POSTERS

Animal, cellular and molecular research in thrombosis

C0052
DIFFERENTIATION OF ANTAGONISTS OF PROTEINASE ACTIVATED RECEPTOR 1 AND 4 IN NONHUMAN PRIMATE MODELS OF HEMOSTASIS AND ANTI-THROMBOSIS

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Background: Platelet activation is a crucial step in the maintenance of hemostasis and in the development of thrombosis. Thrombin is the most potent stimulus of platelet activation. Thrombin-led platelet activation is mediated by activation of the proteinase activated receptors (PAR), a group of GPCR activated by tethered ligands. Platelet activation by thrombin differs across species. Only NHP platelet activation is known to be mediated by PAR1 and 4 similar to humans, which limits the translational value of in vivo studies to NHPs. Earlier studies have demonstrated a range of distinct in vitro activities of PAR1 and 4 in platelet activation. A primary goal of this study is to investigate and compare the roles of PAR1 vs PAR4 in hemostasis and thrombus development.
Methods: Nonhuman primate (NHP) models for pharmacokinetic (PK), ex vivo platelet aggregation (pharmacodynamics, PD) responses, the FeCI3 injury-mediated arterial thrombosis (efficacy) and template bleeding (bleeding risk) were developed in Cynomolgus Macaques. Selective small molecule antagonists with low nanomolar potency of PAR1 and PAR4 were synthesized, characterized in a range of vitro screen and counter-screen assays, and studied head-to-head in those NHP models.
Results: Treatment of animals with antagonists of PAR1 or PAR4 both resulted in strong inhibition of ex vivo platelet aggregation (PD). At doses that led to similar level of inhibitory activity toward PD effect, animals treated with a PAR4 antagonist showed similar levels of anti-thrombosis efficacy, but longer time of bleeding in comparing to animals treated with a PAR1 antagonist.
Conclusions: These findings indicated that antagonism of PAR1 will likely lead to a superior therapeutic index (efficacy vs bleeding risk) profile over antagonism of PAR4.

C0079
INFLUENCE OF THYROLIBERIN AND ITS SYNTHETIC ANALOG DIGIPRAMIN ON ERYTHROCYTE AND PLATELET INTERACTION

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Background: It is known that the condition of the microcirculation system depends on the status of the rheological properties of the blood. Because red blood cells make up 98% of the total blood volume, they have a key role in the rheological parameters. It was shown that only upon activation of platelets by various inducers ascertained interaction formed elements during thrombus formation. It was found that some peptides - nootropics can have a significant impact on blood cells, changing their function. A special place in modern research is the study of the influence of thyroliberin - nootropic drug on hemostasis system and the structural features of red blood cells. The state of erythrocyte membranes depends on their resistance to various harmful agents. The aim of this study was to examine changes in ADP - induced platelet aggregation in the presence of red blood cells under the influence of thyroliberin and its synthetic analogue digipramin.
Methods: Work performed on white rats. Blood was collected from the jugular vein with sodium citrate. Peptides (thyroliberin and digipramin) at a concentration of 10-4M were added to platelet-rich plasma (PRP) or a mixture of erythrocytes and PRP. As a control, used an equal volume of 0.85% NaCl. The precipitate erythrocytes were washed three times with saline and diluted 1: 1000 and added to PRP. Platelet aggregation was measured in by the inductor - ADP - 10 uM. on aggregometer.
Results: In experiments in vitro studies the interaction of red blood cells with activated platelets under the influence of regulatory peptides. It has been shown that both thyroliberin and digipramin reinforce platelet aggregation PRP ($p<0.01$). Aggregation adding thyroliberin amplified by 95%, adding digipramina - 55%. When added to the suspension of erythrocytes and PRP is amplified platelet aggregation 45-50%. While adding to PRP peptides and erythrocyte a decrease aggregation compared to adding only peptide or only erythrocytes.
Conclusions: It is found that the peptides reduced the interaction of activated platelets with the red cells, thereby reducing the risk of thrombotic complications in their use in clinical practice.

C0101
ANTITHROMBOTIC AGENTS, RIVAROXABAN AND CILOSAZOL, PREVENT LUNG AND RENAL INJURY FOLLOWING ABDOMINAL AORTA ISCHEMIA/REPERFUSION IN A RAT MODEL

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Background: Ischemia/reperfusion (I/R) during abdominal aorta surgeries leads to remote organ damage and the major part of this damage occurs upon reperfusion via oxygen free radicals. A novel direct factor Xa inhibitor, Rivaroxaban and an antiplatelet agent, Cilostazol are analyzed in this study for their protective effects on lung and renal tissues following abdominal aota ischemia/reperfusion model in rats.
Methods: Thirty-two male Spraque-Dawley rats were randomized as sham group (I/R, n=8), control group (n=8), and I/R+ Rivaroxaban (n=8, 20mg/kg orally administered before ischemia) and I/R+Cilostazol (n=8, 100mg/kg orally administered before ischemia) groups. Ischemia and reperfusion was induced by clamping the infrarenal aorta for 2 hours and declamping for reperfusion for 4 hours. Lung and renal tissue assays were performed for lipid peroxidation product malondealdehyde (MDA) and Glutathione Reductase (GR) and Glutathione Peroxidase (GPx) levels were also studied. Lung and renal tissues were also examined histopathologically under light microscopy.
Results: Both Rivaroxaban and Cilostazol attenuated lung and renal cell damages occurred by downregulating the level of MDA and upregulating the levels of GPX and GR. These results are confirmed also with the histopathological results.
Conclusions: These results suggested that one dose oral administration of both Rivaroxaban and Cilostazol effectively ameliorates the ischemia/reperfusion induced oxidative damage of lung and renal tissues by virtue of their antioxidant and anti-inflammatory potentials.

Italiano, Buenos Aires, Argentina. MPV was evaluated during the PE event and follow-up was until 90 days or death. MPV was considered high if > 11 fL. Survival was estimated with Kaplan Meier. Cox regression was used to evaluate MPV and death, crude (HRc) and adjusted hazard ratios (HRa) were reported.
Results: We included 147 patients, with a median age of 73 years, 57% were female. The main comorbidities were: 49% cancer, 15% coronary disease, 15% sepsis and 10% stroke. Median MPV was 8 fl (8- 10), serum troponin 22.5 pg/ml (12- 50), proBNP 1055 pg/ml (298-2600). Prevalence of high MPV was 17% (25). Overall mortality was 22.4% (33). 7 day survival estimate was 0.88 (95%CI 0.67-0.95) vs 0.97 (95%CI 0.91-0.99); 30 day survival 0.64 (95%CI 0.42-0.79) vs. 0.91 (95%CI 0.85-0.95); and 90 day survival estimate was 0.52 (95%CI 0.31-0.69) vs. 0.82 (0.74-0.88) for high MPV and normal MPV respectively. Overall survival estimate was statically different (p<0,001). Crude HR of mortality for high VPM was 3.61 (95%IC 1.77-7.35, p<0.001). Age, female gender, sepsis, coronary disease, ProBNP elevation and ventricular dysfunction were not associated with death. TUS over 20pg/dL had a HR of 2.30 (95%IC 1.07-4.96, p=0.033) and cancer had a HR of 3.95 (95%CI 1.83 – 8.50, p<0.001). HR of death for high VPM adjusted by cancer and TUS over 2 pg/dl was 3.45 (95%CI 1.66 - 7.17; p<0.001).
Conclusions: High MPV is an independent risk factor for mortality following an episode of PE.

C0126
THE CORRELATION BETWEEN PLASMA D-DIMER AND PLASMA AND URINE PROTHROMBIN FRAGMENT 1 + 2 IN NON-COMORBID PATIENTS WITH SUSPECTED DEEP VEIN THROMBOSIS.

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Background: D-dimer measured in plasma (pD-dimer) is a feasible test to exclude deep vein thrombosis (DVT) when the clinical probability is low. Prothrombin fragment 1 + 2 (F1 + 2) may also be used as a pretest that can be analysed both in plasma (pF1 + 2) and urine (uF1 + 2). We recently published data that showed positive correlation between pD-dimer, pF1 + 2 and uF1 + 2 in non-selected patients with suspected venous thromboembolism. In the present study we investigated the correlation between these biomarkers in a subset of the population, i.e. in patients with suspected DVT who are otherwise healthy.
Methods: Patients with clinically suspected DVT and without known comorbidities were included. Urine and blood samples were collected before examination with compression ultrasound. The samples were analysed with ELISA kits. To assess differences in biomarker levels between DVT negative and positive patients the Mann-Whitney U test was used. The overall performance was determined with the area under the curve (AUC) of the receiver operator characteristic (ROC) curve. Dependence between the biomarkers was assessed with Spearman`s rank correlation (r_s).
Results: DVT was diagnosed in 39 (22%) of the 176 included patients. Those with DVT had statistically significant higher levels of pD-dimer (2998 ng/mL), pF1 + 2 (460 pmol/L) and uF1 + 2 (53 pmol/L) compared to those without DVT (376 ng/mL, 233 pmol/l and 20 pmol/L respectively), p<0.001. Plasma D-dimer had the highest AUC (0.881) followed by pF1 + 2 (0.835) and uF1 + 2 (0.723). A positive correlation was found between pD-dimer and pF1 + 2 (r_s=0.76) and between pF1 + 2 and uF1 + 2 (r_s=0.44). 86 (49%) patients had levels of uF1 + 2 that were not detectable, i.e. below 20 pmol/L. Exclusion of these patients increased the AUC of pD-dimer and pF1 + 2 with 4% and uF1 + 2 with 9% and the correlation between pF1 + 2 and uF1 + 2 increased (r_s=0.50).
Conclusions: In this selected population significantly higher biomarker levels were found in patients with DVT compared to those without. Plasma D-dimer had the best overall performance followed by pF1 + 2 and uF1 + 2. When excluding patients with non-detectable uF1 + 2 levels, the performance of F1 + 2 in urine increased more than the performance of pF1 + 2 and pD-dimer. In addition, the correlation between uF1 + 2 and pF1 + 2 increased. This indicates that increasing the uF1 + 2 test sensitivity may improve its performance and allow it to be an alternative non-invasive pretest.

C0135
OUR CLINICAL EXPERIENCE IN THE EVALUATION OF MESENTERIC VEIN THROMBOSIS

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Background: Mesenteric vein thrombosis occurs rarely and is responsible for approximately 5-15% of all cases of acute mesenteric ischemia. The aim of this report was to discuss the management of mesenteric vein thrombosis based on our experience with 59 patients.
Methods: In the present study, 59 patients who were admitted to our emergency surgery department between January 2010 and July 2015 with a diagnosis of acute mesenteric ischemia were assessed retrospectively. Patients with peritoneal signs first underwent diagnostic laparoscopy to rule out perforation or bowel necrosis. All patients were administered 100 mg/kg of the anticoagulant enoxaparin twice daily.
Results: CT angiography revealed superior mesenteric vein thrombosis in 14 (23%) patients, portal vein thrombosis in 6 (10%) patients, and splenic vein thrombosis in 2 (3%) patients. Four patients with peritoneal signs underwent diagnostic laparoscopy; two of the patients performed small bowel resection, anastomosis, and trocar insertion. In a patient reactional fluid and edema was seen in 60 cm small intestine and another patient 20 cm segmental edema seen and second look laparoscopy was made.
Conclusions: Early diagnosis with CT angiography, conservative treatment with proper anticoagulation and laparoscopic second look detecting with supportive intensive care are the cornerstones of successful treatment of mesenteric vein thrombosis

C0143
VENOUS THROMBOEMBOLISM IN WOMEN USING HORMONAL CONTRACEPTION. FINDINGS FROM A SINGLE CENTER

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Background: Venous thrombosis including deep-vein thrombosis (DVT) and pulmonary embolism (PE) is considered a multifactorial disease associated with genetic and acquired risk factors. In women of reproductive age, the main cause of venous thromboembolic disease (VTD) is the hormonal contraception. However, other risk factors interact to produce VTD. Identifying these factors, may intervene in risk situations and limit the occurrence of VTD with its potential morbidity and mortality.
Methods: We reviewed the characteristics of our series of 103 women with objectively confirmed VTD associated with hormonal contraception. We analyzed its clinical data and thrombophilia studies which were performed in more than 80% of them and included anticoagulant proteins, genetic tests, antiphospholipid antibodies and factor VIII level. Statistical analysis was performed with SPSS 18.0 software.
Results: See Table 1.