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.

AT was associated to Atherosclerosis in 10 cases and to cardiac embolism in one case. Five patients had Behçet's disease and 3 had another systemic vasculitis. Six patients had an antiphospholipid syndrome (2 with systemic lupus erythematosus). Systemic lupus erythematosus was evident in three cases. Buerger's disease was diagnosed in one patient. AT was associated to a cancer in 2 cases. Protein S and protein C deficiency were noted each one, in a case. *Homocysteine level was high in 13.3% of patients (mean rate was 32.44* μmol/L). Treatment was based on heparin (n=30), vitamin K antagonists (n=28) and/or antiplatelet agents (n=26). Eleven patients underwent surgery, nine patients had a thrombectomy, four patients had an artery bypass graft and three other had a coronary stent placement. AT complication were observed in 24.4% of cases: amputation (n=7), necrosis (n=10), ulcerations (n=6) and infection in 5 cases. Three patients died.
Conclusions: AT were associated to different causes, in our series systemic diseases like vasculitis and antiphospholipid syndrome were the most frequent.

C0099
LIPID METABOLISM AND COAGULATION FACTORS IN PATIENTS WITH CORONARY ARTERY DISEASE AFTER STENTING

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Background: Treatment of coronary artery disease is one of the most complex areas of modern medicine. A breakthrough in the treatment of coronary heart disease is associated with the development of Interventional cardiology. Taking into account of the high coronary heart disease prevalence, the number of surgical interventions for this disease is growing every year.
The aim of our research was to analyze the lipid levels and coagulation parameters in patients with surgical interventions on the heart.
Methods: We analyzed medical cards of the 80 patients' with the coronary artery diseases, myocardial infarction, after stenting on two or three coronary arteries. After stenting, all patients had treated in the cardiology department of Karaganda #1 city hospital.
Results: According to the research results, the number of males predominated over the females and consisted 59 (74%) and 21 (26%) respectively. In the course of laboratory test analysis, it was found the increase of activated partial thromboplastin time in thirty eight (75%) patients, fibrinogen level in twenty two (27.5%) and thrombin time in three (3.75%) patients. The prothrombin index decreased in eights (10%) from the total number of examined patients. Retraction of the blood clot had been reduced in sixty two (77.5%) patients. The positive soluble fibrin monomer complexes were observed in nine (11.25%) patients.
The lipid metabolism analysis showed cholesterol level increasing in fifteen (18.7%), triglycerides in nineteen (23.75%) patients, and high density lipid level increased in twenty one (26. 25%) patients. Increased low density lipoprotein level was observed in only ninths (11.25%), very low density lipoproteins was at five (6. 25%) patients.
Conclusions: Thus, the changes of the lipid metabolism and coagulogramm indexes as fibrinogen, activated partial thromboplastin time can create conditions for the early development of atherosclerosis.

C0133
RETROSPECTIVE EVALUATION OF PATIENTS WITH ACUTE MESENTERIC ISCHEMIA

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Background: Acute mesenteric ischemia is a cause of acute abdomen and bad prognosis. In spite of the recent advances in diagnostic techniques, mortality rate of acute mesenteric ischemia is still 50-70%. Patient's age and comorbidities effects these high mortality rates.
Methods: Patients who were admitted to Istanbul University Istanbul Medical Faculty Emergency Surgery Department between January 2010 and July 2015, were retrospectively reviewed. Age, sex, WBC, CRP, lactate, radiological findings, treatment, mortality, morbidity and hospital stay were recorded.
Results: The study group included 59 patients. 31 (53%) were male, 27 (47%) female. Mean age was 62 (28-94). Mean WBC was 18500, crp 209, INR 1.54, lactate 4.3. 43 (73%) of 59 operated due to physical examination, laboratory values and BT findings. 16 (27%) patients were conservative treatment by antithrombotic injection. (Catheter, fibrinolytic therapy) 5 (8%) patients went into diagnostic laparoscopy. The patients who underwent surgery was performed intestinal resection (32, 54%) and colonic resection (16, 27%). 6 (10%) went into embolectomy. 16 patients performed second look and 7 (43%) of them went into resection because of necrosis. 30 (51%) patients died and mean hospital stay was 17.8 (1-133) days.
Conclusions: Treatment of mesenteric ischemia is best done with a confirmed CT angiogram. Main treatment of mesenteric ischemia is surgical embolectomy and thrombolytic therapy. Evaluation of intestinal ischemia must be done by laparoscopy during a second look procedure after treatment.

C0147
THROMBIN GENERATION IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE WITH INDICATIONS TO ANGIOGRAPHY

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Background: Coronary artery disease (CAD) may be treated by invasive procedures like percutaneous interventions and coronary artery bypass grafting (CABG). In any case preliminary visualisation by coronary angiography is required. The reason for early or delayed complications such as stent/graft thrombosis or restenosis is activation of coagulation cascade with different level of thrombin generation in heart of it.
Methods: 96 patients, suffered from CAD (age 61 (43-79, 75 male, 21 female) and 23 healthy persons without symptoms of atherosclerosis, non smokers of with the same age group and with the same gender distribution were included. According the severity of CAD and angiography results patients were divided into 3 groups: with progressive atherosclerosis and indications for PCI (I group, n=65), stable CAD and indication for CABG (II group, n=16) and those who had no indications to invasive treatment (III group, n=15). Thrombin generation were measured by Thrombinoscope (Netherlands) in duplicate before procedures. Results are presented as Lag Time (min), Endogen Thrombin Potential (ETP, nmol/min), Peak thr. (nmol) and ttPeak (min).
Results: There were obtained prolongation of Lag Time in all patients with CAD. In I group it was significant compared with donors – 3.0 (2.7-3.3) min vs 2.5 (2.4-2.8) min in healthy persons, $p<0.05$. In other groups the bias was statistically non significant: 2.8 (2.6-3.3) min in II group and 2.9 (2.4-3.2) min in the III one ($p>0.05$). We revealed also the tendency to ETP increasing in patients with indications to coronary revascularization (in I and II groups): 1717.4 (1550.4-1967.5) nmol/min and 1766.1 (1557.7-1897.6) nmol/