

Platelet activation and aggregation: Clinical and experimental studies

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i Kammaren, Sahlgrenska Universitetssjukhuset, Göteborg, den 14 december 2018, klockan 9:00 av

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Avhandlingen baseras på följande delarbeten

- I. Singh S, Shams Hakimi C, Jeppsson A, Hesse C. Platelet storage lesion in interim platelet unit concentrates: A comparison with buffy-coat and apheresis concentrates. *Transfus Apher Sci.* 2017; 56(6): 870-874.
- II. Singh S, Malm CJ, Ramström S, Hesse C, Jeppsson A. Adrenaline enhances in vitro platelet activation and aggregation in blood samples from ticagrelor-treated patients. *Res Pract Thromb Haemost.* 2018; 2(4): 718-725.
- III. Singh S, Damén T, Nygren A, Shams Hakimi C, Ramström S, Dellborg M, Lindahl TL, Hesse C, Jeppsson A. Adrenaline improves platelet reactivity in ticagrelor-treated healthy volunteers: A proof of concept study. Submitted.
- IV. Singh S, Damén T, Dellborg M, Jeppsson A, Nygren A. Intraoperative infusion of noradrenaline improves platelet aggregation in patients undergoing coronary artery bypass grafting: A randomized controlled trial. Submitted.

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ABSTRACT

Background: Dual antiplatelet therapy with acetylsalicylic acid (ASA) and the adenosine diphosphate (ADP)-receptor antagonist ticagrelor increases the risk of bleeding complications during cardiac surgery. The overall aim of this thesis was to identify and evaluate current and potential methods to reduce and prevent bleeding complications in patients with ongoing antiplatelet therapy.

Methods: In Study I, three types of platelet concentrates were sampled on day 1, 4 and 7 after donation. In Study II, adrenaline and platelet concentrate were added to blood samples from acute coronary syndrome patients on ASA and ticagrelor. In Study III, blood samples from healthy volunteers were collected after ticagrelor, adrenaline and metoprolol administration. In Study IV, blood samples were collected before and after anesthesia induction from cardiac surgery patients randomized to standard treatment or maintenance of preoperative mean arterial pressure using noradrenaline. Platelet aggregation was assessed with impedance aggregometry (Studies I–IV) while platelet activation was assessed with flow cytometry (Studies I–III). Clot formation was assessed with thromboelastometry (Studies III and IV).

Results: Platelets in interim platelet unit (IPU) concentrates maintained a lower activation state and better aggregation response to the end of storage compared to buffy-coat concentrates (I). More platelets in IPU concentrates were activated and had a lower aggregation response throughout storage compared to apheresis concentrates (I). Adrenaline, but not platelet concentrate, improved ADP-induced platelet aggregation and activation in the presence of ticagrelor *in vitro* (II). Adrenaline infusion improved ADP-induced platelet aggregation, activation and clot formation in healthy volunteers treated with ticagrelor (III). Intraoperative noradrenaline infusion improved ADP-induced platelet aggregation and clot formation in cardiac surgery patients (IV).

Conclusions: The quality of IPU concentrates is at least comparable to buffy-coat concentrates. Adrenergic agents improve platelet reactivity and may thus potentially be used to prevent excessive bleeding during surgery in patients with ongoing antiplatelet therapy.

Keywords: Platelet concentrate, adrenaline, noradrenaline, ticagrelor, platelet aggregation, platelet activation