Review

Tirofiban and emergency coronary surgery

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Summary

The final common pathway of platelet aggregation leading to coronary thrombosis involves cross-linking of platelet receptor glycoprotein IIb-IIIa by primarily fibrinogen. Glycoprotein IIb-IIIa antagonists are being increasingly used as adjunctive therapy during percutaneous coronary intervention, and have shown to reduce the risk of death and myocardial infarction. However, a proportion of these patients continue to remain ischemic and present for emergency coronary grafting. The profound platelet inhibition in these patients enhances the already heightened risk of post-operative bleeding. With the recent approval of tirofiban for patients with acute coronary syndromes, the number of patients receiving tirofiban who subsequently undergo coronary artery bypass grafting is expected to increase substantially. Little clinical data exist, on patients who require immediate coronary artery grafting after receiving tirofiban. This article reviews the evidence for bleeding following tirofiban, discusses the relevant mechanism of action and pharmacodynamics, and analyses the strategies available in patients who need emergency coronary artery grafting after tirofiban.

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1. Introduction

Thrombotic coronary occlusion is the central pathophysiological event underlying the acute coronary syndromes (ACS). The final common pathway of platelet aggregation leading to coronary thrombosis involves cross-linking of platelet receptor glycoproteins (GP) IIb-IIIa by adhesive plasma proteins, primarily fibrinogen [1]. Agents that block this final common pathway are considered the most powerful platelet inhibitors.

The recognition of the pharmacologic shortcomings of aspirin and heparin and mechanistic considerations that favor a more vigorous approach to platelet inhibition [2], have propelled the development of GP IIb-IIIa antagonists, which have reduced the composite occurrence of death, myocardial infarction (MI), and need for target vessel revascularization after PCI [3-7].

Interventional procedures directed against coronary obstructions inevitably produce endothelial damage, and can lead to complications like death, MI, or recurrent ischemia requiring repeat PTCA, stenting or CABG [1]. Abrupt vessel closure [1], coronary dissection, perforation, tamponade, and hemodynamic instability [8] represent the principal indications for emergency surgery. There is a fundamental paradox between the need to prevent coronary thrombosis and the need for therapeutic hemostasis. Profound platelet blockade may enhance the risk of bleeding, which imposes an additional stress in patients with severely compromised myocardial function, following percutaneous intervention.

It is suggested that GP IIb/IIIa inhibitors with a shorter half-life like tirofiban (MK-383, Aggrastat4 Merck and Co, Whitehouse Station, NJ) have an improved safety profile, as platelet function more rapidly returns to baseline [9]. The majority of the earlier data on emergency CABG surgery following these drugs pertains to abciximab. Little clinical data exist, on patients who require immediate CABG after receiving tirofiban.

With the recent approval of tirofiban for patients with ACS, the number of patients receiving tirofiban who subsequently undergo CABG is expected to increase substantially. The outcomes of patients undergoing CABG after treatment with tirofiban will depend on the development of effective strategies to minimize bleeding.

2. Bleeding complications—the evidence

A recent analysis of the Gp IIb/IIIa inhibitor-induced bleeding complications and deaths reported within the FDA adverse drug reactions database revealed 450 deaths related to these drugs over a 3-year period [10]. In real-world applications, higher adverse event rates can be expected [11].

The clinical effect of tirofiban has been shown in three major studies—PRISM (Platelet Receptor Inhibition for
Ischemic Syndrome Management) [12], PRISM-PLUS (PRISM—Patients Limited by unstable Signs and Symptoms) [13] and RESTORE (Randomised Efficacy Study of Tirofiban for Outcomes and Restenosis) [7].

In the PRISM PLUS [13] and the RESTORE [7] trials, the incidence of major bleeding, blood transfusions and thrombocytopenia were higher in the tirofiban plus heparin group (when compared to placebo), all though this was not statistically significant. The demonstrated reduction in early adverse cardiovascular events after angioplasty was achieved at a dose of tirofiban that did not result in any excess major bleeding.

However, most studies have evaluated bleeding in the context of percutaneous coronary intervention, and very few studies have analyzed the incidence of post-operative bleeding in these patients. The few studies that did, have not noted excessive post-operative bleeding after treatment with tirofiban [14]. In most studies however, patients with emergency CABG and prior use of tirofiban showed no enhanced or even reduced bleeding rates [15].

3. Thrombocytopenia

Previous pooled analyses of thrombocytopenia complicating treatment with intravenous GP IIb/IIIa receptor inhibitors have suggested that the use of tirofiban does not cause any significant thrombocytopenia [16-19]. Thrombocytopenia ( nadir platelet count \(< 100 \times 10^9\) cells/L) develops in 0.5% of those treated with tirofiban. Tirofiban in fact had a protective effect on the development of thrombocytopenia. The mean time to onset of thrombocytopenia was 24 h, with no cases occurring > 48 h after PCI. Tirofiban-associated thrombocytopenia resolved after a mean of 2.1 days (range, 1-6 day [20]).

In the RESTORE trial [7], thrombocytopenia was not significantly increased in the tirofiban group in comparison to placebo (1.17 vs 0.9%; \(P=0.831\)). Severe thrombocytopenia \(< 50,000/mm^3\) occurred in 0.2% of the tirofiban group.

4. Post-operative bleeding

Bizzari and associates [15] studied bleeding complications in 20 patients who underwent emergency CABG following tirofiban. The incidence of blood, platelet, and fresh frozen plasma transfusions was higher in the control group (\(n=68\)). Although hemoglobin and platelet levels dropped in the tirofiban and control groups after surgery, they were significantly higher in the tirofiban group in the immediate and late post-operative periods. At discharge, platelet counts in the tirofiban group had increased significantly to 288.8 + / − 115.2 × 10^9 ml−p<0.01). The result showed no significant differences in the postoperative coagulation parameters, nor was there any relationship between the blood loss in the first 24 h and the interval between the end of tirofiban infusion and surgery.

5. Mechanism of action

The hallmark of platelet activation is the metamorphosis of the GP IIb/IIIa receptor from its resting to its active state, in which it serves as a receptor for fibrinogen, and vWF. The GP IIb/IIIa receptor changes the spatial orientation of its extracellular domains during platelet activation, and the fibrinogen binding site is exposed. vWF becomes more important to platelet aggregation at the high shear rates believed to be achieved in stenosed coronary arteries [26]. In addition, an intracellular pool of GP IIb/IIIa becomes surface expressed upon stimulation with strong agonists, which increases the concentration of GP IIb/IIIa antagonist required to achieve a given level of platelet inhibition.

Engagement of these ligands by GP IIb/IIIa mediates platelet aggregation—a pivotal event in thrombosis. Prothrombin is an activation-independent ligand of GP IIb/IIIa. Bound prothrombin is activated to thrombin, and suppression of this interaction by GP IIb/IIIa blockers may contribute to their antithrombotic activity [27].

The participation of GP IIb/IIIa in platelet aggregation, whatever the initiating event or agonist, provides the molecular logic for therapeutic blockade of this receptor.
RGD was the starting-point for the design of tirofiban [28]. Tirofiban is a tyrosine derivative with a molecular weight of 495 kD. Tirofiban is a peptidomimetic that mimics the spatial charge and configuration of the RGD sequence, and occupies the binding pocket on GP IIb–IIIa, thereby competitively inhibiting platelet aggregation mediated by fibrinogen or von Willebrand factor. The potential advantages of tirofiban include immediate onset of action, rapid reversal of antiplatelet activity after drug discontinuation, suitability for multiple repeat administrations, and high specificity for the GP IIb/IIIa receptor.

6. Pharmacodynamics

Tirofiban is administered as an intravenous infusion. The antiplatelet effects are dose-dependent and follow classic competitive pharmacokinetics [17]. Doses of Tirofiban selected for most clinical trials target 80% receptor occupancy of unstimulated platelets. Greater receptor occupancy causes marked prolongation of bleeding times.

Peak plasma concentrations of tirofiban are reached within 1 h after initiation of the recommended regimen. The plasma half-life is approximately 2 h [29]. Tirofiban has low receptor affinity and rapidly dissociates from the receptors. Concentration-independent binding to plasma proteins occurs, with the unbound fraction accounting for approximately 35% of the total circulating pool [17].

After administration, ADP induced platelet aggregation is inhibited by >80% throughout the infusion period [29]. Bleeding times after 2 h are prolonged to more than 30 min [17]. The effects of tirofiban on platelet function are minimal several hours after discontinuation of infusion. At 4 h after stopping the infusion, inhibition of platelet aggregation decreases to 50% and bleeding time returns to normal. The fast recovery of platelet function means that an antidote strategy is not needed for tirofiban [29].

However, rapid reversibility depends on intact renal clearance mechanisms. About 65% of administered tirofiban is excreted in urine. When renal blood flow decreases in a patient with cardiogenic shock, the duration of action is prolonged [17]. A recent subanalysis of the PRISM-PLUS [13] study shows that tirofiban is effective and well tolerated in patients with mild to moderate renal insufficiency. In patients with severe renal impairment, prolongation of bleeding time occurs with lower plasma concentrations of tirofiban. This is explained by the altered response of platelets from uraemic patients rather than a pharmacokinetic mechanism. In such platelets, the granular contents of ADP and serotonin, and thromboane production are reduced, and cytoplasmic calcium and cyclic adenosine monophosphate are increased [30]. Tirofiban requires 50% dosage reduction if creatinine clearance is <30 ml/min and is contraindicated if serum creatinine is >2.5 mg/dl.

7. Platelet assay

Before surgery, it may be desirable to rapidly determine whether the effect of the GP IIb/IIIa antagonist has worn off sufficiently to allow safe surgery without additional interventions to reverse the effect of the GP IIb/IIIa inhibitor.

Currently available assays for evaluating GP IIb/IIIa receptor blockade, including bleeding time, thromboelastography, clot retraction, radiolabeled antibody binding, and flow cytometry, are time-consuming, require extensive standardization, or require specialized equipment. More recent techniques include turbidimetric and receptor occupancy assays, shear-induced platelet aggregation, and whole-blood electric-impedance aggregometry.

To address the need to monitor GP IIb/IIIa receptor blockade, Coller et al. [31] developed an assay to assess platelet function based on observations that platelets will agglutinate fibrinogen-coated beads [32] and that blockade of GP IIb/IIIa receptors with monoclonal antibodies prevents these interactions [33]. They hypothesized that it may be possible, to use a modification of the assay to assess the point at which sufficient numbers of unblocked GP IIb/IIIa receptors have become available after stopping GP IIb/IIIa antagonist therapy to support hemostasis if surgery is required [31].

The Rapid Platelet Function Test (RPFA; Accumetrics, San Diego, CA) [34], and the modified whole-blood aggregometer; Chrono-log Corp., Havertown, PA [35] have been shown to correlate with increased GP IIb/IIIa receptor blockade using c7E3 Fab and platelet aggregometry [36].

8. Platelet anaesthesia

The concept of ‘platelet anesthesia’ postulates that complete, but reversible, inhibition of platelet reactivity during CPB can prevent platelet aggregation, and adhesion and thus preserve platelet number and function for hemostasis after CPB ends. The key requirements for a ‘platelet anaesthetic’ are inhibition of all platelet functions before heparinization and quick and complete reversal of this inhibition after CPB ends.

Edmunds and associates have hypothesized that ‘platelet anesthesia’ may actually improve postoperative platelet function and reduce bleeding [37]. In their baboon model, high-dose tirofiban during CPB, completely preserved platelet number and improved platelet function during cardiopulmonary bypass, prevented platelet aggregation, attenuated alpha granule release and significantly accelerated restoration of normal template bleeding times after bypass [38].

Whether there is a clinical role for the use of tirofiban during cardiac surgery to reduce perioperative myocardial infarction and attenuate platelet dysfunction during CPB requires further investigation.

9. CABG recommendations

Several strategies aimed at prevention and reduction of bleeding in these patients have been recommended.

No delay in urgent or emergency CABG is necessary. Discontinuation of Tirofiban within 2-4 h of elective surgery appears sufficient to ensure a safe surgical procedure [17].
Prophylactic platelet transfusions after tirofiban are unnecessary because it readily dissociates from the GP IIb/IIIa receptor and its antiplatelet effects are reversed rapidly and spontaneously [1]. The stoichiometry of tirofiban is such that the number of molecules of drug overwhelms the number of GP IIb/IIIa receptors by several orders of magnitude [17]. Early and judicious use of replacement blood products could be commenced when clinically indicated, after the discontinuation of CPB. Operating ‘off-pump’ may prevent some of the hematologic disruption associated with CPB [1,14]. This however is not only surgeon specific but may be precluded in patients with intractable cardiogenic shock or haemodynamic instability.

Reduction of heparin dosing has been shown to decrease the incidence of bleeding complications in patients undergoing PCI, and a similar approach has been recommended for patients requiring emergency CABG [1,14]. However, neither the safety nor the efficacy of using reduced heparin doses and shorter ACT levels has been demonstrated for GP IIb/IIIa inhibitor-affected patients requiring emergency CABG [39]. In the absence of hard data to support a reduction in heparin dosing during cardiopulmonary bypass, standard heparin doses should be given to achieve optimal anticoagulation.

Prophylactic aprotinin, and tranexamic acid [29] has been recommended but this strategy requires further evaluation. Tirofiban is a dialyzable molecule. Lewis et al. suggest that intraoperative hemofiltration can minimize the likelihood of postoperative coagulopathy after cardiac surgery [40].

10. Oral drugs

The encouraging results realized with short-term intravenous therapy with GP IIb/IIIa inhibitors have led to the evaluation of extended therapy with several oral GP IIb/IIIa inhibitors. The results of phase 2 trials with these agents suggested that bleeding complications were frequent, with minor hemorrhagic events occurring in 30% of patients [41]. Successful treatment with these agents will require a careful balance of clinical efficacy and safety. Preliminary results currently available from two phase-3 trials of oral agents have been disappointing. Both at 30 days and over the long term, treatment with orbofiban was associated with a trend toward increased adverse cardiac events. Higher doses of orbofiban were also associated with a significant increase in major bleeding events compared with placebo (3.7 vs 1.9%) [42].

The risk of bleeding predicts that with long-term indications, such as in secondary prevention of ischemic events, the desirable levels of inhibition of platelet aggregation are likely to be considerably lower than those targeted for acute short-term use. Will lower levels of platelet inhibition yield a clear therapeutic benefit that is devoid of bleeding effects associated with their antithrombotic action? This is an issue that needs to be addressed if the oral GP IIb/IIIa antagonists are to proceed from novel concept to bona fide therapeutic advance.

11. Conclusions

The current evidence therefore indicates that, with appropriate measures, urgent surgical revascularization can be safely performed in patients within a few hours of discontinuation of tirofiban with little added risk. Preoperative tirofiban should not preclude urgent revascularization. Additionally, experimental data suggest that tirofiban may have a platelet-sparing effect during cardiopulmonary bypass, though this is hypothetical.

References


