Thesis Proposal

Doctoral Program of Applied Medical Science N790

Working Title

The effect of platelet transfusions on platelet function after adenosine diphosphate receptor - inhibitor mediated platelet inhibition in whole blood in – vitro.

Die Evaluierung des Effektes von Plättchentransfusionen auf durch Adenosin Diphosphat - Rezeptorblockade gehemmte Thrombozyten in Vollblut.

Ethik Kommission der Medizinischen Universität Wien : EK Nr. 1218/2012;

Thematic Program:
Clinical Neurosciences (CLINS N790)

Applicant:
Dr. Dieter Adelmann
Department of Anesthesia, General Intensive Care and Pain Control
Medical University of Vienna, Austria

Supervisor:
Ass. Prof. Dr. Gisela Scharbert
Department of Anesthesia, General Intensive Care and Pain Control
Medical University of Vienna, Austria

Senior supervisor:
Ao.Univ.-Prof. Dr. Sibylle Kozek-Langenecker
Department of Anesthesia and Intensive Care
Evangelical Hospital Vienna, Austria
Summary and aim:

Background: Antithrombotic therapy is an integral component of the treatment as well as the primary and secondary prevention of thromboembolic events in the arterial and the venous circulation. Platelet inhibition plays a major role in treatment of cardiovascular diseases such as coronary artery disease, peripheral artery disease and cerebrovascular disease. Inhibition of the plasmatic coagulation system is essential in the treatment and prophylaxis of venous thromboembolic events such as deep venous thrombosis and pulmonary embolism.  

In addition to acetylsalicylic acid and clopidogrel, the two novel platelet-inhibiting agents, Prasugrel and Ticagrelor have been approved for the secondary prevention of acute coronary syndromes.  

Restoration of platelet function in patients on antiplatelet therapy might be necessary in case of bleeding complications or the need for urgent surgery. Platelet transfusions are used as a therapeutic option if rapid restoration of platelet function is required. The effect of platelet transfusion in patients on prasugrel or ticagrelor therapy has not yet been evaluated. For patient suffering from bleeding complications while on ticagrelor therapy, platelet transfusions are considered as potentially ineffective for treating bleeding when given within 12 hours of the last dose of ticagrelor. These recommendations are based on the pharmacological properties of ticagrelor, but no studies on the efficacy of platelet transfusions in patients with ticagrelor have been reported.

Objectives: The aim of this study is to evaluate the effect of platelet transfusions or fibrinogen concentrate on whole blood samples spiked with ticagrelor in increasing concentrations as well as on whole blood samples taken from patients on clopidogrel, prasugrel or ticagrelor therapy.

Methods: Whole blood samples from healthy volunteers will be spiked with ticagrelor to yield ticagrelor plasma concentrations of 400 and 800 ng/ml. In a second step, blood samples will be collected from patients on clopidogrel, prasugrel or ticagrelor maintenance therapy. To simulate the transfusion of platelet concentrates, platelet rich plasma (PRP) from healthy volunteers will be added to the blood samples simulating the effect of the addition of 2 and 3 platelet concentrates. Additional samples will be spiked with fibrinogen concentrate to reach an increase the plasma fibrinogen level by 200 and 400 mg/dl. Multiple electrode platelet aggregometry (MEA), a point of care platelet function test, will be used to evaluate platelet function in the whole blood.
samples prior to and after the addition of transfused platelets or fibrinogen in this in-vitro model for platelet transfusions.

**Originality and relevance:** The introduction of the novel platelet inhibitors Prasugrel and Ticagrelor into clinical practice has the potential to reduce the morbidity and mortality in acute coronary symptoms. Both agents, however, have been associated with an increased risk in major bleeding complications including fatal bleeding.\(^{2,3,5}\) Compared to Clopidogrel, Ticagrelor and Prasugrel are more potent inhibitors of the P2Y\(_{12}\) receptor.\(^{6,7}\) With the increased prevalence of ticagrelor and prasugrel therapy, physicians will be faced with an increasing number of patients suffering from therapy related bleeding complications. Due to the lack of a specific “antidote”, physicians are left with empirical therapy options that have not yet been evaluated.\(^8\) The presented study will help to understand the effect of platelet transfusions and fibrinogen concentrate on patients on P2Y receptor antagonists.