Receptor I (TNFRF), D-Dimer (DD), Thrombomodulin (TM), and C-reactive protein (CRP). As compared to the normal individual, all of the markers studied showed an upregulation in patients with ESRD. Most notably, TNFRF showed a 19.8 fold increase in patients with ESRD (mean 7.8 ± 2.8 ng/ml, range 0.8 to 13.7) compared to the control (mean 0.4 ± 0.2, range 0.1 to 1.0). TM was increased 5.2 fold (mean 6.5 ± 2.6, range 0.7 to 14.1) compared to control (mean 1.2 ± 0.6, range 0.6 to 2.3). NGAL showed a 4.6 fold increase (mean 1390 ± 257, range 406 to 1729), compared to control (mean 299 ± 99, range 115 to 603), and CRP a 4.2 fold increase (mean 5.7 ± 4.2 ug/ml, range 0.6 to 13.2) compared to control (mean 1.4 ± 1.7, range 0.2 to 11.4). DD and NSE were also increased 3.0 and 1.8 fold respectively. These studies show that some newer markers such as TNFRF, NGAL and NSE are upregulated in ESRD. The marked increase in TM is highly suggestive of endolathelial damage. Similarly, the increase in TNFRF supports a state of increased cellular damage. The elevations in NGAL and CRP imply a state of increased inflammation and indicate a polypathologic process which may predispose ESRD patients to both cardiovascular and cerebrovascular thromboembolic events.

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ULTRASOUND MONITORING OF LONG TERM CENTRAL VENOUS CATHETERS. OUR EXPERIENCE IN THE LAST TWO YEARS

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Keywords: central venous catheter, (CVC), CVC complications, deep vein thrombosis

Background: The widespread use of CVC has exponentially increased the request for echocolorDoppler examination to optimize the management of CVC complications, mainly deep vein thrombosis (DVT). However, the ultrasound “surveillance” of CVC is currently being carried out according to different protocols, shared, since guide-lines are not available. We reviewed, retrospectively, the prevalence of CVC related DVT and/or fibrin-shear detected by echocolorDoppler in patients observed in the last two years.

Methods: between December 2007 and December 2009, 353 echocolorDoppler of subclavian-jugular vein were performed in oncologic patients endowed with long-term CVC, 134 men, aged 18-85 years (main age 55±14). We considered as positive the US tests that showed the presence of intraluminal thrombotic material involving the venous wall vessel (sub-occlusive or occlusive DVT), or fibrin-sleeve without wall involvement. US exams were performed in 173 patients without clinical suspect of complications (positive control) and in the remaining 180 for clinical suspect of complications (inflammation and thrombosis). The remaining 126 US exams were performed before CVC removing. 

Results: 75/353 examinations (21.2%) were positive for CVC-related apposition or DVT. And 19% of the 126 US performed before removing were positive. Compared to US exams for generic control, the frequency of positive Doppler was significantly higher in the group of clinically suspected CVC complications (p=0.039) and the probability of US test positivity doubled when CVC complications were clinically suspected (OR 2.12, 95% CI 1.07-4.19, p=0.03). On the contrary, in the absence of clinical suspect, the probability of US test positivity halved (OR 0.47, 95% CI 2.24-0.93, p=0.02).

Conclusions: In the ultrasound monitoring of CVC-related complications, the pretest probability based on clinical suspect of complications was significantly related to the presence of thrombosis. According to our results ultrasound CVC surveillance in absence of clinical suspected complications is questioned.

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EVALUATION OF A NEW AUTOMATED PANEL OF ASSAYS FOR THE DETECTION OF ANTI-PF4/HEPARIN ANTIBODIES IN PATIENTS SUSPECTED OF HAVING HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

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Keywords: HIT, diagnosis, immunosassay

Background/Aims: HIT is a life-threatening complication of heparin treatment; the prognosis depends on early and accurate diagnosis, and prompt start of alternative anticoagulants. Because of high sensitivity, the commercially available immunological assays are widely used, though not suited to be run on single samples and with a turnaround time of 2-3 hours. We evaluated two new, rapid, automated, quantitative chemiluminescent immunosassays in HIT suspected patients: HemosIL AcuStar HIT-IgG(PF4-H) (specific for IgG anti-PF4/heparin antibodies) and HemosIL AcuStar HIT-Ab(PF4-H) (detecting IgG, IgM and IgA anti-PF4/heparin antibodies) (Instrumentation Laboratory).

Methods and results: HIT confirmation/exclusion was based on the flow chart proposed by Poupard et al. (J Thromb Haemost 2007), which combines the results of the HIT pretest probability (PTP), estimated by the “4Ts” clinical score, and of the ID-Heparin PF4 PaGIA, a rapid immunoassay. In patients with positive ID-Heparin PF4 PaGIA test and in those with negative ID-Heparin PF4 PaGIA but with high PTP, a platelet aggregation assay was also performed. 102 patients with suspected HIT were included; HIT was diagnosed in 17 (16.7%). No false negative cases were observed using either the HemosIL AcuStar HIT-IgG(PF4-H) or the HIT-Ab(PF4-H) assay (sensitivity and negative predictive values = 100%; negative likelihood ratios <0.01). The specificity was higher for the HemosIL AcuStar HIT-Ab(PF4-H) in comparison with that of the HemosIL AcuStar HIT-IgG(PF4-H) (96.5% vs 81.2%). Higher values of the HemosIL AcuStar HIT-IgG(PF4-H) were associated with increased HIT PTP. Patients with confirmed HIT and thrombotic complications had significantly higher levels of HemosIL AcuStar HIT-IgG(PF4-H) than those without thrombotic complications.

Conclusions: The HemosIL AcuStar HIT-IgG(PF4-H) and HIT-Ab(PF4-H) assays showed a very high sensitivity and therefore they can reliably be used to rule out HIT in suspected patients. The diagnostic specificity was greatly increased by using the HemosIL AcuStar HIT-IgG(PF4-H). The assays are reproducible (CVs <6%), rapid (turnaround time 30 min), automated, quantitative, and can be run for single sample testing.

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NEW GUIDELINES FOR LA: SENSITIVITY AND SPECIFICITY OF ICA IN MIXING STUDIES AND % OF CORRECTION IN CONFIRMATORY TEST CUT-OFF VALUES OBTAINED WITH PLASMAS FROM HEALTHY CONTROL

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Keywords: lupus anticoagulant, antiphospholipid syndrome

Background/Aims: The updated guidelines for LA diagnosis indicate locally calculate the index of circulating anticoagulant (ICA) for mixing studies and % of correction (%C) or normalized ratio (NR) for confirmatory tests. Our aim was to calculate the index of circulating anticoagulant (ICA) for mixing studies and % of correction (%C) or normalized ratio (NR) for confirmatory tests. ICA-APTT has high SEN but low SPC, and for dRVVT show low SEN and high SPC, but for dRVVT show low SEN and high SPC, but for dRVVT show low SEN and high SPC.

Conclusions: The combination of mixing studies and confirmatory tests for APTT and dRVVT interpreted according the new guidelines can clearly differentiate the presence of LA from other coagulopathies.

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INFLAMMATORY BIOMARKERS AND CLINICAL CHARACTERISTICS DIAGNOSE DEEP VENOUS THROMBOSIS


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Keywords: biomarkers, venous thrombosis, diagnosis

Background/Aims: The combination of D-dimer and Wells score can exclude, but not confirm, the diagnosis of deep venous thrombosis (DVT). Since thrombosis and inflammation are interrelated, this study sought to determine if a combination of inflammatory biomarkers and clinical scores could establish the diagnosis.

Materials and methods: 153 patients presenting with suspected DVT, 45 positive and 108 negative by duplex scan, and 30 healthy controls were prospectively evaluated for soluble P-selectin (sPsel), D-dimer, C-reactive protein (CRP), microparticles (MP) and Wells score.

Results: Biomarkers and characteristics that discriminated DVT positives from negatives were sPsel (94.1vs53.1 ng/ml, p<0.01), D-dimer (5.8vs2.1, p<0.01), CRP (1.91vs0.83 µg/ml, p<0.05) and Wells score (3.3vs 2.0, p<0.01). MP were not found to be significant in the study. Results, using logistic regression are shown in the table.

Conclusions: sPsel + Wells can establish the diagnosis of DVT (>90 ng/ml + <2), with specificity=96% and PPV=100%, and can exclude the diagnosis (≤75 ng/ml + <2) with sensitivity=88% and NPV=100%. Based on our data, 37% (57/153) could potentially be diagnosed with DVT without the need of imaging exams.

Table: Multivariable regression analysis of biomarkers and DVT

<table>
<thead>
<tr>
<th>Variables</th>
<th>ROC</th>
<th>p-value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>sPsel (≥90 ng/ml)</td>
<td>0.82</td>
<td>p&lt;0.01</td>
<td>40%</td>
<td>95%</td>
<td>94%</td>
<td>78%</td>
</tr>
<tr>
<td>sPsel + Wells (≥90 ng/ml + ≥2)</td>
<td>0.82</td>
<td>p&lt;0.001</td>
<td>53%</td>
<td>96%</td>
<td>100%</td>
<td>79%</td>
</tr>
<tr>
<td>D-dimer (≤500 ng/ml)</td>
<td>0.39</td>
<td>p&lt;0.001</td>
<td>92%</td>
<td>33%</td>
<td>32%</td>
<td>96%</td>
</tr>
<tr>
<td>D-dimer + Wells (≤500 ng/ml + ≥2)</td>
<td>0.82</td>
<td>p&lt;0.001</td>
<td>94%</td>
<td>40%</td>
<td>31%</td>
<td>95%</td>
</tr>
<tr>
<td>Wells score (≥2)</td>
<td>0.63</td>
<td>p&lt;0.01</td>
<td>28%</td>
<td>86%</td>
<td>34%</td>
<td>79%</td>
</tr>
<tr>
<td>sPsel + D-dimer (≤50 ng/ml + ≤500 ng/ml)</td>
<td>0.83</td>
<td>p&lt;0.01</td>
<td>30%</td>
<td>98%</td>
<td>98%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Of 153 patients, 108 negatives presented sPsel≤50 ng/ml and Wells<2 and 45 positives had sPsel ng/ml and Wells≥2. Forty-two negatives and only 1 positive presented sPsel≥75 and Wells score≥2. Approximately 37% (57/153) could potentially be diagnosed with venous thrombosis without the need of imaging exams.

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DIFFERENT VARIANTS OF THE THROMBIN GENERATION TEST (TGT) SHOW DIFFERENCES IN SENSITIVITY TO MICROPARTICLES AND THE CONTACT SYSTEM: ANALYSIS OF ECAT SURVEYS

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Keywords: thrombin generation, microparticles, factor XII.

Background: ECAT-surveys on TGTs showed three categories of tests when ordered by time-to-peak (TTP). Rapid tests: Innovin ETP (Siemens) and in-TDT (Pentapharm) (50-60 sec); intermediate tests: CAT 5 and 1 pM (Thrombinscope) (300-550 sec), and slow tests: RCH and RCL (Technoclone) (1200-1600 sec), with a 30-fold difference in TTP. Methods: The survey included pooled plasma, microparticle-depleted plasma and a factor XII-deficient patient plasma. Between 4-11 laboratories participated per test. Analysed were a time (TTP) and quantity variable (AUC).

Results: MP-depleted plasma showed no difference in ETP, but a progressive increase in the other tests by decreasing tissue factor from 11-14% in the CAT T and 19-29% in the RCH T (p=0.002). The same was found for the AUC with the largest decrease of 35% for RCL (p<0.005). Re-addition of MP's restored the original situation. The factor XII deficient plasma showed no effect on TTP for ETP and CAT 1 and 5 pM; for RCH and RCL, TTP increased to 238-327% (p=0.028). The AUC for the ETP was unaffected, with a decline in: CAT 5 pM, -20% (p=0.001); CAT 1 pM, -34% (p=0.002); RCH -68% (p=0.008) and RCL -92% (p=0.003). The effects of factor XII deficiency were not mimicked by addition of CTI, showing only small to moderate effects depending upon the plasma source, but could be confirmed by inhibiting factor XIa.

Conclusions: The different sensitivities of TGTs to MP's and contact activation predicts them to associate differently with clinical situations in which those aspects are important. ETP is apparently insensitive to both; RCL is very sensitive to contact factor activation and MPs. Future ECAT-surveys should include samples with variation in MP's and contact activation to match with features of the TGT variants.

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IMPROVEMENT OF THE POSITIVE PREDICTIVE VALUE OF A COMBINATION OF D-DIMER WITH CONCOMITANT DISEASES FOR DIAGNOSIS OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

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Keywords: thrombosis, pulmonary embolism, positive predictive value

Background/Aims: Patients with suspicion of deep vein thrombosis (DVT) or pulmonary embolism (PE) undergo D-dimer testing or objective methods for identification of the thrombotic event. We hypothesized, that the absence or presence of frequent concomitant diseases may improve the pretest clinical probability for DVT/PE. Patients and methods: Patients were admitted to the emergency room with clinical suspicion of DVT or PE. The biographic data, the additional diagnosis, thrombophilia status, D-dimer and compression ultrasound (DVT-patients) or spiral CT (PE-patients) were documented. Patients with objectively documented DVT or PE were compared with those in whom the suspicion was not confirmed.

Results: DVT was confirmed in 77/132 patients and PE in 53/135 patients. Patients with DVT more frequently had a thrombophilic disorder (p=0.0002) and less frequently an erysipelas (p=0.002) compared to those in whom DVT was not confirmed. Patients with a positive D-dimer had a lower area under the receiver operating curve (ROC-area 0.8045) than those with the additional characteristics area: 0.7541 (p=0.0471). Patients with PE had more frequently a history of DVT/PE (p=0.0003) and less frequently chronic obstructive lung disease (p=0.01), atrial fibrillation without anticoagulation (p=0.02) and coronary heart disease (p=0.006). Patients with a positive D-dimer had a lower ROC curve (area: 0.7538) compared to those with these characteristics (area: 0.8517, p=0.0122). Biographic data, other concomitant diseases, leukocyte, thrombocyte and high sensitive c-reactive protein values did not differ between DVT/PE positive and negative groups.

Conclusions: Prospective studies are warranted to validate the findings compared to published pretest probability scores.

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DOES HIGH SENSITIVITY TROPONIN MEASUREMENT AID IN THE DIAGNOSIS OF VENOUS THROMBOEMBOLISM?

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Keywords: diagnosis, venous thromboembolism

Background/Aims: Diagnosing venous thromboembolism (VTE) can be a multistep, time-consuming process, which is often left to the most junior doctors to coordinate. Errors in the diagnostic process are not uncommon. The THREAD study aimed to assess the potential diagnostic role of new biomarker assays, in attempt to simplify diagnosis. This study reports the results from a new troponin T assay, with a significantly lower detection limit, in the diagnosis of pulmonary embolism (PE) and deep vein thrombosis (DVT).

Materials and Methods: The prospective diagnostic study was conducted at a single general hospital in the UK, between September 2008 and June 2009. Outpatients investigated for DVT and all patients investigated for PE were eligible. Exclusions were age <16, lack of capacity and refusal. All patients underwent an evidence based protocol to diagnose or exclude VTE, along with a three month clinical follow up period. The patients’ serum underwent blinded analysis for troponin T using the Roche high sensitivity troponin assay with a lower limit of detection of 0.005ng/ml. Potential for diagnostic use was assessed by constructing receiver operating characteristic curves for all patients, for patients assessed for DVT alone, for those assessed for PE, and outpatients.

Results: 919/926 patients investigated for VTE were approached for consent and 806 patients were enrolled to the study. DVT was diagnosed in 84/452 (18.6%) patients and PE in 68/354 (19.2%) patients. The mean age was 57, 60% female, 13% inpatients and mean time since symptom onset 13 days. The area under the ROC curve (AUC) for all VTE was 0.57 (95%CI 0.50-0.64), for DVT 0.51 (95%CI 0.44-0.58) and for PE 0.64 (95%CI 0.57 - 0.70). The AUC for PE was 0.71 (95% CI 0.63-0.78) in new patients presenting to the emergency department.

Conclusions: High-sensitivity troponin T cannot be used alone to diagnosed VTE.

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CAN ISCHEMIA MODIFIED ALBUMIN BE USED TO TEST FOR VENOUS THROMBOEMBOLISM?
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Keywords: diagnosis, venous thromboembolism

Background/Aims: Venous thromboembolism (VTE) remains a significant cause of death. Improved diagnostics have not reduced mortality rates. The process of diagnosing VTE remains multi-factorial. The THREAD study assessed novel biomarkers for the diagnosis of VTE, in attempt to identify a future simple test. The aim of this study was to assess the role of ischemia modified albumin (IMA) testing in the diagnosis of VTE.

This was a prospective diagnostic study. Patients age > 16 investigated for PE or DVT at a single hospital were eligible for consent. Exclusion criteria were lack of capacity and refusal. The first blood sample drawn was analysed for IMA. Each patient underwent a reference standard investigation to exclude or diagnose PE or DVT and was followed clinically for three months. Receiver operating characteristic (ROC) curves were constructed for IMA and IMA:albumin in the diagnosis of all VTE, PE, DVT and predefined subgroups. Financial constraints lead to an interim analysis after 380 patients to establish whether further IMA assessment was warranted.

Results: Between September 2008 and June 2009, 354 patients were consented and investigated for PE, and 452 patients for DVT (806 in total). All 354 patients investigated for PE had blinded IMA testing as did the first 199 DVT patients. Interim analysis demonstrated further IMA testing for DVT futile. The prevalence of VTE was 19.7%. The IMA:albumin ratio performed consistently better than IMA alone. The AUC for IMA:albumin in all VTE was 0.60 (95%CI 0.54 – 0.66), in DVT 0.56 (95%CI 0.46 – 0.65) and in PE 0.63 (95%CI 0.56 – 0.71). In patients presenting to emergency department with symptoms of PE, the AUC for IMA:albumin was 0.69 (95%CI 0.60 – 0.78).

Conclusions: IMA testing cannot be used alone to diagnose DVT or PE, although there is a moderate association with PE in emergency department patients.

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CRP TO AID THE DIAGNOSIS OF PULMONARY EMBOLISM
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Keywords: diagnosis, venous thromboembolism

Background/Aims: Diagnosing pulmonary embolism (PE) can be a difficult process for junior doctors, because it relies on clinical probability scoring and knowledge of how to apply and interpret D-dimer, VQ and CT scanning. The THREAD study aimed to assess the potential diagnostic role of novel biomarkers, in attempt to identify a future, more simple test. The aim of this analysis is to assess the potential role of CRP in the diagnosis of PE.

The prospective diagnostic study was conducted at a single general hospital in the UK, between September 2008 and June 2009. All patients investigated for PE were eligible. Exclusions were age <16, lack of capacity and refusal. All patients underwent an evidence based protocol to diagnose or exclude PE, along with a three month clinical follow up period. CRP was not conducted as a blinded research test, instead, the study documented the initial CRP result when the investigating physician ordered the test. Potential for diagnostic use was assessed by constructing receiver operating characteristic (ROC) curves for all patients investigated for PE and emergency department patients investigated for PE.

Results: 411/414 patients investigated for PE were approached for consent and 354 patients investigated for PE were enrolled to the study. PE was diagnosed in 19.2% patients. Of this cohort, 269 patients had CRP testing ordered by their physician. The area under the ROC curve (AUC) for CRP in the diagnosis of PE was 0.72 (95%CI 0.65-0.78). The AUC for PE was 0.77 (95%CI 0.69-0.84) in patients presenting to the emergency department (N=199).

Discussion: This is a limited exploratory analysis. Results will be available for the full cohort of patients (N=354) by the conference.

Conclusions: CRP has a moderate association with PE in emergency department patients, however could not diagnose PE alone.

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REFERENCE VALUES FOR THROMBOELASTOMETRY (ROTEM®) IN CYNOMOLGUS MONKEYS (MACACA FASCICULARIS)
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Background/Aims: The imbalance in clotting homeostasis, tending towards hypercoagulation, is recognized as the real barrier to the long-term survival of porcine xenografts in this species combination. The present study aimed to validate ROTEM® as a rapid bedside monitor allowing an integrated measurement of clot formation as far as strength, firmness and swiftness are concerned.

Methods: ROTEM® (Pentapharm GmbH, Munich, Germany) was used to investigate native coagulation (NATEM®), the intrinsic (INTEM®) and extrinsic (EXTEM®) pathways, the function of fibrinogen (FIBTEM®), and the presence of fibrinolysis in primate and xenograft models. Using classic validation approaches, the normal thromboelastographic profile was defined and the influence of haematocrit (Hct,%) and platelet count (x10⁹/L), fibrinogen (mg/dl), and factor VIII (FVIII,%) was evaluated.

Results: In all four (NATEM®, INTEM®, EXTEM®, FIBTEM®) assays considered, Clotting Time (CT, sec) and Clot Formation Time (CFT, sec) were shorter in primates than human. Moreover, a-ANGLE (°), Maximum Clot Firmness (MCF, mm), and Area Under the velocity Curve (AUC, mm x10⁹) were higher in primate than human. No substantial difference was observed for Hct and platelet count between the two species. On the contrary FVIII was higher in primates than human and, interestingly enough, fibrinogen was lower in monkeys than human.

Conclusions: ROTEM® is a reasonable coagulation monitor in primates as compared to human. Together these data suggest that, with regard to coagulation, xenotransplantation in xenons represent a much more difficult situation than xenotransplantation in humans.

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LABORATORY DIAGNOSIS OF HEPARIN-INDUCED THROMBOCYTOPENIA BY THROMBIN GENERATION ASSAY: EFFECTS OF THROMBOMODULIN AND FONDAPARINUX

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Keywords: HIT, HIT antibodies, thrombin generation test, thrombomodulin, fondaparinux

Background: Type II heparin-induced thrombocytopenia (HIT) is diagnosed on the basis of clinical and laboratory criteria. HIT antibodies (HIT-AbS) may be detected by immunnochemical or by functional methods. ELISA assays are highly sensitive, but functional methods are more specific for the diagnosis of HIT and have a major role in avoiding prolonged anticoagulation in non-HIT patients. Recently, a thrombin generation assay (TGA) for the functional detection of HIT-AbS has been described (Tardy-Poncelet et al, JTH 2009).

Materials and Methods: We have tested for HIT-AbS citrated plasma from 46 consecutive patients with the clinical suspicion of HIT in a modified TGA. Mixture of donor platelets (180-200 x 10^9/L), f.c. and patients’ plasma are incubated with tissue factor (0.5 pM f.e., Thrombinoscope bv, Maastricht, the Netherlands) in presence of unfractionated heparin (UHF 0, 0.2 and 1 IU/mL, f.c.) or with or without the combined addition of thrombomodulin (TM, 5 mM f.c.) and fondaparinux (200 ng/mL, f.c.).

Results: Of the 46 patients, 20 had no HIT-AbS by ELISA (HIPA Asserachrom, Stago, Asnieres sur Sire, France) and only 6 had HIT-AbS by both ELISA and the functional method described by Greinacher et al (HPLA, TH 1991). The table shows the median ETP (nmol of thrombin) and Peak (nmol/min) values observed in the different groups of patients. In the absence of UHF, +/-/+ patients showed increased Peak values both with and without TM and Fondaparinux, and increased ETP values only with the combination of TM and Fondaparinux. Under any assay conditions, the addition of UHF (0.2 IU/mL) reduced by more than 50% ETP and Peak values in +/-/- and +/-/-/- patients (p < 0.001), but did not change significantly either parameter in +/+/+ patients (p>0.58). Interestingly, plasma from two HIPA negative patients was strongly positive for HIT-AbS in the thrombin generation assay. The TGA is a promising tool for the detection of HIT-AbS.

Keywords: meta-analysis, D-dimer, prognosis

Background: Individual patient data (IPD) meta-analysis, even if more resource demanding, as compared to aggregate data (AD) meta-analysis, can more rigorously elaborate time-to-event data and investigate sources of heterogeneity.

Methods: We compared the performance of 2 meta-analyses pooling the same set of studies on the efficacy of D-dimer to stratify the risk of thrombosis recurrence after anticoagulation stopping in patient with a first unprovoked venous thromboembolism (VTE). AD meta-analysis provided annualized recurrence rates and a pooled risk ratio for positive versus negative D-dimer patients by a mixed-effects Poisson model. In addition to annualized rates, in the IPD meta-analysis a Kaplan-Mayer survival analysis was performed to obtain cumulative hazard for recurrence 1, 3 and 5 years after stopping anticoagulation according to D-dimer status, either as defined in each source study or basing on pre-specified cut-off points (250 and 500 ng/ml), also for age and D-dimer test timing subgroups. IPD-based study-stratified multivariable Cox regression was compared to meta-regression based on AD.

Results: Overlapping annualized VTE recurrence rates were found by the two approaches (8.8-9.9 for positive, 3.5-3.7 for negative D-dimer patients). IPD-based cumulative hazard after 3 years was 25.4 (95% confidence interval [CI] 21.3-30.4) for positive and 9.3 (95% CI 7.1-12.1) for negative D-dimer patients. AD-based pooled risk ratio and IPD-based hazard ratio suggested a 2.2-2.5-fold higher recurrence risk for positive versus negative D-dimer patients. Subgroup analysis and Cox regression showed that none of the hypothetical confounders (age, BMI, sex, hormonal therapy, genetic thrombophilia, timing of D-dimer testing, qualitative/quantitative definition of D-dimer status) affected the D-dimer prognostic efficacy. Meta-regression was not able to demonstrate it.

Conclusions: The AD and IPD meta-analyses on D-dimer yielded comparable findings but only IPD was able to explore the trend over time of recurrence risk and the effect of patient-level confounders on the prognostic value of D-dimer.

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D-DIMER TO DETERMINE RISK FOR DISEASE RECURRENCE AFTER UNPROVOKED VENOUS THROMBOEMBOLISM: ADDRESSING UNANSWERED QUESTIONS WITH A LARGE INDIVIDUAL PATIENT META-ANALYSIS

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Keywords: venous thrombosis, D-dimer, oral anticoagulants

Background: In patients with a first unprovoked venous thromboembolism (VTE), an elevated D-dimer after anticoagulant therapy stopping is a risk factor for recurrent VTE. Questions remain about the effect of the timing of D-dimer testing, patient age and the D-dimer cut-point on the ability of D-dimer to distinguish risk for recurrent disease.

Methods: We did a patient-level meta-analysis of prospective studies in patients with a first unprovoked VTE who had D-dimer testing after anticoagulation stopping and were followed for recurrent VTE. Kaplan-Meier analysis was used to determine the cumulative incidence of recurrent VTE in patients with a negative or positive D-dimer according to timing of D-dimer testing (<3 weeks, 3-5 weeks, or >5 weeks post-anticoagulation) and patient age (≤65 years, >65 years, or >75 years). We compared risk for recurrence first according to D-dimer status as defined in the source studies then using a pre-specified cut-point (500 µg/mL). We used the log-rank test to compare the risk for recurrent VTE according to D-dimer status (negative or positive) and the Cox regression analysis to adjust for potential confounders.

Results: We studied 1,818 patients with a first unprovoked VTE who had follow-up for a mean (standard deviation [SD]) of 26.9 (19.1) months. After 3 years, the cumulative incidence of recurrent VTE was significantly higher after a positive D-dimer (25.4%; 95% confidence interval [CI] 21.3-30.4) than after a negative D-dimer (9.3%; 95% CI 7.1-12.1; hazard ratio, 2.5; 95% CI 1.9-3.3), irrespective of timing of post-anticoagulation D-dimer testing. Patient age and D-dimer cut-point.

Conclusions: In patients with a first unprovoked VTE who have D-dimer measured after stopping anticoagulation, the timing of D-dimer testing, patient age and the D-dimer assay cut-point used do not affect the ability of D-dimer to distinguish patients at higher or lower risk for recurrent VTE.
COAGULATION ASSESSMENT BY ROTATION THROMBOELASTOMETRY (ROTEM) ANALYSIS IN PATIENTS WITH SPLANCHNIC VEIN THROMBOSIS WITH AND WITHOUT HEPATIC CIRRHOSIS.

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Background: Splanchnic vein thrombosis (SpVT) developed in the presence of normal liver rather than hepatic cirrhosis have deep differences in etiologic risk factors. The coagulation pattern and the determinants of thrombosis in patients with and without cirrhosis have not been defined yet.

Patients and methods: The following four different groups were enrolled: a) and b) subjects with objectively diagnosis of SpVT with and without hepatic cirrhosis; c) hepatic cirrhosis subjects without SpVT; d) healthy donors. Blood was drawn by each subject and both ROTEM assays (INTEM, EXTEM, FIBTEM and NATEM) and thrombophilia screening were performed.

Results: In INTEM, EXTEM, NATEM and FIBTEM assays, there were no differences in any of measured parameters (MCF, AUC, α-angle) among cirrhotic patients, both with and without splanchenic vein thrombosis. Patients with SpVT and healthy liver, had higher MCF, AUC, α-angle in INTEM (p=0.004, 0.003, 0.004, respectively), EXTEM (p=0.01, 0.02, 0.01, respectively) and FIBTEM (p=0.01, 0.05, 0.01, respectively) than patients with SpVT and hepatic cirrhosis. ROTEM® parameters correlate with platelet counts, FIX, FXI, Fibrogenin, AT, PC, PS plasma levels that were significantly lower in cirrhotic patients and with FVIII plasma levels that were significantly higher in cirrhotic patients than subjects with healthy liver (180 ± 75 vs 163 ± 79%, p=0.02). Moreover, MCF and AUC in INTEM and α-angle in EXTEM, correlated with the reduction of PT.

Conclusions: Correlation between ROTEM parameters and lower plasma levels of natural inhibitors of coagulation and with impaired PT levels, suggests sensitivity of rotation thromboelastometry to liver failure. Differences in ROTEM parameters have been found between patients with and without cirrhosis but not between those with and without splanchenic vein thrombosis.

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A GLOBAL ASSAY SENSITIVE TO ACTIVATED PROTEIN C ABNORMALITIES IS PREDICTIVE FOR CHEMOTHERAPY-ASSOCIATED VENOUS THROMBOEMBOLISM

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Keywords: Chemotherapy, venous thromboembolism, thrombophilia

Background/Aims: Consensus guidelines by multiple cancer organizations do not recommend routine prophylaxis for the primary prevention of venous thromboembolism (VTE) for out-patients receiving chemotherapy. Nonetheless, identifying patients with cancer who are most at risk for VTE is essential to improve time-delivered chemotherapy and quality of life. Thus, the need for the identification of novel candidate biomarker(s) to be used as predictors for VTE in cancer out-patients.

Patients and Methods: This study was designed to investigate the adequacy of a global assay designed to evaluate the functionality of the activated protein C (APC) system to predict VTE in cancer patients undergoing chemotherapy. Analysis was performed on citrated plasma samples of 208 out-patients prior to and before starting the second cycle of a new chemotherapy regimen.

Results: Patients' were classified as low, intermediate or high-risk according to a risk assessment model recently validated by Khorana and colleagues. Analysis of samples obtained during chemotherapy showed an impairment of the APC system in patients who developed VTE compared to those who did not (p<0.0001). Cox proportional hazards regression analysis for event-free survival of patients stratified on the basis of steady vs. impaired APC function demonstrated in the latter a worst cumulative event-free survival (56%) compared to patients with stable values (90%, p<0.0001) with a 0.21 HR (CI 0.05-0.39). This assay fully retained its predictive value in a Cox proportional hazards survival regression analysis even after risk-set stratification of patients according to the Khorana’s class of risk (p<0.0001) with a 0.18 HR for steady vs. impaired APC function (p<0.0001) in the intermediate risk group.

Conclusions: Use of this novel global assay sensitive to APC abnormalities in out-patients on active chemotherapy, especially in combination with Khorana’s risk assessment model, may help identifying a population of cancer patients at risk for VTE that might benefit from thromboprophylaxis.

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ANALYTICAL PERFORMANCES OF A NEW LIQUID ANTI-XA ASSAY FOR UFH/LMWH AND FONDAPARINUX

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Keywords: anticoagulation, assay

Aims: We evaluated the analytical performances of the new ready-to-use chromogenic assay, STA® Liquid Anti-Xa, for the automated determination of anti-Xa activity in plasma from patients treated with UFH, LMWH and fondaparinux.

Materials and methods: Specific calibrator sets for fondaparinux or for UFH/LMWH were used. UFH/LMWH calibration set allows determination of both UFH and LMWH anti-Xa activities using either dedicated and hybrid calibration. Stability, detection limit, linearity and precision were evaluated on three different lots of reagents on STA® ROTEM® R analyser. Manufactured lyophilised controls and normal pool plasma spiked with fondaparinux, UFH/LMWH International Standards or marketed LMWH preparations (enoxaparin, nadroparin, dalteparin) were used. Anti-Xa activity in plasma from 149 patients treated with either UFH or LMWH was assessed using STA® Liquid Anti-Xa and commercial STA® ROTEM® R analyser. Results expressed with dedicated and hybrid calibrations for both reagents were compared.

Results: The three reagent lots were stable up to 7 days on STA® R and 3 months at 2-8°C. Detection limits were 0.1µg/mL and 0.1-anti-Xa IU/mL for fondaparinux and LMWH/UFH, respectively. Linearities were up to 2.0µg/mL, 2.0 anti-Xa IU/mL and 1.1 IU/mL for fondaparinux, LMWH and UFH, respectively. A good agreement was shown between anti-Xa activities measured in plasma spiked with LMWH International Standard or LMWH LH preparations (maximum variation < 2.0 vsanti-Xa IU/mL). Inter/ intra assay coefficients of variation for UFH/LMWH and fondaparinux levels ranged from 2.0 to 7.0%. Good correlations of plasma anti-Xa activity levels from patients treated with either UFH or LMWH were observed using the two reagents (R2 > 0.96), with either dedicated or hybrid calibration.

Conclusions: STA® Liquid Anti-Xa, without prior reconstitution, is suitable for measuring a wide range of anti-Xa values, including supra-therapeutic ones. It provides a reliable tool for monitoring and clinical investigations for UFH/LMWH and fondaparinux.

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VALIDATION OF A NEW POINT-OF-CARE INR ANALYZER

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Keywords: POCT, INR, self management

Background/Aims: A point-of-care hand-held analyzer (INRatio2, Inverness Medical) utilizing in strip electrical impedance clot detection technology in combination with recombinant tissue factor activation in whole-blood was recently launched in Denmark. We aimed to validate this device using preset national quality specifications for intra-assay variation (CVa) and analytical bias of point-of-care INR analyzers.

Materials and methods: 36 unselected patients on warfarin, and in for scheduled INR measurement at our out-patient clinic had blood drawn by standard antecubital venipuncture. Citrated samples were prepared for routine automated INR measurements, whereas unstabilized whole-blood was immediate applied onto two analyzers for parallel duplicate measurement. The preset quality specifications were 5% for CVa, and 6% for bias. Bias was further evaluated after adjusting the routine method’s raw values to perfectly fitting the mean calibration of all Danish laboratories (N=82) participating in a regular national external QC programme.

Results: The analyzer INR’s averaged 2.6 (range 1.6-4.3). CVa of the 36 duplicates was 4.7%. Analyzer variation averaged 0.025 INR-points. Bias against the routine method was 5.4% over the measured range and slightly higher (7.1%, 0.14 INR-points) at 2 INR than at 4 INR (2.9%, 0.12 INR-points). Bias against the contemporary Danish INR calibration was 2.2%, and slightly higher (4.2%, 0.08 INR-points) at 2 INR than at 4 INR (0%, 0 INR-points).

Conclusions: The INRatio2 qualified for use in general practice and patient self monitoring of oral anticoagulant therapy in Denmark.

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DIFFERENT D-DIMER CUT OFF VALUES IN HIP INJURY PATIENTS WITH HIGH VTE RISK

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Keywords: D-dimers, hip injuries

Patients undergoing lower-extremity orthopaedic procedures are in the highest-risk category for developing VTE. Interpretation of increased D-dimer (Dd) values and objective testing to exclude VTE could be hard due to trauma, increased age and significant comorbidity. Likewise, false results also can be expected in case of use of inappropriate cut off values. Our aim was to generate separate receiver operating characteristic curve to determine whether different Dd cut-off values on admission and after surgery could be more informative in patients admitted during one year to our hospital due to hip injuries. Data from 57 patients (median age 76 y) were collected retrospectively. D-dimer values were obtained from plasma samples by immunofiltration method (Nycocard ReaderII, Arixtral, Norway, cut off value 0.3 mg/L). According to comprehensive physician report, VTE was suspected in 19 patients (33%) during hospitalization but confirmed only in 9 patients (16%) by doppler ultrasonography. Obtained cut off value with a NPV of 90% on admission day was 1.0 mg/L (sensitivity 56% and specificity 77%). After the surgery obtained cut off value of 1.4 mg/L have the same NPV (90%) with improved sensitivity of 78% and concomitant decrease in specificity to 58%. By the using increased cut off levels limited additional information could be provided. Further investigation on this issue is necessary and apart from surgery, subgroups of patients with coexisting conditions that could influence on D-dimer levels should be considered.

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MONITORING OF ANTI-XA INHIBITORS: TEST PERFORMANCE OF SPECIAL CALIBRATOR AND CONTROL PLASMAS

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Aims: The aim of this study is to evaluate the performance of five different calibrator and control plasma sets for their use in monitoring Orgaran, Arixtra, rivaroxaban, LMW Heparin and UF Heparin respectively.

Methods: Calibration curves were established with each of the five Technoview calibrator sets using the Coamatic Heparin and the Technochrom Anti Xa assays.

Result: The calibration curves obtained are linear over a wide concentration range and covers the usual concentrations currently observed during therapy:

- Orgaran® between 0.0 and 1.6 IU/mL
- Arixtra® between 0.0 and 2.0 µg/mL
- Rivaroxaban between 0 and 450 µg/mL
- LMW heparin between 0.0 and 1.6 IU/mL
- UF Heparin between 0.0 and 1.5 IU/mL

Correlation data between Coamatic Heparin and the Technochrom Anti Xa are:

- Orgaran® y = 0.9206x + 0.00177 and r2 = 0.9857
- Arixtra® y = 1.0026x – 0.0229 and r2 = 0.9957
- Rivaroxaban y = 1.0122x + 10.445 and r2 = 0.9591
- LMW heparin y = 0.8894x + 0.0768 and r2 = 0.9489
- UF Heparin y = 1.0096x – 0.0009 and r2 = 0.9924

Quality control plasmas show a good precision in all concentration ranges, reporting CVs below 6% in the high range controls and below 5.3% in the low range controls.

Conclusions: We are reporting the validation of a complete set of calibrators suitable for anticoagulant monitoring with a new anti Xa assay and sets of controls. Thus, this group of calibrators and controls allows reliable monitoring of all mentioned anticoagulants.

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Spatially heterogeneous experimental model of blood coagulation: from basic research to diagnostics of prothrombotic and bleeding tendencies


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Keywords: experimental models of coagulation, in vitro, diagnostics

Background/Aims: An important but often underestimated aspect of blood coagulation functioning. The purpose of experimental models of coagulation, in vitro, diagnostics is necessary and apart from surgery, subgroups of patients with coexisting conditions that could influence on D-dimer levels should be considered.

Materials and methods: Blood was collected from patients with several types of coagulation disorders, including prothrombotic defects due to septic shock, spontaneous clotting. The assay was also able to monitor coagulation correction in prothrombotic disorders.

Conclusions: The data indicate that these spatially heterogeneous experimental approaches have a good potential for coagulation diagnostics.

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A NEW AND SPECIFIC RAPID CHROMOGENIC “ANTI-XA” ASSAY FOR TESTING RIVAROXABAN IN PLASMA

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Keywords: Anti-Xa chromogenic assay, rivaroxaban specific, new anticoagulants

Background: Drug measurement in patients receiving the direct oral anti-factor Xa inhibitor, rivaroxaban, is useful, especially when it is used for curative indications, in presence of decreased clearance or of overdosage. Current Anti-Xa heparin assays are not appropriate as they are designed for catalytic indirect factor Xa inhibitors such as heparin-like molecules, sodium danaparoid or fondaparinux. Direct factor Xa inhibitors interact in a mole to mole model, and inhibition kinetics are different.

Aims: To develop a specific assay, insensitive to heparin-like molecules, in order to measure specifically rivaroxaban concentration in plasma.

Methods: New two stage chromogenic assay, based on the inhibition of human factor Xa in presence of a chaotropic buffer, in which the AT dependent heparin activity is ineffective whilst all the rivaroxaban activity is preserved: in a first step human factor Xa in a constant in and in excess concentration is incubated with the sample; the residual factor Xa is measured in a second step using a specific factor Xa substrate. The assay offers a dynamic range from 0.000 to 0.025 µg/ml of rivaroxaban in the assayed dilution. For the expected therapeutic concentrations, plasma samples are assayed diluted 1:20, with an assay range from 0.00 to 0.50 µg/ml. Rivaroxaban recovery is identical whether spiked in assay buffer or in plasma. The method is highly robust, has an inverse and linear dose response curve (r²=0.999), is highly reproducible from run to run (precalibration possible with only 3 concentrations: 0 0.25 and 0.50 µg/ml), without any incidence of the duration of the first incubation. Recovery is of 100 % +/- 4% in plasma, and no protein interference is evidenced. LLOQ is 0.0020 µg/ml in plasma and 0.001 µg/ml in the assayed dilution. This assay has been used in a recent multicentric study (Rivamos, Switzerland) and demonstrated its excellent specificity and accuracy for measuring rivaroxaban in plasma samples (GTH, Nuremberg, February 2010).

Conclusions: This new simple assay, insensitive to heparins, is fully automatable. It offers an original and reliable laboratory method for measuring anti-Xa activity induced by rivaroxaban.

Figure Dose response curves of rivaroxaban and fondaparinux with the new assay.
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IMAGING OF LIVING PLATELETS IN NORM AND PATHOLOGY BY QUANTITATIVE PHASE MICROSCOPY

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Keywords: Platelet, morphology, phase-interference microscopy

Background: Quantitative platelet disorders are always associated with qualitative platelet alterations. The circulating platelet multiplicity reflects cell distinctions in size, density, metabolic, functional, biochemical features and the level of megakaryocyte polymorphism. Quantifying the optical phase delays associated with living cells provides access to information about morphology and dynamics at the nanometer scale.

Materials and Methods: Morpho-functional status of peripheral blood platelet was determined by express-method of vital computer morphometry using computer phase-interference microscope Cytoscan (Russia). The microscope is a modification of a Linnik interferometer with a He-Ne laser (1+633 nm) as a source of coherent light. The microscope is equipped with the dissector image tube to register the interference signal, and an electronic unit for computer-assisted cell imaging. Measurements of optical phase difference (OPD) were performed sequentially at each point of the image. To register the interference signal and to convert it into local phase values, a linear periodic modulation of the reference. The complex algorithm of morphometry included definition of optic and geometrical characteristics of unfixed and unstained living platelets, statistical analysis of data and creation of medical documents. We have analyzed the computer platelet images (three dimensions of whole cells and their parts, different cross-sections and histogram), the optic-geometrical parameters of each isolated platelet and the distribution of platelets by sizes to detect the heterogeneity of cell population. It allowed to identify four platelet forms that have different morphological features and different parameters of size distribution (Pic).

Conclusions: The technology is now available to investigate single living platelet, its morphology and function, together with analyzing heterogeneity of all circulating platelet population. Moreover morphometric parameters of living platelets can be predictors of possible following hemostasiological disorders. The proposed method opens additional perspectives for analyzing the heterogeneity of all circulating platelet population. Moreover morphometric parameters of living platelets can be predictors of possible following hemostasiological disorders. The proposed method opens additional perspectives for analyzing the heterogeneity of all circulating platelet populations without sophistics experimental techniques.

Figure: Scheme of phase-interference images of living platelets.

1- resting form; 2 - platelet with low activation level; 3 - platelets with high activation level; 4 - degenerate functionally incomplete platelet

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INFLUENCE OF WARFARIN ON MULTIPLE ELECTRODE PLATELET AGGREGOMETRY (MULTIPLATE).

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Background: The newly developed point-of-care instrument, the multiple electrode platelet aggregometry (Multiplate, Dynabyte Medical, Munich, Germany), allows platelet aggregation to be measured after adding commonly used agonists by determining the attachment of platelets onto the Multiplate sensors generates an increase in impedance which is transformed into arbitrary aggregation units (AU) and plotted against time.

Results: In all four assays considered, patients undergoing OAT showed a lower platelet aggregation (mean ± Standard Deviation, AU/min) than healthy subjects. The difference was not statistically significant except for ASPItest (Student’s t-test p value 0.005) [Table].

Conclusions: Our study shows that subjects undergoing OAT present with a significantly reduced mean level of platelet aggregation performed by whole blood Multiplate analyser as compared to a group of healthy controls only when ASPItest is used. Further investigations are needed to evaluate the clinical meaning of Multiplate platelet aggregometry in patients undergoing OAT.

Table

<table>
<thead>
<tr>
<th>Cases (mean ± SD, AU/min)</th>
<th>Controls (mean ± SD, AU/min)</th>
<th>p value*</th>
</tr>
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<tbody>
<tr>
<td>ADP test</td>
<td>43±19</td>
<td>46±15</td>
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<tr>
<td>COL test</td>
<td>40±19</td>
<td>56±29</td>
</tr>
<tr>
<td>ASPI test</td>
<td>30±23</td>
<td>60±18</td>
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<tr>
<td>TRAP test</td>
<td>60±21</td>
<td>75±21</td>
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* Student’s t-test; SD: Standard Deviation

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WELLS RULE AND D-DIMER FOR THE DIAGNOSIS OF ISOLATED DISTAL DEEP VEIN THROMBOSIS

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Keywords: isolated distal deep venous thrombosis, diagnosis, D-dimer, clinical probability

Background: Wells and colleagues developed a diagnostic rule to estimate the probability of the presence of proximal symptomatic deep venous thrombosis (DVT). The accuracy of the Wells rule has not been validated for use in primary care patients in whom symptomatic isolated distal deep venous thrombosis (IDVT) is suspected.

Aims: To validate the diagnostic accuracy of the Wells rule and D-dimer testing for IDVT.

Patients and methods: Cross-sectional study with data collection from 1 September 2009 to 15 February 2010, including 190 consecutive outpatients who were referred by the emergency department or by a primary care physician to our ultrasound laboratories. All patients underwent history-taking and physical examination to calculate the Wells rule score, D-dimer testing, and a comprehensive real-time B-mode and colour Doppler ultrasonography examination of both legs by a vascular medicine physician. The proximal deep veins were examined first, then, only in patients with normal proximal findings, the calf veins were evaluated, including the axial (peroneal and posterior tibial) and the muscular veins.

Results: The prevalence of IDVT was 11%. 8 patients in the low-risk group according to Wells rule had IDVT, whereas 10% of patients in the high-risk group had IDVT. The Wells rule had a sensitivity of 47%, a specificity of 59% with a predictive negative value of 91%. D-dimer was higher in patients with IDVT versus those without IDVT. Two patients with negative results on a D-dimer test (<500 ng/mL) had IDVT. Sensitivity and specificity of D-dimer were 87% and 55%, with a predictive negative value of 98%.

Conclusions: The Wells rule does not guarantee estimation of risk in patients in whom IDVT is suspected. D-dimer <500 ng/mL does not exclude the presence of IDVT.

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Correlation between D-dimer and the persistence of residual thrombosis on ultrasound Doppler at the end of anticoagulant treatment in deep vein thrombosis

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Keywords: D-dimer, residual thrombosis, deep vein thrombosis

Introduction: The performance of Doppler ultrasound (DU) is laborious and involves a care burden. There is evidence of the prognostic value of both D-dimer (DD) or the persistence of residual thrombus (RT) and recurrent deep venous thrombosis (DVT).

Aims: To find the correlation between DD levels and the persistence of RT on DU in DVT of lower limbs followed one month after oral anticoagulant therapy withdrawal.

Materials and methods: This a prospective study including consecutively patients with DVT who have completed anticoagulant therapy after a minimum of three months and show no exclusion criteria: patients under 18 years, coexistence of pulmonary embolism, bilateral DVT, neoplasia, indication of persistent anticoagulation or needing for early withdrawal anticoagulant treatment. A lower limb DU and a determination of DD (IL Test) were performed one month following oral anticoagulant therapy withdrawal, approximately.

Results: 32 patients have been included, 59% were male, with a mean age of 59.8 ± 19.8 years. Regarding the location, 3% were originated in the cava vein, 16% at iliac, 41% at the femoral and 37% in the popliteal veins. All patients received low-molecular weight heparin (LMWH) as initial therapy at a minimum of 5 days. Treatment was followed with warfarin (72%), acenocoumarol and LMWH (6%) as long-term therapy, with a mean duration of 12 ±6 months. A determination of DD and a lower limb DU at 35 ±15 and 35 ± 17 days of anticoagulant treatment withdrawal, respectively, were made. Determination of DD was positive in 19% of cases and 47% showed RT. Among patients with positive levels of DD, 83% had RT, while 61% of patients with a negative determination of DD, showed vein recanalization.

Conclusions: There is relationship between a positive determination of DD and RT, and between negative values of DD and vein recanalization one month after oral anticoagulant therapy withdrawal in DVT of lower limbs.

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Evaluation of HIT suspected patients with polyspecific antigen (IgG/A/M) and monospecific (IgG) EIA assay

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Keywords: HIT

Background: In suspected heparin-induced thrombocytopenia (HIT), the EIA polyspecific antigen assays (IgG/A/M) recognize PF4/heparin-reactive antibodies, most of which are not platelet activating. Those clinical insignificant antibodies mostly are of IgM/ A classes. When activation assays are not available the clinical decision of replacing heparin with an alternative anticoagulant, is difficult as these drugs have increased bleeding risk. The use of the IgG-specific EIA assays may enhance the diagnostic specificity of the EIA assays.

Aims: Evaluation of HIT suspected patients with polyspecific antigen (IgG/A/M) and monospecific (IgG) EIA assay.

Patients and methods: Samples of patients suspected to have HIT were collected between November 2008 and February 2009 and tested with both assays (EIA IgG/A/M and only 1 patient has positive result with EIA IgG/A/M and only 1 patient has positive result with EIA IgG. The last patient had the highest 4T’s score (score 6, development of new thrombosis under heparin treatment) and was also the only patient who was treated with a direct thrombin inhibitor. All the patients with a negative EIA IgG/A/M result were also EIA IgG negative. 1 patient with positive EIA IgG/A/M result has negative the confirmatory step in EIA IgG assay (table, arrow).

Conclusions: The use of EIA IgG assay decreased the positive results from 54.5% to 9.1%. In those laboratories where the activation assays are not available the incorporation in the diagnostic algorithm of a EIA IgG assay confers to a better specificity in HIT suspected cases.

Figure EIA IgG/A/M and EIA IgG OD values

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Thrombin generation assessment in cynomolgus monkey using cat method.

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Background/Aims: Microvascular thrombosis due to activation of clotting cascade is a key feature of the rejection process of pig organs transplanted into primates. Such coagulopathy is a barrier to the long-term survival of porcine xenografts in this species combination. Little is known about coagulation assessment in primates.

Aim of the study: to evaluate thrombin generation (TG) in cynomolgus monkey; to compare TG between cynomolgus and human.

Materials and methods: We evaluated TG profiles in cynomolgus monkeys and in healthy human controls. TG assay was performed in poor platelet plasma (PPP) using the calibrated automated thrombogram (CAT) the thrombinoscope BV method. TG was triggered using the PPP-reagent (Thrombinoscope BV) and parameters considered were: ETP (endogenous thrombin potential, nM*min), Cmax (maximum thrombin concentration, nM) and lag time (time to clot, min).

Results: We evaluated TG in 22 cynomolgus monkeys and 50 human controls. Mean ETP measured (nmol*min ± SD) was 1971.79 ± 276.88 in monkey and 1089.32 ± 292.79 in human (p < .0000); mean Cmax (nmol ± SD) was 401.64 ± 60.83 in monkey and 288.04 ± 63.73 in human (p < .0000); mean Lag Time (min ± SD) was 1.35 ± 0.19 in monkeys and 1.76 ± 0.85 in human (p = .002).

Conclusions: Thrombin plays a vital role in vivo a pivotal role in the coagulation system being involved in clot formation, platelet activation and PC anticoagulant pathway. Our method (CAT) revealed significantly lower lag time in monkey than in human while ETP and Cmax values were higher in monkey than in human. This data are consistent with a higher prothrombotic profile in cynomolgus as compared to humans suggesting that, with regard to coagulation, xenotransplantation in cynomolgus may represent a much more difficult situation than in humans.

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ROLE OF MULTIDETECTOR CT PULMONARY ANGIOGRAPHY IN THE DIAGNOSTIC ALGORITHM OF PULMONARY HYPERTENSION

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Keywords: pulmonary hypertension, CT Angiography, diagnosis

Aims: describe the prevalence of right ventricular dysfunction signs in patients suffering from pulmonary hypertension. To establish the usefulness of MDCT angiography versus ventilation/perfusion (V/Q) scintigraphy in the diagnostic algorithm of pulmonary hypertension.

Materials and methods: MDCT angiographies of 76 patients were recorded between November 2006 and January 2010. The inclusion criterion was a threshold of systolic main pulmonary artery (MPA) pressure of 40 mmHg or higher at rest. In 44 patients (56.5%) the V/Q scintigraphy was available. MDCT pulmonary angiographies were evaluated for right ventricle (RV) dysfunction signs (RV/LV ratio>1), left bowing of interventricular septum and vascular prognostic ratios. Patients were divided into two groups (A pulmonary artery < 29 mm and B > 29 mmHg) for the statistical analysis.

Results: The mean and standard deviations of MPA and RV were recorded, being higher in group B. The RV/LV and the MPA/Aorta ratios were significantly higher on group B (> 0.001). Twenty patients (45%) presented a correct match between the MDCT angiography and the V/Q scintigraphy. Four negative V/Q scintigraphy presented signs of chronic thromboembolism in the MDCT angiography. MDCT also contributed to diagnosis of interstitial lung disease.

Conclusions: MDCT angiography is an accurate tool depicting RV dysfunction signs. It is more sensitive for detection of chronic thromboembolism as it shows thromboembolic signs in patients with negative V/Q scintigraphy and can assess coexisting parenchymal lung disease. Hence, it may be used as a first-line-tool in the diagnostic approach of PH.

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STANDARDIZATION OF HEPARIN THERAPY MONITORING

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Keywords: APTT, heparin

Background: Activated partial thromboplastin time (APTT) is the most widely used method for laboratory monitoring of heparin therapy. APTT reagents have different heparin sensitivity that results in a variance in the amount of heparin administered to the patients. Standardization of this monitoring was recommended by ISTH/ICSH.

Aims: To determine by APTT in-vitro and ex-vivo heparin therapeutic range using the particular heparin-APTT reagent-instrument system.

Materials and methods: The index APTT dependence on unfractionated heparin was studied by automatic coagulometer ACL Elite Pro (IL) and six APTT reagents (Coagulotest, APTT-reagent, Actin FS, Actin FSL, APTT SP and Dapttin). 43 samples were considered positive when at least one of the screening tests was positive. In patients with dPT, in 1 patient with MixConLA, in 8 patients with KCT and in 3 patients with dRVVT.

Results: The index APTT dependence on unfractionated heparin was studied by automatic coagulometer ACL Elite Pro (IL) and six APTT reagents (Coagulotest, APTT-reagent, Actin FS, Actin FSL, APTT SP and Dapttin). 43 samples were considered positive when at least one of the screening tests was positive. In patients with dPT, in 1 patient with MixConLA, in 8 patients with KCT and in 3 patients with dRVVT.

Conclusions: APTT indexes correspond to heparin therapeutic range to the hemodialysis patients were established for each used APTT reagents. It’s seems necessary to standardize APTT monitoring of heparin therapy for applicable APTT reagents.

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USEFULNESS OF INNOVIN DILUTED PROTHROMBIN TIME FOR THE DETECTION OF LUPUS ANTICOAGULANT

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Keywords: dPT, diluted prothrombin time, lupus anticoagulant

Aims: Lupus anticoagulants (LA) are antibodies which inhibit in vitro phospholipid-dependent tests of coagulation. No single screening test can detect all LA-positive patients, so the SCC Subcommittee for the Standardization of LA recommends at least two independent tests for LA screening. Commonly used screening tests are based on the Kaolin Clotting Time (KCT), a LA-sensitive aPTT or on the dilute Russell’s viper venom Time (dRVVT). Dilute prothrombin time (dPT) has also reported as a sensitive test for LA-screening. Therefore, we evaluated the usefulness of a homemade dPT in comparison to different commercial available tests.

Methods: All tests were performed on the BCS analyser (Siemens Healthcare Diagnostics, Germany). In a first step quality and performance of the homemade dPT using recombinant thromboplastin Innovin (Siemens Healthcare Diagnostics, Germany) in a 1/200 dilution was evaluated. Subsequently, we estimated in 22 patients, who were previously tested positive for LA, dPT, KCT (Kaolin, Life Diagnostics, USA), dRVVT (LA1, LA2, Siemens Healthcare Diagnostics, Germany) and MixConLA (Instrumentation Laboratories, Germany).

Results: Intra-assay coefficient of variation (CV) for dPT was 1% and inter-assay CV 5.6%. Normal values assigned in 50 healthy individuals ranges from 35 to 51 sec. 51 sec were chosen as the cut-off value. We obtained negative results in 2 patients with dPT, in 1 patient with MixConLA, in 8 patients with KCT and in 3 patients with dRVVT.

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RESEARCH OF LUPUS ANTICOAGULANT - LABORATORY PROFILE OF PATIENTS OF HOSPITAL OF SCHOOL MEDICINE OF UNIVERSITY OF SÃO PAULO, BRAZIL

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Keywords: lupus anticoagulant, laboratory

The antiphospholipid antibodies, lupus anticoagulant (LA) is one of the markers of antiphospholipid syndrome, systemic acquired condition and may be primary or secondary, and is characterized by recurrent thromboses in the arterial, venous, or both, recurrent fetal loss and thrombocytopenia. These antibodies may be present in normal, autoimmune diseases; neural diseases, use of medications, viral infections and some parasites. Guidelines have been published, recommending criteria for laboratory diagnosis, and suggest to perform a screening that is the use of at least two functional tests, based on the presence of phospholipids in order to improve identification of the antibody. The main options for testing include the time activated partial thromboplastin time and viper venom Russell diluted. Our objective was to determine the positivity for lupus anticoagulant in patients who are investigated by the Central Laboratory of Coagulation, Clinical Hospital, of both sexes, different ages, from various clinics of medical specialties, and from various detention centers, so as, the interference of the use of anticoagulation in this investigation. We performed laboratory research to LA in 504 patients. Blood samples were collected in tubes with sodium citrate 3.2%, followed by double centrifugation to obtain platelet-poor plasma. We also performed the PTTA and dRVVT as tests triadores; and dRVVT with excess phospholipid as the confirmatory test, using reagents Dade Behring ®, and processed in the BCS ® System, Behring company. Of the 504 patients, 67.8% were female, 11.9% were male, and 20.3% were children, ranging from 02 months to 18 years age among both sexes. The average age among women was 49.5 years of age, while for men the average was 54 years. In 94% of patients, 67.8% were female, 11.9% were male, and 20.3% were children, ranging from 02 months to 18 years age among both sexes. The average age among women was 49.5 years of age, while for men the average was 54 years. In 94% (474/504) of patients the search results were negative. Of the remainder, 6.0% of cases was positive, 70% in women, 16.7% in men and 13.3% in children. 12.5% of samples were considered positive when at least one of the screening tests was corrected by the mix test. Negative samples were those that were not corrected by the mix. In these cases, the use of oral anticoagulants or heparin was proven. Reagent dRVVT showed sensitivity of 100% compared to PTTA [73.3% (22/30)]. The presence of another inhibitor was suggested in 03 cases, two of them in the male group, and the other in pediatric patients. Our results show consistency with the literature data. There was a predominance of research in female patients and positivity in this group. In paediatric patients the results were as expected. There was no prejudice to the investigation in most anticoagulated patients and dRVVT was the most sensitive of screening tests.

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Aims: We have evaluated the progression of isolated superficial venous thrombophlebitis to deep-vein thrombosis in patients with no initial deep venous involvement using duplex ultrasonography.

Methods: Patients with thrombosis isolated to the superficial veins, with no evidence of deep venous involvement by duplex ultrasound examination, were evaluated by follow-up duplex ultrasonography to determine the incidence of disease progression into the deep veins of the lower extremities. Initial and follow-up duplex scans evaluated the femoropopliteal and deep calf veins in their entirety. Follow-up studies were done at an average of 6.3 days. In patients with embolicogenic ascending thrombophlebitis in the area of the SFJ, SPJ or thrombophlebitis of perforating veins depending on sonography finding we perform retrograde venous thrombectomy (RVT), assisted by sonography or only crossectomy. In ligation of thrombosed perforating veins (PV), its junction with adjacent magistral deep vein is marked using intraoperative sonography.

Results: From January 2002 to January 2009, 286 patients were identified with isolated superficial venous thrombosis. Forty (14%) patients had documented progression to deep vein involvement. The most common site of deep-vein involvement was progression of disease from the greater saphenous vein into the common femoral vein (19 patients, 47.5%), with 11 of these, extensions noted to be nonocclusive, and 8 having a free-floating component. Five patients had extended above-knee saphenous vein thrombi through thigh perforators to occlude the femoral vein in the thigh. Nine patients had extended below-knee saphenous disease into the popliteal vein, and 7 patients had extended below-knee thrombi into the tibioperoneal veins with calf perforators.

Conclusions: Superficial thrombophlebitis is not always benign and self-limiting disease. Affecting of SFJ, SPJ or thrombophlebitis of perforating veins, can cause complications as a DVT, which requires careful evaluation, active conservative therapy, often ultrasonography follow up and if necessary timely and adequate operation.

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PERFORMANCE OF COAGULOMETRIC FUNCTIONAL METHODOLOGY BASED ON THE DILUTE RUSSELL’S VİPER VENOM TIME ON DETERMINATION FROM ACTIVATED PROTEIN C RESISTANCE SECONDARY THE PRESENCE OF LEIDEN MUTATION

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Keywords: Leiden mutation, protein C resistance

Our objective was to assess the sensitivity of dRVVT test, a new test, to analyze the functional activated protein C resistance by comparing our results with those obtained in molecular research for the presence of Leiden mutation.

We selected 108 patients samples from Vascular Surgery Department that were reported at the same time to the Coagulation Laboratory to perform the functional APCR test, and to the Heart Institute of University School of Sao Paulo (INCOR) for to investigate the presence of Leiden mutation. The functional test based on dRVVT was analyzed using coagulometric methodology, while the presence of mutation was investigated by polymerase chain reaction, a molecular assay. Of all patients, the women group represented the majority, 60.2% (65/108) (Figure 1). 98.1% of the samples (106/108) showed concordant results between methodologies, 87.9% (95/108) negative results (no mutation) and 10.2% (11/108) the presence mutation in its heterozygous form (Figure 2). Positive samples showed values below cut-off. Two cases were discordant, one of them a false positive result, and the other, a false negative result. Both cases were repeated with the maintenance of the results. In the situation of false positive result we made the dRVVT with the sample diluted in factor V deficient plasma, in an attempt to remove the causes of acquired APCR, but the situation of false positive result we made the dRVVT with the sample diluted in negative result. Both cases were repeated with the maintenance of the results. In the situation of false negative result we made the dRVVT with the sample diluted in factor V deficient plasma, in an attempt to remove the causes of acquired APCR, but the result remained unchanged. The frequency of mutation was higher in the group of male patients, 11.4% (4 / 35) (Figure 1). The sensitivity, specificity and efficiency of the dRVVT test was 91.6%, 98.9% and 0.98, respectively. Given our results, we consider the methodology of dRVVT suitable for search of functional activated protein C resistance, and thus allow its use in laboratory routine as a screening test for patients with suspected thromboembolic disease secondary to factor V Leiden mutation.

Figure 1: Sex distribution and positivity by group

Figure 2: Comparison between both methodologies

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Inherited and acquired thrombophilia

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THE FACTOR V HR2 HAPLOTYPE (FV A4070G) AMONG WOMEN WITH VENOUS THROMBOEMBOLISM

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Keywords: factor V HR2, venous thromboembolism, risk factor

Background: The HR2 haplotype in the factor V (FV) gene produces a mild increase of FV activity, paralleling APC resistance. It is doubtful if it is a risk factor for venous thromboembolism (VTE) and if it increases the risk conferred by FV Leiden (FVL). It is unknown whether FV HR2 could be relevant in some situations leading to acquired APC resistance such as pregnancy or use of oral contraceptives.

Aims: To investigate the prevalence of HR2 among women with VTE due to different provoking factors.

Patients and Methods: We investigated 393 women with deep venous thrombosis in the legs in 348 cases (in 87 of them with pulmonary embolism, PE) and isolated PE in 45 cases. The first thrombosis occurred at a median age of 33 years (range 14–82), and was provoked in 303 patients (pregnancy or puerperium n=101; oral contraceptives n=84; surgery or other transient risk factors n=118). A group of 204 healthy women (median age 37, range 19–61) were the controls. All women were tested for inherited thrombophilia; the presence of FV HR2 was checked by a PCR assay for the A4070G polymorphism in the FV gene.

Results: Inherited thrombophilia was found in 141 patients (35.8%) (deficiency of natural anticoagulants n=22, FVL n=71, PTG20210A n=33, multiple abnormalities n=15) and 19 controls (9.3%) (FVL n=8, PTG20210A n=11). The FVA4070G was found in 59 patients (15.0%) and in 18 controls (2.0%) (8.8%). The odds ratio for FV associated with FVA4070G was 1.82 (95% CI 1.04-3.18), and 1.95 (95% CI 1.49-2.55) after adjustment for thrombophilia. The prevalence of FV A4070G was similar among the overall patients with different circumstances of first VTE (p=0.34), and in the subgroup of patients with thrombophilia (p=0.07), or heterozygous FVL (p=0.11), or no other inherited traits (p=0.47).

Conclusions: Factor A4070G is a mild risk factor for VTE; its prevalence is uniform among the patients, independently either of the circumstances of first VTE or the presence of other inherited thrombophilic traits.

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SELECTION CRITERIA OF PATIENTS WITH VENOUS THROMBOEMBOLISM FOR LABORATORY INVESTIGATION OF INHERITED THROMBOPHILIA

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Keywords: inherited thrombophilia, venous thromboembolism, laboratory screening

Background: Laboratory screening for inherited thrombophilia is warranted in young patients, especially those with severe venous thromboembolism (VTE) occurred spontaneously or recurrently. Laboratory screening in older patients is discouraged, especially in the case of mild clinical manifestations or provoked events. Such policy could miss a number of carriers, leaving undiagnosed their kindreds.

Aims: To investigate whether clinical parameters are predictive of the presence of inherited thrombophilia in VTE patients.

Patients and Methods: We analyzed the files of 1,835 patients referred to our Thrombosis Center between 1996 and 2009. The median age at the first thrombosis was 37 years (range 0–89); 736 were males (40.1%). Patients were stratified according to their age or to the borderline significance (p=0.0001) kept associated to mild thrombophilia, whereas family history had a 0.03) and recurrent events with severe thrombophilia, clinical severity of VTE (p=0.03) and recurrent events (p=0.0001) kept associated to mild thrombophilia, whereas family history had a borderline of either of the circumstances of VTE or a first unprovoked event were associated to overall thrombophilia (p=0.0001) in 415 (22.6%). Diagnoses of overall thrombophilia (AT, PC, PS deficiency, multiple defects) was detected in 141 patients (35.8%) (defined severe in the case of proximal DVT and/or pulmonary embolism and mild in the case of distal DVT or superficial vein thromboembolism), the circumstances of the first thrombosis occurred at a median age of 33 years (range 14–82), and was provoked in 303 patients (pregnancy or puerperium n=101; oral contraceptives n=84; surgery or other transient risk factors n=118). A group of 204 healthy women (median age 37, range 19–61) were the controls. All women were tested for inherited thrombophilia; the presence of FV HR2 was checked by a PCR assay for the A4070G polymorphism in the FV gene.

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Conclusions: Factor A4070G is a mild risk factor for VTE; its prevalence is uniform among the patients, independently either of the circumstances of first VTE or the presence of other inherited thrombophilic traits.

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HEREDITARY DEFICIENCY OF NATURAL INHIBITORS OF COAGULATION (ANTITHROMBIN, PROTEIN C OR PROTEIN S) CONFER A RISK FOR ARTERIOVENOUS THROMBOEMBOLIC EVENTS. RESULTS FROM A PROSPECTIVE FAMILY COHORT STUDY

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Keywords: thrombophilia, arterial thrombosis

Background: Whether hereditary antithrombin (AT), protein C (PC) or protein S (PS) deficiency is associated with arterial thromboembolic events is controversial.

Methods and results: The objective of this study was to prospectively assess the incidence of arterial thrombotic events in subjects with a deficiency of natural inhibitors of coagulation. We conducted a prospective cohort study in asymptomatic family members of unselected patients who presented with a venous thromboembolic event and who were found to have a deficiency of antithrombin, protein C, or protein S.

All arterial thrombotic events were diagnosed by objective diagnostic tests. A total of 640 consecutive subjects belonging to 86 families with hereditary deficiency of AT, PC or PS with a mean age (at the baseline) of 38 years (range, 15 to 79) in the carrier and in the non carrier group were enrolled in the study. A total of 4240 and 3810 patient observation years was obtained respectively in the two groups. Atherosclerosis risk factors were similar in both the two groups. Nineteen arterial thrombotic events occurred in the carrier group (5.6%), compared with seven events in the non carrier group (2.3%) (p=0.07).

Conclusions: Compared with nondeficient family members, subjects with antithrombin, protein C or protein S deficiency have an higher risk for arterial thrombotic events.

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Higher urinary 8-iso-PGF2α (<15 μmol/L. Carriers with hyperhomocysteinemia had lower folate levels (higher 8-iso-PGF2α (p<0.01) and 11-dehydro-TXB2 (p=0.0002) than those with tHcy over 45). PCR-RFLP was used to analyse G894T and T786C polymorphism in the 40 aged less than 45 and 32 aged more than 45. Results: We found statistically significant differences between the two groups of patients studied with respect to polymorphism T-786C in eNOS. Conclusion: In conclusion, our results have provided novel insights into mechanism of prothrombin expression regulation, pointing the out potential importance of downstream sequence in 3'-end of prothrombin gene.

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Keywords: thrombosis, eNOS, polymorphisms

Background: The traditional cardiovascular risk factors are largely environmental. However, variations in incidence and risk observed in a series of epidemiologic studies have already demonstrated that a great number of thrombotic events occur in patients without such risk factors. Especially in the last decade, several genes and their polymorphisms have been found to increase thrombotic predisposition and risk of cardiovascular disease. In this perspective, the finding of genes related to thrombotic risk, polymorphisms associated with platelet hyper or hyporeactivity began to be studied. Uncontrolled platelet activation might facilitate the formation of a pathologicale platelet plug that could lead to a thrombotic disorder.

Aims: The aim of the present study is to investigate the allelic and genotypic frequencies of polymorphisms that influence platelet function in patients that suffered early (aged less than 45 years) or late thrombotic events (aged more than 45 years).

Material and methods: Genetic analysis was performed in a control sample of 160 individuals and 72 patients with thrombotic events (40 aged less than 45 and over 45). PCR-RFLP was used to analyse G894T and T786C polymorphism in the 3'-end of prothrombin gene downstream sequence. Nucleic Acids Res 2005; 33:1010-20. Conclusion: Our results suggest that different genetic risk factors associated with platelet functionality could be associated in the presence of early thrombotic events. Understanding the functional role of this polymorphism may give us the opportunity to design and develop inter-individually based therapeutic strategies in the prevention of thrombotic events as well as in antiplatelet therapy schedules.

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Keywords: thrombosis, eNOS, polymorphisms
Keywords: Factor XIII activation, fibrin cross-linking, individuals with Factor V Leiden mutation: a novel downstream mechanism that might contribute to the increased risk of thrombosis.

Conclusions: Without the presence of heparin, there was an inverse relationship between TG and phospholipids on a Fluoroskan Ascent.

Materials and methods: Three groups were included in this study: group 1, carriers of the PT mutation without previous thrombotic events (n=22); group 2, carriers of the mutation and previous thrombotic events (n=17); the control group, subjects without antithrombin deficiency or family history of thrombosis (n=22). The generation of thrombin test was determined using fluorometric method (Thromboscience, Synapse BV, Maastricht, the Netherlands). The results were expressed as medians and the percentiles 25 and 75. The statistical analysis were carried out using SPSS (SPSS Inc, Chicago, IL, USA) version 17.0, using the U de Mann Whitney test and with Spearman’s correlation test. All significant differences were defined as p<0.05.

Results: The variables of peak of thrombin and the ETP were significantly higher in carriers of the PT G20210A mutation, with respect to the control group. In carriers of PT G20210A mutation, the variables of the peak of thrombin and ETP were significantly higher in those that had previously an episode of thrombosis. In addition, a positive correlation was observed (p<0.01) between the D-dimer and ETP (r = 0.392) and the Start tail (r = 0.353).

Conclusions: On the basis of our results, we suggest that the determination of ETP could be considered to identify asymptomatic carriers of PT G20210A with higher risk of venous thrombosis.

Table: Thrombin generation. Median, percentil 25th and 75th.

<table>
<thead>
<tr>
<th>Control</th>
<th>Mut. FV Leiden</th>
<th>Mut. PT</th>
<th>Mut. con. thromb.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETP (min)</td>
<td>PEAK (nM)</td>
<td>PEAK TT (min)</td>
<td>START TAIL (min)</td>
</tr>
<tr>
<td>2.7 (2.5–3.5)</td>
<td>421 (341–456.5)</td>
<td>4.7 (4.5–6.1)</td>
<td>22 (19.9–24)</td>
</tr>
<tr>
<td>2.5 (2.3–3.37)</td>
<td>240 (2158.5–2719.1)</td>
<td>4.8 (4.6–6.1)</td>
<td>21 (19–23.1)</td>
</tr>
<tr>
<td>4.17 (2–4.5)</td>
<td>331.5 (3055–3599.8)</td>
<td>5.67 (5.4–7.8)</td>
<td>28 (24.5–31)</td>
</tr>
</tbody>
</table>

P396 MARKERS OF ACTIVATED COAGULATION IN PATIENTS WITH HEREDITARY DEFICIENCY OF ANTITHROMBIN, PROTEIN C OR PROTEIN S

Keywords: thrombophilia, activation markers

Background/Aims: Hereditary deficiencies of antithrombin, protein C or protein S create a state of blood hypercoagulability because of increased thrombin generation. Theoretically, measurement of blood hypercoagulability may enable identification of individuals with high risk of thrombosis, but the results of several studies are contradictory and inconclusive in that regard.

Materials and methods: In this study we investigated the levels of thrombin-antithrombin complex (TAT), prothrombin fragment F1+2 and D-dimer in 117 patients with hereditary deficiency of antithrombin (n=60), protein C (n=30), and protein S (n=27). Seventy-nine patients experienced clinical manifestations of thrombophilia as follows: venous thrombosis (n=63), arterial thrombosis (n=11) or recurrent pregnancy loss (n=5), while 38 individuals were asymptomatic carriers of thrombophilia. Results were compared to those obtained in 71 healthy persons without thrombophilia or family history of thrombosis.

Results: The mean values of F1+2, TAT and D-dimer were significantly higher in symptomatic thrombophilia carriers than in asymptomatic carriers or healthy persons, but with broad overlaps between these three groups. In carriers who experienced venous thrombosis the mean levels of F1+2, TAT and D-dimer were significantly higher than in those who experienced arterial thrombosis. Significantly higher mean value of F1+2 was observed in carriers who experienced spontaneous venous thrombosis than in carriers with provoked thrombosis. Interestingly, this difference was not observed when TAT and D-dimer were compared between these two groups. The levels of activation markers were not different between carriers with recurrent and carriers with single episode of venous thrombosis.

Conclusions: Measurement of activation markers is not reliable tool for prediction of thrombotic risk in thrombophilia carriers because of broad overlap between symptomatic and asymptomatic individuals. Increased thrombin generation seems to play important role in onset of spontaneous venous thrombosis but not in occurrence of arterial thrombosis in thrombophilia carriers.

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Keywords: thrombophilia, antithrombin deficiency

Background: Antithrombin deficiency is associated with an increased risk of venous thrombosis and is reported to show heparin resistance, which is clearly important as affected patients are usually treated with unfractionated (UFH) or low-molecular-weight (LMWH) heparin. We were struck by how rare this phenomenon was in our population of >150 individuals with this deficiency and decided to study it initially in vitro.

Materials and methods: We investigated the effect of UFH (5th International Standard) at concentrations of 0-6.0U/ml and LMWH (1st International Standard) at concentrations of 0.1-3.0U/ml on platelet free plasma samples of healthy volunteers. We measured the effects of the multiple UFH and LMWH concentrations on each. We measured a standard APTT (Synthasil) and thrombin generation (TG) in a platelet poor assay using 5pM tissue factor and 4pM phospholipids with or without recombinant human thrombomodulin (rhTM). Clots were recovered and analysed by SDS-PAGE and Western blotting for FXIII-A and α2PI. The extent of FXIII activation, the cross-linking of fibrin γ-chains and the incorporation of α2PI into the clot was evaluated by quantitative densitometry.

Results: The presence of rhTM significantly slowed down the activation rate of FXIII in the plasma of wild type individuals as compared to FV Leiden carriers. Time required for half maximal FXIII activation was approximately 1.5-fold prolonged in wild types (mean±SEM: 629±75.3 sec) in the presence of rhTM as compared to carriers of FV Leiden (mean±SEM: 457±43.6 sec). The delay of FXIII activation caused by rhTM in wild type individuals was more than 4-fold reduced in heterozygotes and more than 8-fold in homozygotes. The inefficiency of rhTM on delaying FXIII activation in FVLeiden carriers resulted in earlier cross-linking of fibrin γ-chain and α2PI to fibrin.

Conclusion: Earlier FXIII activation and, as a consequence, earlier cross-linking reaction might represent a novel mechanism contributing to the increased thrombosis risk in FV Leiden carriers.

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EVOLUTION OF ANTIPHOSPHOLIPID ANTIBODY TITERS AND CLINICAL EVENTS IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Keywords: antiphospholipid syndrome, antiphospholipid antibodies

Introduction: Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis, repeated abortions, thrombocytopenia and antiphospholipid antibodies (aPLs). After a thrombotic event, current treatment guidelines advised on oral anticoagulation indefinitely. Knowledge of its evolution over time could help to change the long-term treatment.

Aims: To assess the development of aPLs titers in patients with APS and describe the clinical events associated with APS.


Results: 34 patients, median age 45 with thromboembolic disease (62%), APTT elongation (12%) and events associated with arterial disease (26%). Most patients had varices (27%), hyperlipidemia (21%) and hypertension (18%); 18 patients (65%) had final APS as the international consensus criteria of 2006; 15 patients (45%) probable APS; 64% APA positive (55% IgG, 27% IgM, 18% both) and the confirmation 27.39 GPL U / ml IgG, 11.4 GPL U / ml IgM; 24% positive B2GP titers (50% IgG, 25% IgM, 25% each) mean titer of 23.56 U / ml IgG, 17.19 U / ml IgM, 20% positive AL.

At 9 months, 26% showed negative result for APA titers. No patient developed new arterial or venous thrombotic events. Treatment given at diagnosis of APS (oral anticoagulants or aspirin) not was changed.

Conclusions:
- A significant percentage of patients have negative result for APA titers after 9 months of follow-up and no new onset of symptoms following appropriate treatment;
- We recommend the study and monitoring of SAF in patients with thrombotic events in determining the risk of recurrence after a first episode;
- We also recommend an interhospital study in patients with negative antibodies to determine the therapy and the safety after suspending treatment in low risk patients.

Figure: Titers of antiphospholipid antibodies at diagnosis of APS

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THE PREVALENCE OF THE MOST COMMON CAUSES FOR PRIMARY THROMBOPHILIA AMONG SAUDI PATIENTS ATTENDING THE ANTICOAGULANT CLINIC

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Keywords: inherited thrombosis, DVT, pulmonary embolism

Aims: The purpose of our study was to determine whether the activated protein C resistance (APC resistance), factor V Leiden and prothrombin mutation are the most common inherited risk factors for venous thrombosis among Saudi patients attending an anticoagulant clinic.

Methods: The study describes the results of screening all patients attending our anticoagulant clinic with a history of proven recurrent venous thromboembolism (VTE), pulmonary embolism, the first spontaneous life threatening thrombosis or at an unusual site, and patients with unexplained repeated abortion.

The tests done were antithrombin (AT ), protein C (PC), protein S and activated protein C resistance (APC). Molecular testing to detect the mutation of factor V Leiden (FVL) and prothrombin G20210A and MTHFR C677T mutation.

A total of 3,875 patients were referred. 580 patients have been fulfilled the criteria of the study, between October 1998 to November 2008, age (14-51 years old) and 9 patients were neonates. This study was conducted at King Abdul Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

Results: Summarized in the Table.

Conclusions: Factor V Leiden is the most common cause of inherited thrombosis among Saudi patients followed by protein S. Homozygous protein S & C deficiencies are a serious cause of extensive thrombosis with high mortality during neonatal period, an affected neonate is a marker for a group at a high genetic risk. High prevalence MTHFR mutation among repeated abortion which need a further clinical studies.

Reference

Table: The causes of inherited thrombosis among Saudi population in Jeddah, with DVT/PE and recurrent abortion

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Figure: The age distribution of patients treated at outpatient anticoagulant clinic, Jeddah, Kingdom of Saudi Arabia

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Background: Evidence suggests that the G58A polymorphism on fibrinogen α-chain is associated with increased fibrinogen levels in healthy individuals. However, it is still unclear whether this polymorphism is associated with coagulation or thrombosis in patients with coronary artery disease (CAD). In the present study we examined the impact of this polymorphism on fibrinogen levels, D-dimers levels and plasminogen levels.

Methods: The study population consisted of 395 subjects, 246 of whom were patients with CAD. The G58A polymorphism was detected by polymerase chain reaction (PCR) and appropriate restriction enzymes. Fibrinogen levels were measured by immunonephelometry, while plasminogen and D-dimers levels were measured by standard coagulometry techniques.

Results: The genotype distribution was GG: 37.8%, GA: 43.4% and AA: 22.8% for patients with CAD, while GG: 33.5%, GA: 44.3% and AA: 22.2% for controls. Patients with CAD had significantly higher fibrinogen levels (mg/dl) than controls (435.6±131.1 vs 441.1±140.6, p<0.0002). However, in patients with CAD fibrinogen levels were not significantly higher for 58A homozygotes vs 58G carriers (453.6±131.4 vs 441.1±140.6, p<NS), while similar difference occurred in controls (AA: 385.2±129.4 vs GG+GA: 392.6±103.0, p<NS). Moreover, D-dimers levels (mg/L) were significantly higher in CAD patients than controls (409.7±188.2 vs 332.8±199.4, p<0.001). In addition, there was a significant difference for 58G carriers vs 58A homozygotes for CAD patients (506.4±418.8 vs 662.2±627.1, p<0.05), but not for controls (AA: 415.6±289.6 vs GG+GA: 434.7±132.7, p<NS). Finally, CAD patients and controls had no significant difference in plasminogen levels (mg/L) (119.8±79.1 vs 113.9±22.9, p<NS). Patients with CAD had no difference in plasminogen for 58A homozygotes vs 58G carriers (110.2±20.6 vs 112.2±17.2, p<NS), while no significant difference was observed for controls (AA: 112.3±16.7 vs GG+GA: 114.3±23.5, p=NS).

Conclusions: Our findings indicate that the G58A polymorphism on fibrinogen α-chain gene affects D-dimers levels in patients with coronary artery disease. These findings provide a possible mechanism by which this polymorphism may affect thrombotic process/coagulation independently of fibrinogen levels and may have important clinical implications.

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Keywords: antithrombin, conformational, thrombosis

Background: Conformational diseases are a group of disorders that ensue from the instability of proteins, turning active molecules into latent or inactive forms. Alterations in antithrombin, physiological inhibitor of blood coagulation are associated with thrombosis. Different circumstances like the increase of the corporal temperature associated with infections might cause the conformational change.

Aims: Conformational alterations are not easily detected by routine tests because they do not significantly affect antithrombin’s functional activity. Our aim was to investigate their presence, applying genetic analysis, in young patients with spontaneous venous thrombosis, associated with infections and without other known thrombotic defect.

Materials and methods: The present study (3B, 4 and 6) related with conformational alterations were performed in 18 selected patients. Mutations were investigated by heteroduplex analysis of exons 3B and 6 were normal in this patient. DNA Sequencing of exon 4 showed two silent changes of bases: G7596A and G7626A. The prevalence of the polymorphisms in the 18 patients was a-G7596A: 12 homozygous GG; 4 heterozygous GA and 2 homozygous AA and b-G7626A: 8 homozygous GG; 6 heterozygous GA; 4 homozygous AA. Both polymorphism, reported as 295V and 295R respectively, are non-associated with thrombosis.

Conclusions: None of the analyzed patients showed a molecular alteration that could be related to the presence of unstable antithrombin; perhaps, due to the small number of patients. Anyway, conformational defects of antithrombin should be looked for patients with venous thrombosis and no other known thrombophilic defect.
PREVALENCE OF THROMBOPHILIA AND HOMOCYSTEINE IN PULMONARY THROMBOEMBOILIC PATIENTS

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Aims: To describe prevalence of thrombophilia and homocysteine in acute pulmonary thromboembolic patients.

Methods: Review of charts of 120 consecutive patients in a cohort of 605 patients with thromboembolic pulmonary disease (TED) to study prevalence of thrombophilia and hyperhomocysteinemia in patients without any other factor associated with first TED.

Results: 120 patients seen between June 2007 and October 2008 were reviewed. Age was 64 years (range 22-88), 58 were men. There were non risk common factors associated with venous thromboembolism in 70%. We studied the presence of thrombophilia in 54 patients and homocysteine in 61 patients. We found the presence of a thrombophilic factor (TF) in 26 patients (48% patients studied for the presence of TF) i.e.: mutation of 20210 gene of prothrombin (4 patients), protein S deficit (6 patients), factor V Leiden (2 patients), 20210 and FV associated in 2 patients, Lupus anticoagulant in 5 patients and others (7 patients). Of 61 patients studied for hyperhomocysteinemia (HC), elevated homocysteine was found in 33 patients (52%): average 16.2 g/ml, max 62.5 g/ml, min 10.2 mg/dl. In 41 patients (67% of HC tested patients) HC was the only factor associated with pulmonary thromboembolism.

Conclusions: Current guidelines do not recommend thrombophilia study in older patients at first episode of pulmonary thromboembolism but there is a great prevalence of thrombophilia factors and hyperhomocysteine. Homocysteine is the only factor associated with venous thromboembolism in a not decreased number of patients. TF and HC should be considered in addition with other factors in the assessment of risk of thromboembolic disease.

Keywords: thrombophilia, homocysteine, thromboembolism

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DOES MTHFR C677T HETEROZYGOSITY CONTRIBUTE TO HYPERHOMOCYSTEINEMIA IN CHILDREN?


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Aims: To investigate the necessity for therapeutic intervention considering hyperhomocysteinemia in children, in cases of inadequate folic acid supply through environmental factors.

Methods: Thirty-one children were MTHFR C677T heterozygotes (62% versus 38.5% respectively). Personal history of thrombosis: 10/31 children. Comparing pre and post: 8.1±4.3, resulted in homocysteine levels reduction (pre: 10.7±4.1 vs post: 8.1±4.3, p = 0.229). Three out of eight children had a history of thrombosis.

Conclusions: MTHFR C677T heterozygosity is occasionally associated with venous thromboembolism but there is the necessity for therapeutic intervention considering hyperhomocysteinemia in children, in cases of inadequate folic acid supply through environmental factors predispose to high plasma homocysteine levels. Hyperhomocycteinemia is implicated in endothelial damage and potentially has on thrombophilia tests.

Keywords: MTHFR, hyperhomocysteinemia, folic acid replacement, children

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INFLUENCE OF TIME DELAYS ON THROMBOPHILIA SCREENING TESTS

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Aims: To investigate the effect of storing citrated whole blood at room temperature on thrombophilia tests.

Methods: Four samples were taken into BD vacuum tubes (2.7mls, 0.109M) from each of 16 healthy donors. One samples was then centrifuged (2000g for 10 mins) and plasma frozen at -70°C (time 0). The remaining were stored at 20-25°C for 24, 48 or 72 hours and then processed. Samples were tested for antithrombin (AT) [chromogenic thrombin-based assay], protein C (PC) activity [chromogenic assay], free protein S (FPS) antigen by automated immunobias (FPS-IL) [Instrumentation Laboratory] and ELISA (FPS-EL) [Woodhams method] and screened for the Factor V Leiden mutation (FVL-S) [Diagnostic Reagents].

Results: Samples (n=16) demonstrated no statistically significant change in AT over time, mean change in activity of 0.3% at 72 hours (range -5 to +9%), (p=0.131). PC samples (n=16) showed a statistically significant fail at 24 hours (p=0.0068) with a mean change of -2.8% (range +1 to -11%), samples from 48 and 72 hours showed an increasingly significant change (p=0.0001). FVL-S samples (n=10) demonstrated a statistically significant decrease at 48 hours (p=0.0067) and 72 hours (p=0.0004). A statistically significant fall in FPS was seen in PS-IL group (n=10) at 24 hours (p=0.0006), 48 hours (p=0.0001) and 72 hours (p=0.0001). Mean change in PS-IL antigen was -14% (range -5 to -32%) at 24 hours and -37% (range -23 to -46%) at 72 hours. FPS-EL samples at 24 hours (n=10) demonstrated no significant change (p=0.5178).

Conclusions: AT samples were stable for 72 hours stored as citrated whole blood (BD vacutainer) at room temperature. PC and FPS-EL samples were stable for 24 hours, while PS-IL samples were stable for less than 24 hours. Change in FVL-S samples did not alter interpretation.

Figure Influence of Time Delays on Thrombophilia Screening Tests

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FACTOR V LEIDEN TESTING AND LIVER TRANSPLANTATION

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Aims: Hepatic vessel thrombosis may occur after orthotopic liver transplantation (OLT) and lead to graft failure and retransplantation. Genetic testing for assessing factor V Leiden and other thrombophilias may be used. However, in OLT patients, genetic testing of the patient peripheral blood lymphocytes DNA may not provide accurate results for proteins expressed by donor hepatocytes in what may be considered inappropriate genetic testing. We describe 6 patients who, following OLT in our Liver Transplantation Center, presented discrepancies between activated protein C resistance (APCR) in a functional coagulation-based assay, and F V Leiden genotype.

Methods: A total of 126 consecutive patients, submitted to primary OLT in our Transplantation Center, between March 2007 and June 2008, were studied. Five patients presented APCR positive in pre-OLT testing. These 5 patients were retested post-OLT and also assessed by genetic testing. One of the patients, a para-amiloïdotic female, donated her liver to another patient who tested APCR negative before OLT. He also was retested after the sequential OLT.

Results: The 5 patients that presented APCR positive in pre-OLT testing were negative post-OLT. Yet genetic testing of peripheral blood lymphocytes DNA confirmed FV Leiden heterozygosity. The one APCR negative patient who received the sequential OLT from the APCR positive patient, became APCR positive while the genetic testing remained negative for the FV Leiden mutation.

Conclusion: These cases illustrate the difficulties of thrombophilia testing after OLT and emphasize the need for evaluating both FV Leiden by coagulation and genotype assays in order to accurately assess thrombotic risk in such patients.

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Keywords: thrombophilia, time
THE IMPACT OF PROTHROMBIN 20210A POLYMORPHISM AND FACTOR V LEIDEN ON DEEP VEIN THROMBOSIS IN THE SOUTH IRANIAN PATIENTS


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Keywords: factor V Leiden, prothrombin 20210A, deep vein thrombosis

Background/Aims: Multiple genetic variants are predisposing factors for thrombosis, but the impact of each factor on disease developing can vary in different ethnic groups. The prevalence of each hereditary factors and their combination is different in diverse ethnic groups. Factor V Leiden (FVL), and prothrombin 20210A mutation were described as risk factors for thrombosis and their role on morbidity of deep vein thrombosis (DVT) are less clear.

Patients and methods: In total 135 patients with objectively documented DVT from academic clinics were studied at the south of Iran. All patients with lower limb DVT had sonography or venography for confirm diagnosis.

Results: The Prothrombin 20210A polymorphism and FVL mutation analysis was performed on genomic DNA by using the RFLP and multiplex ARMS techniques. The allele frequency of FVL and prothrombin 20210A were 0.196 and 0.181 respectively. The effect of FVL (OR = 11.9, 95% CI = 5.6-25.5), and age > 50 years were found to be significant factors in this model (P=0.0001). Homozygosity for FVL mutation was found in the 19 patients (14.1%), while 6 patients (4.5%) of them had a compound prothrombin 20210A either in homozygote (n=3) or heterozygote (n=7) status with FVL.

Conclusions: FVL and prothrombin 20210A mutations should be taken into account for prophylaxis treatment and counseling in individuals who predispose for acquired thrombophilia and DVT in the south Iranian provinces.

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CEREBRAL VENOUS THROMBOSIS IN CHILDREN: EVALUATION OF THE ASSOCIATION WITH PROTHROMBOTIC RISK FACTORS

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Background: Cerebral venous thrombosis (CVT) in childhood is a serious disease. Its pathophysiology is still poorly understood. Predisposing factors (infections, trauma, cancer, leukemia, cardiac and autoimmune diseases) should be unraveled at risk and establish therapy. Multiple additional factors, including prothrombotic risk factors, contribute to the symptomatic onset of CVT. The aim of this study was to assess the role of prothrombotic risk factors in association to underlying diseases as risk factors for CVT in children.

Methods: From 1999 to 2009, 15 patients aged from 6 months to 16 years with CVT were studied. Clinical conditions were investigated. The following prothrombotic risk factors were evaluated: factor V Leiden mutation, factor II G20210A and methylenetetrahydrofolate reductase (MTHFR) (677TT) polymorphisms, homocysteine levels, antithrombin, protein C and S levels, activated protein C resistance, lupus anticoagulant and antiphospholipid antibodies (anticardiolipin and anti-beta2GPI).

Results: Underlying diseases were documented in 11 patients (73.3%): 6 had infectious diseases, 2 presented cardiac malformations, 1 had leukemia, 1 had a cranial trauma and 1 had neurological congenital malformations. Prothrombotic risk factors were detected in 4 patients (26.7%): 3 patients with no detected underlying disease (1 with MTHFR homozygote and homocysteine > 100 mol/l, 1 with positive IgM anticardiolipin antibodies and 1 with IgG anti-beta2GPI antibodies); 1 patient had a cerebral abscess and positive IgM anti-beta2GPI. All patients were treated with unfractioned heparin for at least 5 days. For secondary long-term prophylaxis, warfarin was given for 3 months minimum.

Conclusions: The present results suggest that specific clinical conditions play the most important role in the origin of CVT in children. However, additional prothrombotic risk factors should not be underestimated, as 4 patients had positive results in our tests which could explain the CVT. It can also be useful to establish therapy strategies.

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AN NOVEL 110 BP INSERTION IN A PATIENT WITH HOMOCYSTINURIA

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Keywords: CBS, homocystinuria

Background/Aims: Homocystinuria due to cystathionine-beta-synthase (CBS) deficiency is the most common genetic defect of sulfur containing amino acids, transmitted as an autosomal recessive disorder. Cystathionine beta synthetase enzyme catalyses the synthesis of cystathionine from homocysteine and serine in the methionine pathway. This results in accumulation of homocysteine and methionine in plasma and leads to excretion of excessive uritary homocysteine. Here we report a novel mutation at CBS gene in a patient with homocystinuria.

Materials and methods: All of the exons of the CBS gene screened. Exon 8 was amplified by polymerase chain reaction (PCR). Patients’ sample was sequenced, using a DNA sequencer (Beckman Coulter DNA Sequencer, USA).

Results: Direct PCR analysis and sequencing revealed a 110 bp insertion at exon 8 in CBS gene. 110 bp insertion start at base pair 855 up to 965 ending a new aminoacid formation. In exon 8; the serin aminocid which is coded by TCC codone changed to tryptophan (TGG) with the 110 bp insertion. And also a missense mutation at exon 8 in CBS gene. This mutation is caused T-C transition at base pair 833, resulted in aminocid change from iseucloline to threonin was determined (Figure). 833 T-C was described previously. However 110 bp insertion is reported for the first time.

Discussion: Previously 68 bp deletion was reported in the same region (exon 8). The frequency of this polymorphism is 5.9 % in Turkish population. New 110 bp insertion shows that this region is a hot spot for mutation.

Conclusions: In our study we describe a 14 year old patient with homocystinuria due to two mutations at cystathionine β-synthase (CBS) gene in compound heterozygosity state of which one of the mutation (110 bp insertion) was not described.

Figure: CBS gene 833 T-C transition at exon 8

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ANTICARDIOLIPIN ANTIBODIES IN PATIENTS WITH CHRONIC HEPATITIS VIRUS INFECTION: IMPLICATION OF HCV AS A CAUSE OF ANTIPHOSPHOLIPID SYNDROME

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Keywords: HCV, aCL, APS

Background: Infectious agents have been implicated in the induction of anticardiolipin (aCL) antibodies and the development of the antiphospholipid syndrome (APS). Hepatitis C, a worldwide viral infection, is a great health problem in Egypt. The APS is usually defined by the association of clinical manifestations that comprise venous and/or arterial thrombosis and thrombocytopenia, along with the presence of anticardiolipin (aCL) antibodies. However, these antibodies are not usually associated with thrombotic events, as happens with autoimmune diseases, in which these antibodies need the presence of β2-glycoprotein I.

Aim: The aim of this research was to screen for the presence of aCL antibodies (IgM and IgG ) and β2-glycoprotein I in 184 Egyptian patients with chronic HCV infection and 40 healthy subjects as a reference group.

Methods: The levels were determined by enzyme-linked immunosorbent assay. Results: aCL antibodies (IgG)were found to be positive (> 9.8 GPL) in 11 patients (5.9%) and aCL (IgM)>9.6 MPL in 17 patients (9.2%) in comparison to the negative results of the reference group. Seven patients with positive aCL antibodies were β2-glycoprotein I-dependent. No significant association was found between aCL antibodies and clinical manifestations of APS. Finally, no cross-reactivity between aCL antibodies and HCV antigens was observed.

Conclusions: We concluded that Egyptian individuals chronically infected with HCV present a significant production of aCL antibodies, which mainly are not associated with the clinical manifestations of APS.

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Keywords: thrombosis, factor VIII, venous thromboembolism, risk factor, thrombophilia.

Background/Aims: Thrombus formation may form enhanced coagulation or impaired fibrinolysis. An increased tendency for the blood to clot is referred to as the hypercoagulable state or thrombophilia which includes various inherited and acquired clinical disorders or mixed conditions. There are many studies suggesting that elevated factor VIII may be a common and independent risk factor for thrombotic events. We tried to assess the level of factor VIII in patients with idiopathic thrombosis.

Materials and methods: Our cases were patients with idiopathic venous thrombosis having referred for hypercoaguable studies to Coagulation Lab in Tabriz University. The inclusion criterion was the occurrence of thrombotic event confirmed by objective diagnostic methods coupled with three months of follow-up without any other disorder. Our controls were from healthy blood donors and matched with the cases on sex, ethnicity, and age. Plasma of a healthy person was used to establish the normal reference range according to which our patients are compared. Factor VIII levels were measured using a one-stage assay, the PTT based Diagnostica Stago on the STA compact automated coagulation factor analyzer. SS and Chi-square were finally used for data analysis.

Results: One-hundred-fifty-two cases and 130 controls enrolled. The mean factor VIII level for cases was 157.26 IU/dl (SD±53.8) with the minimum level of 66 and maximum of 364 IU/dl. For controls, the mean factor VIII level was 111.78 IU/dl (SD: 29.68) with the minimum level of 42 and the maximum of 195 IU/dl. These levels were statistically significant and higher in the case group. The elevated FVIII level was higher in females than males (35.3% vs 23.8%) and increased with age. The normal range in the control group varied within 52-171 IU/dl, which is higher than the normal level of 50-150 IU/dl.

Conclusions: There are many studies showing that increased FVIII level may be an independent risk factor for thrombosis. Our results suggested elevated FVIII level in 28.9% of the patients with thrombosis compared to 3.1% in the control group. So, factor VIII measurement is recommended to be practiced in routine thrombophilia screening programs.

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MULTIPLES OF MARKERS FOR HYPERCOAGULATION FOUND IN PATIENTS WITH HISTORY OF THROMBOEMBOLIC DISEASE (TED).

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Keywords: thrombosis, hypercoagulation

Background: Markers for hypercoagulation are often obtained to explain why patients have had deep-vein thrombosis, pulmonary embolus or other TED events. Such information can then be used to evaluate the risk for additional events occurring for these patients or for their family members. This study describes the aggregate results of clinical consultations wherein the hematologists were asked to comment upon risk for additional surgeries and for recommended anticoagulation. Those hematologists determined which laboratory tests were ordered; thus all patients had all tests.

Methods: Hospital computer logs were initially probed for patients having had protein C, factor V Leiden or anti-cardiolipin antibodies measured from 11/7/01 until 8/1/07. Laboratory records of any patients having had any one of these tests were searched further for any additional hypercoagulation laboratory studies. Additional assays performed may have included protein S, anti-thrombin III (ATIII), homocysteine, prothrombin 20210 genome, lupus anticoagulant (LA), plasminogen activator inhibitor-1 (PAI-1), and markers for the antiphospholipid syndrome (APS) including anti-phosphotidyl serine, anti-phosphotidyl ethanolamine and anti-β2-glycoprotein1.

Results: A total of 520 patients were identified in the initial survey. Abnormal diagnostic results were found for 293 (56.3%) of these patients. More than one abnormality was found for 103 (35.6%) of these patients. The table below demonstrates the frequency of the multiples of laboratory diagnoses and the frequency of abnormal markers for hypercoagulation found. Linear regression analysis demonstrated no links among these markers.

Conclusions: These results demonstrate that laboratory explanations for TED may be found in a large proportion of patients with TED. It is not uncommon to find more than one such abnormality among these patients. This information may be useful in advising patients as to the risks of surgical procedures and life styles.

Table: Test for hypercoagulation among 520 patients with TED and the frequency of clusters of abnormal results among these patients

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormal %</th>
<th>&lt;90%</th>
<th>&lt;50%</th>
<th>Homozy.</th>
<th>ATIII</th>
<th>APS</th>
<th>V. Leiden</th>
<th>Pro2810</th>
<th>LAD</th>
<th>PAI-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VII</td>
<td>28.9%</td>
<td>20.6%</td>
<td>15%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>35.3%</td>
<td>23.8%</td>
<td>52%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
</tr>
<tr>
<td>Factor IX</td>
<td>42%</td>
<td>35.6%</td>
<td>40%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
</tr>
<tr>
<td>Factor X</td>
<td>35.6%</td>
<td>28.9%</td>
<td>30%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
<td>&gt;50%</td>
<td>&gt;100%</td>
</tr>
</tbody>
</table>

Clusters of abnormal results: 44 (8.5%) | 30 (5.8%) | 19 (3.7%) | 16 (3.1%) | 57 (11%)

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A63
Background: Platelet activation occurs in both coronary and carotid artery stenting as a result of vessel wall damage. The dual antiplatelet regimen (aspirin-thienopyridine) has a significant impact on reducing stent thrombosis and adverse outcomes. Whether differences exist in the degree of platelet activation among stent-treated coronary and carotid vessel is not known.

Aims: To compare platelet activation in patients who underwent carotid versus coronary revascularization.

Patients and methods: 20 patients with carotid stenosis and 20 stable angina patients who underwent BMS implantation were studied. To assess platelet function, blood was withdrawn 1 month (T1) after stenting procedure and 2 months after thienopyridine discontinuation (T2). Platelet activation markers (PAI-1, CD62 and tissue factor [TF] and the % of monococyte-platelet aggregates [MPA]) were assessed by whole blood flow cytometry in resting conditions and upon in vitro ADP stimulation.

Results: Results of platelet activation in patients who underwent revascularization with stent implantation compared to patients with carotid artery stenting, both 1 month after stenting and 2 months after monococyte-platelet aggregates discontinuation. This prothrombotic platelet phenotype may have implications for thrombotic complications in coronary patients.

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THE RISK FACTORS OF STROKE AMONG PERIPARTUM IN TAIWAN

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Keywords: stroke, peripartum

Background/Aims: Stroke is a recognized complication of pregnancy, contributing to more than 12% of all maternal deaths. Estimated incidence rates vary considerably from 4.3 to 210 strokes per 100,000 deliveries. However, few studies have evaluated stroke risk in Asian populations and followed women beyond the early postpartum period. Thus, the present study determined the risk of stroke in women in Taiwan during pregnancy and the first postpartum year.

Aims: The three most important risk factors for stroke during pregnancy were cesarean delivery, systemic lupus erythematosus and preeclampsia-eclampsia. The individual respective relative risk ratios of the risk of hemorrhagic and ischemic stroke during pregnancy and within the first postpartum year. There were 139 cases of hemorrhagic stroke and 107 cases of ischemic stroke. The results of this analysis were used in multivariate logistic regression models to determine the adjusted odds ratios of the risk of hemorrhagic and ischemic stroke in pregnant women.

Results: There were 575 MI, 284 incident IS, and 824 deaths during a median of 13.2 years of follow-up. Models were used to estimate crude and adjusted hazard ratios (HR) for clinical events. In our large population-based cohort study serum OPG concentration was associated with increased risk of MI (HR 1.20; 95% CI 1.11-1.31), IS (HR 1.32; 95% CI 1.18-1.47), and total mortality (HR 1.41; 95% CI 1.29-1.54) after adjustment for traditional cardiovascular risk factors such as age, sex, current smoking, systolic blood pressure, BMI, HDL cholesterol, total cholesterol, creatinine, hs-CRP and diabetes mellitus.

Conclusions: In our large population-based cohort study serum OPG concentration at baseline was associated with future MI, IS and total mortality independent of traditional cardiovascular risk factors. It may be suggested that OPG has a prothrombotic impact on the cardiovascular system as long as it is known that serum OPG does not promote plaque growth or formation.

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A MUTATION IN THE INNER MITOCHONDRIAL MEMBRANE PEPTIDASE 2-LIKE GENE (IMMP2L) INCREASES INFARCT VOLUME AFTER A TRANSIENT CEREBRAL FOCAL ISCHEMIA

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Keywords: mitochondria, cerebral ischemia, oxidative stress, gene mutation, brain damage

Mutation of Immp2l gene affected the signal peptide sequence processing of mitochondrial proteins cytochrome c1 and glycolate phosphate dehydrogenase. 2. Mutant Immp2l impairs fertility by enhancing oxidative stress [1]. Although mutation of Immp2l gene is associated with Tourette syndrome [2] its influence in the CNS is unknown. The objectives of this study are to explore the effects of mutant Immp2l on ischemic outcome and to determine the effects of hyperglycemia on brain damage in both WT and mutant mice. Male Immp2l mutant and WT mice were subjected to 1 hour MCAO under normo- and hyperglycemic conditions. Their brains were harvested after 5- and 24-hrs of reperfusion. Cerebral infarct volumes, edema, and production of superoxide were measured. The results showed that average infarct volume increased from 12% of hemisphere in the WT to 30.9% in the mutant mice (p=0.004). Hyperglycemia enlarged infarct volume in the WT but did not increase the damage in the mutant mice. There was no significant difference observed in cerebral edema among the experimental groups. In situ detection of superoxide revealed a significant elevation of superoxide production in the mutant mice compared to the WT animals. Our results suggest that mutation of Immp2l gene increases ischemic brain damage by enhancing superoxide production and that hyperglycemia enhances ischemic brain damage in WT animals but did not further enhance the damage in mutant mice because maximum damage was already reached in the mutant animals.

References

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EFFECT OF INTRAHOSPITAL TREATMENT WITH ANTIPLATELETS AND OTHER CARDIOVASCULAR DRUGS ON THE SEVERITY OF ACUTE ISCHEMIC CEREBROVASCULAR EVENTS. THE GIFA STUDY

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Background/Aims: The pathophysiology of ischemic stroke dictates that treatments be administered shortly after symptom onset to be beneficial. No information exists, to our knowledge, about the possible role of cardiovascular drugs administration in the acute phase of ischemic stroke and possible effects on stroke outcome. On this basis the aim of our study was to evaluate the relationship between intra-hospital treatment with cardiovascular drugs in patients with acute ischemic stroke on some outcome indicators.

Methods: 1096 subjects enrolled in the GIFA study, who had a main discharge diagnosis of ischemic stroke represent the final sample. Drugs considered for the analysis were the following: ACE-inhibitors (ACE-I), angiotensin II receptor blockers (ARBs), statins, calcium-channel-blockers (CCBs), antiplatelet (APL) drugs, antivitamin-k (VKAs), and heparins. As outcome indicators we choose intra-hospital mortality, cognitive function evaluated by Hodkinson Abbreviated Mental Test (HAMT), and functional status evaluated by evaluation of activity daily living (ADL). Indicators of a good outcome were: no intra-hospital mortality, HAMT > 6 and 0 ADL impaired.

Results: Subjects with no-intrahospital mortality, HAMT > 6 and 0 ADL impaired were more likely to have: a lower age, lower blood glucose level at admission, higher SBP at admission, higher plasma levels of total cholesterol, lower white blood cell count, lower Charlson index. Moreover, patients with a good outcome showed a higher rate of intra-hospital treatment with Ace-inhibitors, calcium-channel blockers and a lower rate of pre-treatment with heparin.

Conclusions: Our study suggests that if a patient with acute ischemic stroke has higher SBP at admission, higher total cholesterol plasma levels, a lower Charlson index and if it is treated with ace-inhibitors, calcium channel blockers and antiplatelets the short term outcome is better in terms of intra-hospital mortality and of functional indicators such as cognitive and functional performance at discharge.

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EFFECT OF PRE-HOSPITAL TREATMENT WITH ANTIPLATELETS CARDIOVASCULAR DRUGS ON THE SEVERITY OF ACUTE ISCHEMIC CEREBROVASCULAR EVENTS. THE GIFA STUDY

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Background/Aims: Previous data have underlined the possible prognostic role of demographic and clinical variables at admission in stroke patients, but few studies have examined the role of drugs with a known cerebrovascular preventive effect on acute ischemic stroke prognosis. The aim of this study is to evaluate the relationship between some clinical and laboratory variables and pre-treatment with cardiovascular drugs and a favourable outcome in subjects with acute ischemic stroke.

Methods: 1096 subjects enrolled in the GIFA study, who had a main discharge diagnosis of ischemic stroke represent the final sample. All drugs prescribed during pre-hospital time were taken from hospital charts and codified according to the anatomical therapeutic chemical classification. Drugs considered for the analysis were the following: ACE-inhibitors (ACE-I), angiotensin II receptor blockers (ARBs), statins, calcium-channel-blockers (CCBs), antiplatelet (APL) drugs, antivitamin-k (VKAs), and heparins. As outcome indicators we choose intra-hospital mortality, cognitive function evaluated by Hodkinson Abbreviated Mental Test (HAMT), and functional status evaluated by evaluation of activity daily living (ADL). Indicators of a good outcome were: no intra-hospital mortality, HAMT > 6 and 0 ADL impaired.

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THROMBOPHILIC RISK FACTORS AND OUTCOME IN PATIENTS UNDERGOING ENDOVASCULAR INTERVENTION FOR PERIPHERAL ARTERIAL DISEASE

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Keywords: peripheral arterial disease, arterial thrombosis, thrombophilic risk factors

Aims: Few data are available on thrombophilic risk factors and clinical outcome in patients undergoing percutaneous transluminal angioplasty (PTA) for peripheral arterial disease (PAD). We investigated the role of homocysteine, fibrinogen, Factor VIII (FVIII), Factor V Leiden (FV Leiden), Factor II G20210A, and FXIa. The percentage of patients positive for PAD (Fontaine’s stages: II through IV; aged 69 +/- 1 years, male/female 119/78).

Design and methods: A longitudinal study. End-points of the study were total mortality, cardiovascular events and restenosis after PTA. Patients were followed up for an average time of 32 +/- 2 months.

Results: During the follow-up, total mortality was 16%, 45.5% of patients had a cardiovascular event. According to Cox regression analysis, age and the presence of critical limb ischaemia were predictors of mortality and cardiovascular events, whereas diabetes, hyperlipidaemia, homocysteine, and FXIa were predictors of cardiovascular events. Considering as dichotomous the following variables: fibrinogen, homocysteine, FVIII, presence of LAC, FII G20210A, and FXIa mutations, the frequency of patients with at least two thrombophilic alterations was 31%. During the follow-up, cardiovascular events were more frequent in the patients with at least two thrombophilic alterations versus those with one or without thrombophilic alterations (37 vs. 17% log-rank p<0.001). Rates of restenosis during the follow-up were not different in the two groups (26 vs. 20%, p=ns).

Conclusions: The presence of two or more thrombophilic risk factors in patients who underwent PTA 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.

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CHANGES OF HAEMOSTATIC PARAMETERS IN PATIENTS WITH CAROTID STENOSIS

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Keywords: haemostasis, carotid stenosis

Background/Aims: Disturbances in various components of the haemostatic system may account for clinical manifestations of atherothrombosis and are considered as valuable prognostic factors. The aim of our study was to evaluate changes in fibrinogen concentrations and activities of antithrombin III, plasminogen, PAI 1 and von Willebrand factor in patients with carotid stenosis.

Materials and methods: The study compared levels of the above mentioned parameters between a group of 80 patients with carotid stenosis (43 men and 37 women) and a control group of 55 age-matched controls (29 men and 26 women). Plasma samples were analyzed using standard methods and results were compared using Student’s t-test.

Results: Mean fibrinogen levels in patients (5.43 g/L) and in controls (2.86 g/L) were significantly different (p<0.001). Comparison of antithrombin III activity between patients (98.5 %) and controls (106.6%) revealed significant difference (p<0.001). Plasminogen activity in patients (133.8%) was significantly higher (p<0.001) compared to that measured in controls (103.9%), while the difference in PAI 1 activities (3.99 U/mL in controls vs. 4.14 U/mL in patients) did not reach the level of significance. Activity of von Willebrand factor was significantly higher (p<0.001) in patients (164.8%) than in controls (90.1%). Gender related differences in levels of all measured parameters had no significance.

Conclusions: We can conclude that patients with carotid stenosis have increased fibrinogen levels and decreased antithrombin III activity. Plasminogen activity is also increased in these patients, while the PAI 1 activity is not significantly affected. Additionally, we can state that patients with carotid stenosis have increased activity of von Willebrand factor.

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WHAT IS MORE EFFECTIVE AND SAFE: LOW MOLECULAR WEIGHT HEPARIN OR UNFRACTIONATED HEPARIN DURING ARTERIAL RECONSTRUCTIVE SURGERY?

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Keywords: thrombosis, arterial reconstructions

Background: Early thrombosis of reconstructed arteries presents an important problem in the surgery of arterial disease. A limited number of trials highlight intra-operative use of low-molecular-weight heparins (LMWH) in preventing thrombotic complications in vascular surgery. We speculated that weight-adjusted LMWH infusion during infrainguinal reconstructive vascular surgery is at least as safe and effective as standard UFH.

Materials and methods: One hundred and four patients with occlusive arterial disease of lower extremities were randomly assigned to get either 100 IU/kg of LMWH (nadroparin) (n=54) or 100 IU/kg UFH (n=50) intravenously before clamping. Pre-, intra- and postoperative coagulation and adrenaline-induced platelet aggregation were evaluated. Early thrombosis rate, blood loss volume and rate of thrombosis, arterial reconstructions complications and long-term results.

Conclusions: Intraoperative weight-adjusted LMWH usage decreases both thrombogenic activity, fibrinogen level, activated partial thromboplastin time (APTT), factor XIII, thrombin time, time needed to provide hemostasis after the reconstruction and hematoma formation rate after surgery all appeared to be significantly lower in the LMWH group. The majority of analyzed parameters, including fibrinolytic activity, fibrinogen level, activated partial thromboplastin time (APTT), factor XIII, thrombin time, prothrombin ratio, antithrombin III level as well as aggregation parameters significantly changed after the intra-operative infusion of 100 IU/kg nadroparin bolus or the same dose of UFH. (Table).

Results: There were no intra- or post-operative thromboses in the LMWH group in comparison with 4 (8%) in the UFH group (p<0.05). Mean intra-operative blood-loss level, activated partial thromboplastin time (APTT), factor XIII, thrombin time, bolus or the same dose of UFH significantly changed after the intra-operative infusion of 100 IU/kg nadroparin bolus or the same dose of UFH. (Table).

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ILIAC AND INFRAINGUINAL ENDOVASCULAR REvascularization PROCEDURES IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE: COMPLICATIONS AND LONG-TERM RESULTS.

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Keywords: PAD, peripheral PTA

Aims: To compare ilioc and femoro-popliteal percutaneous transluminal angioplasty (PTA) procedures in patients with peripheral arterial disease (PAD) with regards to rates of periprocedural and antithrombotic treatment-related complications, long-term (3 years) restenosis and r ethrombosis, need of further revascularization procedures and leg amputations.

Methods: Consecutive PAD patients undergoing PTA were prospectively followed-up at 1-6-12 months, then yearly. Visits included echo color doppler with Ankle-Brachial-Index (ABI) measurement. After PTA double antiplatelet therapy was administered for 30 days, then aspirin alone, for infrainguinal procedures LMWH (half therapeutic dosage) was added for a week. All patients received statins for at least six months.

Results: 201 patients were enrolled. Mean age was 68.5 ± 9.62 years, 83% of patients were male. Mean follow-up was 36 months. Indications for PTA were claudication (58.2%), rest pain (10.95%), tissue loss (18.4%), acute thrombosis (12.4%). In 396 lesions in 272 limbs, 220 procedures were performed. Iliac procedures were 141 (51.8%), infrainguinal 99 (34.6%), and both sites 32 (11.8%). The last two groups were analyzed together. Stent was used in 79% of 200 iliac lesions and in 6% of 196 infrainguinal ones. Thirty-day mortality was 0.5%. Periprocedural and 30-day antithrombotic treatment-related haemorrhagic complication rates were 9.1% and 2.7% respectively (Table). One-year and 3-year ≥75% restenosis or rethrombosis cumulative rates were 1.3% and 7.7% respectively in iliac-treated patients (Figure). Corresponding rates of infrainguinal restenoses were 25.3% and 41.6% (p<0.0001). Among 18 late reinterventions, only 2 concerned iliac vessels. Baseline <0.70 ABI values were significantly related to recurrence. Endovascular or surgical reinterventions were performed in 29 and 14 patients respectively. Ten patients underwent major amputation, 5 within the first month after PTA.

Conclusions: Iliac PTA has a long-term sustained better prognosis than infrainguinal procedures, the second strongest predictor of recurrent disease being baseline ABI. Periprocedural and 30-day antithrombotic treatment-related haemorrhagic complications are relevant.

Table: Procedural complications (232 procedures, 12 for restenosis treatment)

<table>
<thead>
<tr>
<th>Complications</th>
<th>N</th>
<th>%</th>
<th>Corrective Interventions</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoneuropathy</td>
<td>13</td>
<td>5.6</td>
<td>Surgical suture</td>
<td>4</td>
</tr>
<tr>
<td>Large inguinal haematomata</td>
<td>8</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus dislocation</td>
<td>13</td>
<td>5.6</td>
<td>Thrombolysis</td>
<td>10</td>
</tr>
<tr>
<td>Dissection</td>
<td>7</td>
<td>3.0</td>
<td>Stent</td>
<td>4</td>
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<tr>
<td>Cholesterol embolization</td>
<td>5</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon rupture</td>
<td>2</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closure device-related thrombosis</td>
<td>2</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter access A-V fistula</td>
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<td>0.4</td>
<td>Surgical suture</td>
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<tr>
<td>Total</td>
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</tbody>
</table>

Figure: Kaplan-Meier restenosis risk curves in relation to treated lesion localization.

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BLOOD LIPIDS, P-SELECTIN AND TPA ARE ASSOCIATED WITH ADVERSE OUTCOME OF FEMOROPОPLITEAL PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

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Keywords: percutaneous transluminal angioplasty, peripheral artery disease

Our understanding of the mechanisms of restenosis/reocclusion of the superficial femoral artery after percutaneous transluminal angioplasty (PTA) is incomplete. No associations between blood constituents and success of PTA have been documented yet, and were therefore, tested in this study.

142 consecutive patients treated by femoropopliteal PTA because of disabling claudication or critical limb ischemia were followed-up by vascular ultrasound imaging at 1, 6 and 12 months after the procedure. The technical success of PTA was assessed by peri-procedural angiography. Adverse outcome of PTA was defined by peri-procedural angiography. At six months blood was drawn for routine laboratory analysis. In addition, closure time, fibrinogen, von Willebrand factor, D-dimer, homocysteine, P-selectin, VCAM-1, tissue plasminogen activator (tPA) and several genetic polymorphisms were also determined.

During the 12-month follow-up, restenosis occurred in 54 (38%) patients, reocclusion in 31 (22%) patients and in the remaining 57 (40%) patients PTA was considered successful. Patients with restenosis had higher triglycerides (2.0±1.4 vs 1.5±0.7 mmol/L), lower LDL cholesterol (2.4±0.9 vs 2.8±1.1 mmol/L) and higher P-selectin (31.1±11.2 vs 26.8±11.0 μg/L). All post hoc p < 0.03) than patients with good outcome, while in patients with reocclusion tPA was significantly higher compared to both patients with good outcome and patients with restenosis (14.1±5.8 vs 11.7±3.8 and 10.5±3.6, respectively, both p < 0.02). Time of the adverse event (1, 6 or 12 months after PTA) had no effect on any of the measured variable either in patients with restenosis or patients with reocclusion.

Blood lipids, P-selectin and tPA were associated with adverse outcome of the PTA in this study. The possible prognostic value of any of these variables should be tested in prospective studies.

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CAROTID ATHEROSCLEROSIS AND CHLAMYDOPHILA PNEUMONIAE INFECTION IN TYPE 2 DIABETES MELLITUS PATIENTS

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Keywords: atherosclerosis, chlamydia pneumoniae, diabetes mellitus

Background/Aims: Infectious agents, especially the intracellular Chlamydia pneumoniae, have been supposed to be involved in the atherosclerotic process. We performed a cross-sectional, multicenter, outpatient protocol to study Chlamydia pneumoniae DNA in leukocytes measured by a real-time PCR in patients with type 2 diabetes with different degrees of atherosclerosis evaluated by carotid ultrasound.

Methods: One hundred thirty-five consecutive type 2 diabetic patients were studied. Clinical, metabolic (HbA1c, lipids) and inflammatory (high-ultrasensitive C-reactive protein, tumor necrosis factor-alpha, interleukin-6) variables were measured. Previous clinical macrovascular disease was registered and B-mode ultrasound was performed. Real-time PCR protocol for Chlamydia pneumoniae (Tib Molbiol, Berlin, Germany) in a LightCycler thermocycler (Roche, Basel, Switzerland) was performed in all patients, using adequate positive and negative internal controls.

Results: Patients mean age was 62 ± 7 years. Mean diabetes duration was 16 ± 9 years. Mean HbA1c was 7.1 ± 1.1%. In relation to carotid ultrasound results, 40.7% patients presented high wall shear rate, 32.5% subclinical atherosclerosis and 26.6% no evidence of atherosclerosis. All groups were homogeneous in anthropometrical data. Biochemical determinations were similar in all groups except for cholesterol and non-HDL-cholesterol levels. Patients with clinical atherosclerosis had greater carotid intima-media thickness compared to the other two groups. No Chlamydia pneumoniae DNA was detected in any of the type 2 diabetes patients regardless of the presence of clinical or subclinical atherosclerosis.

Conclusions: The lack of detection of Chlamydia pneumoniae DNA in leukocytes suggests that this bacterium does not have an active systemic role in the pathogenesis of atherosclerosis in middle-aged type 2 diabetic patients, and it is not a reliable marker for atherosclerosis in high risk patients.

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BLOOD LIPIDS, P-SELECTIN AND TPA ARE ASSOCIATED WITH ADVERSE OUTCOME OF FEMOROPОPLITEAL PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

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CAROTID ATHEROSCLEROSIS AND CHLAMYDOPHILA PNEUMONIAE INFECTION IN TYPE 2 DIABETES MELLITUS PATIENTS

J.C. Reverter 1, S. Pellitero 2, J. Montagueo 3, N. Alonso 4, B. Soldevila 5, A. Sanmarti 6, J.L. Reverter 7, D. Tassies 8

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Conclusions: The lack of detection of Chlamydia pneumoniae DNA in leukocytes suggests that this bacterium does not have an active systemic role in the pathogenesis of atherosclerosis in middle-aged type 2 diabetic patients, and it is not a reliable marker for atherosclerosis in high risk patients.

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**EFFECT OF PROTHROMBIN 19911 A→G POLYMORPHISM ON THE RISK OF CEREBRAL SINUS-VENOUS THROMBOSIS**

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Keywords: cerebral sinus-venous thrombosis, thrombophilia, factor V Leiden, prothrombin 19911 A→G

**Background/Aims:** The A→G polymorphism at position 19911 of the prothrombin gene is associated with a mildly increased risk of venous thromboembolism, alone or in association with such common thrombophilia mutations as factor V Leiden and prothrombin 20210 GA. Its role in cerebral sinus-venous thrombosis is not known.

**Materials and methods:** The presence of prothrombin 19911 A→G was investigated in a case-control study of 108 patients with cerebral thrombosis and factor V Leiden (n=25), prothrombin 20210 GA (n=48), without thrombophilia (n=35) and 842 healthy individuals with the corresponding coagulation profile.

**Results:** Prothrombin 19911 A→G did not increase the risk of cerebral sinus-venous thrombosis in carriers of factor V Leiden (adjusted odds ratio 1.6, 95%CI 0.6-4.7), prothrombin 20210 GA (odds ratio 1.2, 95%CI 0.6-2.4), nor in patients without thrombophilia (odds ratio 1.3, 95%CI 0.5-3.1).

**Conclusions:** Prothrombin 19911 A→G polymorphism does not appear to be a risk factor for cerebral sinus-venous thrombosis, alone or in association with factor V Leiden or prothrombin 20210GA.

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**RECURRENCES OF STROKE IN PATIENTS WITH ATRIAL SEPTAL ANEURYSM AND PATENT FORAMEN OVALE: LONG-TERM FOLLOW-UP**

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Keywords: atrial septal aneurysm, patent foramen ovale, stroke

**Background/Aims:** It is uncertain whether anticoagulants and antiplatelet agents are effective therapy in preventing stroke among patients with atrial septal aneurysm (ASA) and/or patent foramen ovale (PFO). The aim of the present study was to evaluate in a long-term follow-up recurrences of stroke in patients with ASA and PFO.

**Patients and methods:** We prospectively evaluated 490 patients: 245 patients who had a previous stroke (Group A) and a control group (B) of 245 patients. Transthoracic echocardiography showed ASA in 104 patients; 68 patients (27.7%) in group A and 36 (14.7%) in group B (p<0.001). ASA+PFO was found in 72 patients (69%). The frequency of ischemic events was evaluated over 7 years. Treatment assignments were at the discretion of the consulting cardiologist.

**Results:** In Group A 140 patients received aspirin (14 had ASA, 2 had PFO and 16 had ASA+PFO) and 98 received warfarin (2 patients with ASA, 2 with PFO and 36 patients with ASA+PFO). In Group B 200 patients received aspirin. In group A 21 patients had percutaneous closure of PFO. In a 7-year follow-up we do not observed a significant reduction of recurrent stroke and death in patients with ASA treated with aspirin compared with those treated with warfarin (17% vs 11%; OR 0.46 95%CI 0.3-2.71). Similarly we did not find differences in patients with PFO treated with aspirin compared with warfarin (19% vs 12%). No embolic events or deaths in patients who underwent percutaneous closure of PFO were reported.

**Conclusions:** No reduction of recurrent stroke and death was observed in patients receiving aspirin compared with those receiving anticoagulants, suggesting that both are reasonable therapy. The limitations of the study were: therapeutic regimen was not randomized, nevertheless the follow-up was done for a long period.

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PROTHROMBOTIC RISK FACTORS IN CHILDHOOD ISEMIEIC STROKE AND TRANSIENT ISCHEMIC ATTACK IN CROATIA

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Background: The etiology of stroke in children is still undetermined in up to one third of cases. There is increasing evidence that inherited or acquired prothrombotic disorders may be important in the etiology of stroke in childhood.

Methods: We investigated 17 prothrombotic risk factors in blood samples from 124 children with an established diagnosis of AIS (N=47) and TIA (N=77) and in 42 children who represented the control group. Prothrombotic risk factors were classified into five groups: natural coagulation inhibitors (antithrombin, protein C, and free protein S antigen), blood coagulation factors (factor V Leiden and factor II A2061G), thrombocytopenia or thrombocytopathy (total platelet count, plateletcrit, platelet size), serine protease inhibitors (alpha2-antiplasmin, antithrombin, tPA inhibitor), and prothrombotic mutations (Factor V Leiden, prothrombin G20210A), homocysteine pathway factors (total homocysteine, vitamin B12, folate, and methylenetetrahydrofolate reductase C677T), lipid and lipoprotein profile (lipoprotein a, triglycerides, total, high- and low-density lipoprotein cholesterol), and antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and antiphosphatidylserine antibodies).

Results: At least one prothrombotic risk factor was identified in 87.2% children with AIS, in 88.3% with TIA and in 88.1% controls. A high number of various individual and combined prothrombotic risk factors, distributed among all risk factor groups, was found either in children with AIS or TIA. Three most common prothrombotic risk factors: low serum folate, MTHFR C677T and elevated Lp(a), were identified in approximately 30% of children in both patient groups. A more than two-fold higher frequency of positive IgG antiphosphatidylserine antibody titer, was identified in children with AIS (17.2%), compared to controls (7.1%). The overall rate of three or more prothrombotic risk factors was significantly higher in children with AIS compared to controls (p=0.016).

Conclusions: High frequency of multiple prothrombotic risk factors found in our study corroborates previous reports that a combination of risk factors rather than individual risk factors could contribute to AIS in children.

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PLASMA MATRIX GLA PROTEIN LEVELS IN PATIENTS WITH BUERGER’S DISEASE

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Background/Aims: Matrix Gla Protein (MGP), which is a vitamin K–dependent protein, has been expressed in lung, kidney, heart, cartilage and arterial walls. Biochemical and genetic studies have established MGP as an inhibitor of calcification in cartilage and blood vessels. The protective effects of MGP in arterial calcification were demonstrated in studies with warfarin-treated rats and MGP knockout mice. Thrombus formation in Buerger’s disease is a consequence of arterial and venous thrombosis, non-atherosclerotic vascular disease of unknown etiology, which affects mainly the small and medium arteries, veins and nerves. Although smoking is considered to be the most important risk factor of Buerger’s disease, the essence of this relationship remains unclear.

The aim of this study is to investigate whether there is a relationship between plasma MGP levels and Buerger’s disease.

Materials and methods: Plasma MGP levels were determined by ELISA kit from BioPab (San Nicolas, Argentina). Fasting plasma samples were obtained at baseline (before disease diagnosis) and in patients with Buerger’s disease at the time of earliest diagnosis. The relationship between plasma MGP levels and disease severity was assessed by comparison of plasma MGP levels in patients with Buerger’s disease.

Results: The plasma levels of MGP (16.36±4.46 nM) were significantly lower in patients with Buerger’s disease than those of the control group (21.78±2.75 nM) (P<0.001).

Discussion and conclusion: There are no reports about the relationship between plasma MGP levels and Buerger’s disease. We obtained the preliminary results indicating that plasma MGP levels were significantly lower in patients with Buerger’s disease. Further in vivo and in vitro studies will answer the question whether there is a relationship between MGP and Buerger’s disease.

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DELETED STROKE THERAPY WITH ROSIGLITAZONE

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Keywords: Cerebral ischemia, rosiglitazone, neuroprotection

Rosiglitazone (RGZ), a peroxisome proliferator-activated receptor-gamma (PPAR-gamma), has been shown to provide neuroprotective and anti-inflammatory effects in a number of brain disorders, and traumatic or surgical brain injuries. However, the effect of delayed post ischemia administration of this compound is still unclear. This study was designed to evaluate the neuroprotective effects of RGZ when first administered at 24 h after the embolic model of stroke. Embolic focal cerebral ischemia was induced in rats by placing a preformed clot into the middle cerebral artery (MCA). RGZ (5 mg/kg, intraperitoneally) was injected at 24 and 72 h after stroke, and blood and brain tissues were then collected for determination of blood cell counts and assessments of infarct volume and DNA fragmentation, respectively. Compared to the control group, the administration of RGZ, starting 24 h after cerebral ischemia, reduced infarct volume by 56% (P<0.05) and decreased neurological deficits at 72 h after cerebral ischemia (P<0.05). Also, delayed administration of RGZ prevented neutrophilia in blood (P<0.005) and significantly decreased DNA fragmentation (P<0.05), 72 h after MCA occlusion. Therefore, our data demonstrate that treatment with RGZ, starting 24 h after stroke, can reduce ischemic injury, improve neurological outcome, and prevent neutrophilia. These findings may support the idea that RGZ has an extended therapeutic window for the treatment of ischemic stroke, as it targets delayed pathways.

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TREATMENT OF PERIPHERAL VASCULAR Atherosclerotic Disease WITH LOCAL DELIVERY OF PACLITAXEL AFTER BALLOON ANGIOPLASTY

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Keywords: Peripheral vascular atherosclerotic disease

Background: Percutaneous transluminal angioplasty (PTA) and percutaneous transluminal coronary angioplasty (PTCA) are established, proven methods for re- opening stenotic or occluded arteries in a minimally invasive way. The balloon is placed in the stenotic segment of the artery and then expanded until the lumen reaches its original diameter. To this end, very high pressure is applied, which unavoidably causes vessel wall injury. Hyperproliferation resulting in lumen narrowing is the natural reaction to this injury A single short contact of tissue with a small dose of paclitaxel has been shown to efficaciously inhibit local cell proliferation antiproliferative taxanes such as paclitaxel seem to be suitable due to their high lipophilicity and tight binding to various cell constituents, resulting in effective local retention at the site of delivery. Paclitaxel as a hydrophobic compound possesses preferential tissue retention.

Methods: 23 patients, all subjects between 65 and 86 years of age with symptomatic claudication (Rutherford category I-6) with TASC II type A, B, or C lesions in lower limbs were invited to participate in this study under signed informed consent. The vascular peripheripheral stenoses were localized in FSA, 16 lesions, popliteal arteries 9 lesions, anterior tibial artery, 6 lesions, posterior tibial artery, 12 lesions, peroneal artery 2 lesions. All stenoses were treated with classic balloon angioplasty (PTA) with adequate diameter balloon for each arterial diameter, after successfully procedure paclitaxel mixed with the contrast medium was administered intra-arterially through the guiding catheter to treat segment of treated artery. The balloon used for PTA was introduced distally to the treated plaques and inflated with low atmospheres with the objective to stagnate the flow during 3 minutes. Dosing used was based on the lesion surface area and was calculated using the following formula: dose = 227 x diameter (mm) x length (mm) x 3 micrograms/mm3^3. All the procedures was completed without complications and no collateral effects of the drug were seen, no acute thrombosis was reported, all the patients returned home after 24 hours with aspirin 100mg and clopidogrel 75mg.

Evolution: Patients were followed with pheripherical vascular echo duplex during 1 year and the treated plaques did not show more decay of the initial diameter obtained than 18% (Lumen loss), all patients improved the walking more than 800 meters and only 14 patients. accepted to be submitted to new control angiography. In this study the lesions treated were maintained opened with minimal re-stenosis (12%).

Conclusions: Local delivery of paclitaxel resulted in reduced neointimal re-stenosis using low doses to avoid collateral effects with stagnation of flow during the procedure and it would be important to treat lower limbs arteries.

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AUDIT ON APPROPRIATE ANTI-PLATELET THERAPY IN THE PREVENTION OF OCCLUSIVE VASCULAR EVENTS

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Aims: Anti-platelets play an important role in the prevention of occlusive vascular events (OVEs). OVEs includes myocardial infarction (MI), transient ischemic attack (TIA), ischaemic stroke and symptomatic peripheral arterial disease (PAD). We reviewed our own clinical practice based on current existing guidelines and hope to make appropriate recommendations to improve practice.

Methods: A prospective audit was conducted for 5 weeks from 2 March 2009 in patients who presented either to the inpatient or outpatient service of the hospital with an OVE. Data were collected from the medical notes. Statistical software was used to gauge our current practice is based on NICE TA090 - clopidogrel and modified release diprymidole in the prevention of occlusive vascular events, JBS 2, National Clinical Guidelines for Stroke-2008 and the ESC guideline.

Results: A total of 168 patients (103 male and 65 female) were audited. A majority presented with only a single vascular bed affected (41% presented with either a TIA or an ischaemic stroke; 30.4% with a MI; and 24.4% with symptomatic PAD). The remainder presented with an OVE with a pre-existing involvement of another vascular bed (2.4% presented with a TIA or ischaemic stroke and pre-existing heart disease due to MI; and 1.8% with a MI and a pre-existing PAD). No patients in our audit had 3 vascular beds affected. All patients presented with either a MI or symptomatic PAD were prescribed antplatelet according to current guidelines. Only 86% of patients with TIA or ischaemic stroke were prescribed antplatelets based on current guidelines.

Conclusions: Anti-platelet prescribing in MI and PAD met audit standards. Deviation from guidelines in TIA and ischaemic stroke was due to the use of clopidogrel instead of aspirin alone in patients unable to take diprymidole MR and is supported by PrOFESS trial. Guidelines on anti-platelet therapy in TIA or ischaemic stroke need updating in the light of current evidence.

Table: Audit standards for antplatelet prescribing

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</tr>
<tr>
<td></td>
<td>Clopidogrel only if intolerant to Aspirin</td>
</tr>
<tr>
<td>MI</td>
<td>Aspirin and Clopidogrel</td>
</tr>
<tr>
<td>Sympmatomic PAD</td>
<td>Clopidogrel / Aspirin only if intolerant to aspirin</td>
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ASSOCIATION BETWEEN PULSE PRESSURE AND BLOOD RHEOLOGY IN HEALTHY AND HYPERTENSIVE SUBJECTS

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Keywords: pulse pressure, blood rheology, hypertension

Aims: Study purpose was to determine whether blood rheological factors are associated with pulse pressure (PP) level among hypertensive and healthy middle-aged men and women.

Methods: A population-based sample of 57 hypertensive and 17 normotensive (35-60 years of age) subjects was studied. Ambulatory monitoring of blood pressure and haemorheological investigation were performed in each case. Hypercholesterolemic subjects, diabetics, smokers, patients with manifested heart disease, Raynaud’s phenomenon, history of clinical evidence of cardio-, cerebro- and peripheral vascular diseases, coagulopathy, renal and liver diseases were excluded from the study.

Results: Compared with normotensive control subjects, hypertensive patients had significantly higher level of platelet aggregative and adhesive activity (97.68±2.42 vs. 87.18±1.47, P=0.000 and 40.83±1.53 vs. 28.35±1.39, P=0.000; respectively), fibrinogen concentration (3.71±0.15 vs. 2.97±0.09, P=0.000), hematocrit (40.28±0.06 vs. 38.24±0.09, P=0.001), erythrocyte aggregation (r=0.847; P=0.000), erythrocyte deformation (r=0.847; P=0.000), hematocrit (40.28±0.06 vs. 38.24±0.09, P=0.001), erythrocyte aggregation (27.2±3.71 vs. 14.59±3.78, P=0.000) and plasma viscosity (1.75±0.07 vs. 1.54±0.04, P=0.002). Total pulse pressure, as well as average daytime pulse pressure did not show any correlations with haemorheological characteristics in the hypertensive group. Among hypertensive patients, nighttime average pulse pressure correlated with fibrinogen concentration (r=0.275; P=0.039), plasma and whole blood viscosity (r=0.274; P=0.039 and r=0.276; P=0.038; respectively). Average daytime pulse pressure in healthy subjects correlated with platelet aggregative and adhesive activity (r=0.297; P=0.002 and r=0.299; P=0.002; respectively). Night-time average pulse pressure in control subjects showed significantly high correlations with most haemorheological indices, namely platelet aggregation (r=0.583; P=0.014), platelet adhesion (r=0.616; P=0.008), erythrocyte aggregation (r=0.847; P=0.000), erythrocyte deformation (r=0.532; P=0.028), plasma and whole blood viscosities (r=0.261; P=0.008 and r=0.654; P=0.004; respectively).

Conclusions: Obtained data indicate on the high importance of nighttime pulse pressure in healthy and hypertensive subjects. We can conclude that subjects with normal blood pressure level, but high nighttime pulse pressure have higher tendency of thrombotic complications. Therefore, this population needs more attention to avoid future vascular complications.

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THE ROLE OF APC RESISTANCE AND PATENT FORAMEN OVALE IN PATIENTS WITH ISCHEMIC STROKE

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**Conclusions:** Resistance and PFO could be proven among patients with cryptogenic stroke. The prevalence of APC resistance did not differ significantly between patients with cryptogenic and non-cryptogenic stroke (7.2% vs. 8.3%, p=0.6). Among patients with cryptogenic stroke, APC resistance was not more prevalent in patients with PFO than in patients without (7.1% vs. 7.3%, p=0.9). Follow-up is still ongoing; to date complete follow up was obtained in 540 patients (55%). Among the responding patients with PFO (n=179), recurrence of cerebral ischemia was observed in 1 patient (11.1%) positive for factor V Leiden and in 7 patients (4.5%) with no evidence of APC resistance (p=0.4).

**Discussion:** Our results question the theory of paradoxical embolism because the prevalence of APC resistance did not differ significantly between patients with cryptogenic stroke and those with non-cryptogenic stroke. Moreover, no association between APC resistance and PFO could be proven among patients with cryptogenic stroke.

**Conclusions:** Our data suggest that APC resistance is not a strong risk factor for ischemic stroke among patients with PFO.

**Figure:** Prevalence of factor V Leiden mutation and patent foramen ovale among 973 patients with ischemic stroke.

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GENE POLYMORPHISMS IN PATIENTS WITH CHRONIC CEREBROVASCULAR DISEASES, ACCOMPANIED BY COGNITIVE DYSFUNCTION

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**Keywords:** cerebrovascular disorders, cognitive dysfunction, gene polymorphism

**Background:** Cerebrovascular disorders take first place among nervous system diseases. Outcome of these is cognitive dysfunction. Aim was to study the gene polymorphisms associated with dysfunction of platelet haemostasis, coagulation and vessel wall in patients with dyscirculatory encephalopathy as manifestation of chronic cerebrovascular diseases.

**Material and methods:** 46 patients (70-73 years old), with dyscirculatory cognitive syndrome were investigated. DNA was extracted from the leucocytes. Polymorphisms of genes GpIIa(T1565C), MTHFR(C677T), ATG(Met235Thr), ATGR1(A1166C), PON1(Gln192Arg), Sstl(3238G) were detected by polymerase chain reaction (PCR).

**Results:** It was established that average number of mutations of genes, detected in patients is 2.6. More extent cognitive dysfunction showed in men. Mutation GpIIa(T1565C) was observed in 19.4%, Sstl(3238G) in 30.6% women and not detected in men. All patients with GpIIa(T1565C) polymorphism suffered from stroke earlier and HHD. In subjects with more frequently widespread MTHFR(C677T) mutation the cognitive dysfunction extended slightly (MMSE test - 21.3 ±2.1 points, Clock-test 8,1±2 points). But 75% of these had arterial hypertension and HHD. ATG (Met235Thr) is more frequently detected mutation in patients and combined with ATGR1(A1166C) thickly. Possessors of abnormal paraoxonase (PON1 Gln192Arg) mutation demonstrated the least signs of cognitive function (MMSE test - 20.8 ±2 points). In 37.6% of these patients the acute stroke registered earlier.

**Conclusions:** These results suggest that gene polymorphism predisposed to dysfunction of platelet haemostasis, coagulation and vessel wall may be associated with various manifestations of cognitive disorders in patients with chronic cerebrovascular diseases.

**Table:** Gene polymorphisms in patients with chronic cerebrovascular disorders, accompanied by cognitive dysfunction (n=48)

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THE ROLE OF FVII PROMOTER POLYMORPHISMS IN TURKISH ATHEROSCLEROSIS PATIENTS

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**Background/Aims:** Several polymorphisms in the promoter region of the F7 gene associated with low or high plasma levels of FVII have been previously identified. Some studies have reported altered plasma FVII levels in groups with manifest or risk of coronary arterial disease (CAD), whereas others did not. Among -323ins10bp polymorphism as is known to be associated with low FVII levels and has been suggested that a protective role against CAD and allele association with -401G/T polymorphism in Caucasians. -402 G/A polymorphism has been associated opposite effect on FVII plasma level. The studies showed that the effect of the three FVII polymorphisms are ethnicity-dependent. In this study we aimed to evaluate the effect of three F7 gene polymorphisms on CAD in Turkish population and find out the related haplotypes.

**Methods:** Three polymorphisms of the F7 gene (-323ins10bp, -401G/T, -402 G/A) were studied in 101 healthy controls and 224 patients with CAD. These polymorphisms were analysed by PCR, SSCP and DNA sequencing methods.

**Results:** In Turkish population we identified 6 haplotypes of which one is not reported previously (Haplotype V). We did not find any significant difference between CAD patients and control group (Table).

**Conclusion:** The promoter polymorphisms, -323ins10bp, -401G/T, -402G/A, were not found to be associated with a risk of an initial coronary event.

**Table:** Haplotype frequency and chi-square test, odds ratio value

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