

Commentary

Does tirofiban prevent platelet loss in patients after cardiogenic shock during continuous renal replacement therapy?

Christian Storm and Achim Jörres

Department of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany

Corresponding author: Achim Jörres, achim.joerres@charite.de

Published: 24 November 2008

This article is online at <http://ccforum.com/content/12/6/193>

© 2008 BioMed Central Ltd

Critical Care 2008, **12**:193 (doi:10.1186/cc7083)

See related research by Link *et al.*, <http://ccforum.com/content/12/4/R111>

Abstract

Link and colleagues present a pilot study investigating platelet function and platelet numbers in patients with cardiogenic shock and acute kidney failure undergoing continuous venovenous haemodialysis. Their data indicate a significantly reduced platelet loss with combined therapy of unfractionated heparin plus tirofiban, the glycoprotein IIb/IIIa antagonist, compared with unfractionated heparin therapy alone. Owing to the small sample size, however, the potential impact of additional treatment variables (antiplatelet agents, intraaortic counterpulsation) could not be clarified. A substantially larger, adequately powered study is therefore called for to establish the potential clinical relevance of these findings.

In a recent article for *Critical Care* Link and colleagues reported that the reversible platelet glycoprotein IIb/IIIa antagonist tirofiban may prevent platelet activation and preserves platelet numbers during continuous venovenous haemodialysis in patients with cardiogenic shock [1].

Acute kidney failure is a frequent complication in the critically ill, particularly so in patients with severe sepsis/septic shock or with acute myocardial infarction/cardiogenic shock [2,3]. Often this complication will entail the need for renal replacement therapy until kidney function recovers. Contact of blood with artificial surfaces of extracorporeal systems, however, may lead to platelet activation, to formation of platelet-monocyte aggregates, and to induction of inflammation. In the majority of cases, extracorporeal therapy thus requires an effective anticoagulation strategy that, in turn, may put the patient at risk of bleeding complications. Especially during continuous renal replacement therapy (CRRT), platelet dysfunction may occur with increased activation and aggregation and – ultimately – with platelet loss.

In recent years, glycoprotein IIb/IIIa antagonists have found their way into clinical routine, serving as powerful receptor

blockers in the final stage of platelet activation; for example, in patients with acute coronary syndromes and percutaneous transluminal angioplasty [4-6]. These antagonists have also been proposed as a pharmacological strategy to prevent platelet loss during extracorporeal circulation, especially in cardiac surgery (platelet anaesthesia) [7,8]; however, their potential role in extracorporeal renal replacement therapies is unclear at present.

In their pilot study Link and colleagues randomly assigned 40 patients with cardiogenic shock and acute kidney failure requiring CRRT to two groups, either receiving unfractionated heparin (UFH) ($n = 20$) or receiving a combined anticoagulation with UFH and tirofiban ($n = 20$) [1]. They found in the group receiving only UFH that the percentage of platelet-monocyte aggregates was significantly increased ($P < 0.001$) and the platelet number was significantly decreased ($P < 0.001$). In contrast, platelet-monocyte aggregates and the decrement in platelet numbers were significantly reduced under combined therapy ($P < 0.001$). There were no significant differences between the groups regarding the efficacy of CRRT, the haemofilter lifespan, or bleeding events. Platelet transfusions were only necessary in three patients of the UFH group ($P = 0.016$). The authors conclude that, in patients with cardiogenic shock and acute kidney injury requiring CRRT, the use of tirofiban in addition to UFH prevents platelet loss and platelet-monocyte interaction and may preserve platelet function.

Whilst these findings are of interest and are of potential clinical relevance, caution needs to be exercised in their interpretation. As is also reflected in the present study, patients with acute coronary syndromes and cardiogenic shock will often be subjected to a variety of specific (pharmacological and nonpharmacological) interventions that may

CRRT = continuous renal replacement therapy; UFH = unfractionated heparin.

impact on platelet function and/or number. This includes the administration of anticoagulants (heparins, heparinoids, thrombin inhibitors), antiplatelet agents (glycoprotein IIb/IIIa antagonists, acetylsalicylic acid, thienopyridine), and catecholamines [9], as well as treatment with intraaortic counterpulsation. In a fairly small and heterogeneous cohort it is not feasible to dissect out their respective influences on the study outcomes. The same holds true for the potential influence of the type and mode of the extracorporeal treatment and materials, and, last but not least, for the metabolic control/uraemic state of the patient. Moreover, the response of individual patients to acetylsalicylic acid and/or thienopyridin may vary considerably up to the point of the new and not completely understood phenomenon of thienopyridine nonresponders [10,11], an issue that will also have to be carefully considered in a subsequent study.

Another finding of the present study may raise concerns. The platelet numbers in the UFH therapy group were more than halved, dropping from an average of $(216 \pm 64.3) \times 10^9/l$ to as low as $(87.3 \pm 41.1) \times 10^9/l$ within 4 days – three patients with platelet counts $<20 \times 10^9/l$ even requiring platelet transfusions. Given the fact that the authors used modern polysulphone capillary haemofilters and employed a continuous venovenous haemodialysis regime that reduces transmembrane pressures and thus reduces shear stress compared with postdilution continuous venovenous haemofiltration, the observed extent of platelet loss seems unusually large and remains unexplained.

In summary, the study by Link and colleagues raises the important question of whether platelet anaesthesia with tirofiban prevents platelet activation and loss during CRRT. The data presented indicate a significantly reduced platelet loss with additional glycoprotein IIb/IIIa antagonist therapy compared with UFH therapy alone. Owing to the small sample size, however, the potential impact of additional treatment variables could not be clarified. A substantially larger, adequately powered study is therefore warranted before these results can be generalized.

Competing interests

The authors declare that they have no competing interests.

References

1. Link A, Girndt M, Selejan S, Rbah R, Böhm M: **Tirofiban preserves platelet loss during continuous renal replacement therapy in a randomised prospective open-blinded pilot study.** *Crit Care* 2008, **12**:R111.
2. John S, Eckardt KU: **Renal replacement strategies in the ICU.** *Chest* 2007, **132**:1379-1388.
3. Oppert M, Engel C, Brunkhorst FM, Bogatsch H, Reinhart K, Frei U, Eckardt KU, Loeffler M, John S: **Acute renal failure in patients with severe sepsis and septic shock – a significant independent risk factor for mortality: results from the German Prevalence Study.** *Nephrol Dial Transplant* 2008, **23**:904-909.
4. **Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of**

- Tirofiban for Outcomes and REstenosis.** *Circulation* 1997, **96**:1445-1453.
5. **A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators.** *N Engl J Med* 1998, **338**:1498-1505.
6. **Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators.** *N Engl J Med* 1998, **338**:1488-1497.
7. Kanemitsu S, Nishikawa M, Onoda K, Shimono T, Shimpo H, Yazaki A, Tanaka K, Shiku H, Yada I: **Pharmacologic platelet anesthesia by glycoprotein IIb/IIIa complex antagonist and argatroban during in vitro extracorporeal circulation.** *J Thorac Cardiovasc Surg* 2003, **126**:428-435.
8. Straub A, Schiebold D, Wendel HP, Azevedo R, Dietz K, Ziemer G: **Platelet anaesthesia during extracorporeal circulation: differential effects of GP IIb/IIIa blockers on platelet activation marker P-selectin expression at hypothermia.** *Thromb Res* 2008, **122**:383-389.
9. Tschuor C, Asmis LM, Lenzlinger PM, Tanner M, Harter L, Keel M, Stocker R, Stover JF: **In vitro norepinephrine significantly activates isolated platelets from healthy volunteers and critically ill patients following severe traumatic brain injury.** *Crit Care* 2008, **12**:R80.
10. Grossmann R, Sokolova O, Schnurr A, Bonz A, Porsche C, Obergfell A, Lengenfelder B, Walter U, Eigenthaler M: **Variable extent of clopidogrel responsiveness in patients after coronary stenting.** *Thromb Haemost* 2004, **92**:1201-1206.
11. Weerakkody GJ, Jakubowski JA, Brandt JT, Farid NA, Payne CD, Zhu J, Warner MR, Naganuma H, Winters KJ: **Comparison of speed of onset of platelet inhibition after loading doses of clopidogrel versus prasugrel in healthy volunteers and correlation with responder status.** *Am J Cardiol* 2007, **100**:331-336.