

Antifibrinolytics

SCHMARTS

INTRODUCTION

In order to spare blood products, clinicians have for long years attempted to interfere with the normal hemostasis mechanism. Fibrinolysis provides an important mechanism to limit propagation of intravascular thrombosis. The vascular endothelium releases tissue plasminogen activator (t-PA), resulting in conversion of plasminogen to plasmin, which is the primary mediator of fibrinolysis (1). Plasmin can also interfere with coagulation pathways, notably by degradation of cofactors Va and VIIIa, consumption of alpha2-antiplasmin, degradation of platelet receptors as well as fibrin and fibrinogen (2). Numerous studies have tried to intervene at this level with drugs acting by blocking the fibrinolytic pathway with the aim of limiting blood loss during medical or surgical conditions, decreasing the requirements for blood transfusion and ultimately aiming at a better patient outcome. These studies have recently been reviewed in order to establish evidence-based facts on antifibrinolytic drugs used in order to minimize perioperative blood transfusions (3).

TYPE OF ANTIFIBRINOLYTIC DRUGS

Two classes of antifibrinolytic drugs are available for clinical use : the synthetic lysine antagonists, epsilon-aminocaproic acid (EACA), tranexamic acid (TXA) ; and the natural serine protease inhibitor aprotinin. Their mechanisms of action are different and we will review both classes separately.

EFFECTIVENESS OF ANTIFIBRINOLYTIC DRUGS

Ideally all interventions are aimed to reduce morbidity and/or mortality. However most studies have used blood transfusion as a surrogate endpoint. Another surrogate endpoint used is the reduction in reoperation due to a haemostatic problem. These surrogate endpoints are commonly

substituted to morbidity or mortality judging that this is clinically and economically sound (4). The recent publication by HERBERT *et al.* gives evidence that blood transfusions are related to a poorer clinical outcome and higher mortality (5). Other surrogate endpoints like a reduction in blood loss without reduction in transfusion requirements or better laboratory hemostasis parameters are clearly insufficient to determine the effectiveness of antifibrinolytic drugs.

Aprotinin

Aprotinin is a non-specific inhibitor of serine proteases and acts on many biological pathways. It is capable of inhibiting trypsin, plasmin, kallikrein by binding to their active site and forming a reversible complex protease-aprotinin. It is also capable of inhibiting thrombin, the complex tissue factor – factor VIIa as well as protein C (4). Aprotinin has a variable affinity for each protease and so its effects depends on its plasma concentration. Table 1 lists the plasma concentrations necessary to inhibit different proteases.

Table 1

Trypsin	25 KIU/mL
Plasmin	50 KIU/mL
Kallikrein (tissue)	125 KIU/mL
Kallikrein (plasma)	200 KIU/mL
Thrombin	600 KIU/mL

The small doses necessary to inhibit plasmin favor the view of aprotinin as an antifibrinolytic, but its effects are clearly more complex. Inhibition of fibrinolysis, preservation of platelet function, kallikrein inhibition as well as inhibition of the contact phase activation are all hypothesis for its action in cardiac surgery (6). Some authors attribute an anti-inflammatory effect to aprotinin (7) ; others were unable to demonstrate this effect (8).

Results of aprotinin studies to reduce allogeneic blood transfusion

Most of the aprotinin studies were done in cardiac surgery, so we have the best information in this area. The great majority of studies, as well as the meta-analysis concluded on the efficacy of aprotinin to reduce blood loss as well as transfusion needs during cardiac surgery (6, 9, 10). The same studies showed also a significant reduction in the number of patients needing a reoperation for post-operative bleeding. More important, the study by LEVI *et al.* focused not only on transfusion needs, but demonstrated a reduction in mortality and morbidity in first-time operations as well as in reoperations or complicated procedures (10). It is difficult to get a clear picture of the effectiveness of different dosages of aprotinin. Some studies support the greater effectiveness of high dose aprotinin (9, 10) this conclusion is not found in the Cochrane review where the author could not demonstrate a significant difference between high or low dose aprotinin in cardiac surgery (3). However using only a priming dose of aprotinin is less potent than low or high dose aprotinin treatments (3, 11).

Aprotinin has also been used in liver transplantation, where a high potential exists for a hyperfibrinolytic state. The European multicenter study showed a reduction in blood loss and a reduction in the transfusion requirements in patients undergoing liver transplantation (12). An increase in thromboembolic events was not observed, however only 137 patients participated in this study. It remains unclear which dose of aprotinin should be used in liver transplantation, as well as it is not known if aprotinin should be used on a prophylactic basis or only on demand.

Aprotinin has also been proposed in orthopedic surgery with variable results. Most studies showed a reduction in blood loss, but no or only a modest reduction in allogeneic blood transfusion (13, 14).

The Cochrane study (3) identified 61 trials comparing aprotinin to control in order to reduce the perioperative blood transfusion. In these trials 7027 patients were enrolled and 4055 of them received aprotinin. Overall aprotinin significantly reduced the amount of allogeneic blood transfusion. The overall reduction in transfusion was 30% (RR 0.7 with 95% confidence interval 0.64 to 0.76). It is to be noted that there is significant heterogeneity between the different studies.

Most of these studies (55 out of 71) were conducted in cardiac surgery and resulted in a reduction of blood transfusion by 31% (RR 0.69, 95%

confidence interval 0.63 to 0.76). Again significant heterogeneity exists between the different studies. Only 7 trials addressed patients outside of cardiac surgery and in this group the relative reduction in the need for blood transfusion was 27%, which did not reach statistical significance. Again the Cochrane reviewers found a great heterogeneity between these trials.

The use of aprotinin resulted in a saving of 1.08 units of blood and reduced the risk for reoperation for bleeding by 60% (RR 0.40, 95% confidence interval 0.25 to 0.66).

Adverse events of aprotinin treatment

Allergic reactions

Aprotinin can lead to an allergic reaction, especially in the case of a readministration of the drug. Prevalence of allergic reaction ranged from 2 to 5% in case of readministration, the shorter the period between the treatments, the higher the incidence of allergic reactions (15). This risk has to be balanced against the benefits of a reduction in blood transfusion and in cardiac surgery a reduction in mortality.

Thrombotic events

In cardiac surgery aprotinin, especially high doses have been suspected for an increased myocardial infarction (10). The Cochrane review did not find a higher incidence of non-fatal myocardial infarction in the pooled analysis of the aprotinin studies (3). The pooled relative risk of sustaining a non-fatal myocardial infarction was 0.97 (95% confidence interval 0.9 to 1.36). One may insist that in cardiac surgery an adequate preoperative heparinisation is obtained; as well as the immediate postoperative use of aspirin (16). The risk for a cerebrovascular accident, deep venous thrombosis or pulmonary embolism seems not to be increased by aprotinin (3). There have been reports about massive pulmonary embolism during liver transplantations, raising the question about the potential implication of aprotinin. However to date, we have no proof of a higher incidence in thrombosis during liver transplantation due to aprotinin use.

Renal insufficiency

As aprotinin accumulates in the renal tubular cells and because of the inhibition of the kinin-kallikrein system, some authors raised the question about a possible negative effect on renal perfusion

and renal function. However no study reported a lasting negative effect on renal function. The Cochrane review analyzed 13 trials including 3776 patients, which reported data on renal function. There was no significant increase in the risk of developing renal insufficiency (3).

Lysine analogues

The second class of antifibrinolytics are the lysine analogues tranexamic acid (TX) and epsilon-aminocaproic acid (EACA). They act as lysine substitutes, blocking the fixation of plasminogen to fibrin. This prevents the formation a fibrin-plasminogen-t-PA complex and thus fibrinolysis. Because of their short half-life (80 min for TA and 77 min for EACA), these compounds are used essentially as a continuous infusion. TA as well as EACA are excreted mostly unchanged by the kidneys. EACA is no longer commercially available in some European countries.

Results of TA and EACA studies to reduce allogeneic blood transfusion

18 randomized clinical trials are reported by the Cochrane review for TA, including 1342 patients (3). The Ispot meta-analysis reviews only 3 studies on TA, including 118 patients (9). Again, as with aprotinin, most of the studies were done in cardiac surgery, so 15 out of the 18 TA trials were done in cardiac surgery.

EACA studies date back to a time when CPB circuits were much more likely to induce a severe fibrinolysis. The 3 studies reviewed in the Ispot meta-analysis reported only a trend, statistically not significant, towards a reduced blood transfusion in cardiac surgery (9). TA is used for about 20 years in cardiac surgery; the Ispot review showed that in cardiac surgery it reduces blood requirements by about 1 unit (9). LEVY *et al.* found the same results in a meta-analysis of 11 studies in cardiac surgery analyzing indifferently TA or EACA (10). The Cochrane review (15 studies, 1151 patients) showed also a 29% relative reduction in the rate of exposure to allogeneic blood transfusion in cardiac surgery (3). As in the aprotinin trials, there was also significant heterogeneity in the TA trials. The Cochrane group reviewed 4 studies on EACA in cardiac surgery; there was no significant reduction in the need for allogeneic blood transfusion, probably due to the low number of patients and the important heterogeneity in the studies (3).

The use of TA in liver transplantation has been studied only in a few small trials. One concluded that high doses (40 mg/kg/h; max 20 g) reduces blood loss by about 45% and reduces transfusion requirements essentially of platelets and fibrinogen (17). Another study using low doses of TA (2 mg/kg/h) showed a reduction in fibrinolysis, but no reduction in blood transfusion (18).

TA has also been successfully used in orthopedic surgery to reduce blood loss and transfusion requirements after total knee arthroplasty, but there is a great variation in blood loss and transfusion in this type of surgery (19).

Lysine analogues have been proposed after aneurismal subarachnoid hemorrhage, but in a review of 9 trials it has been clearly shown that any benefit in bleeding reduction is clearly offset by an increase in poor outcome caused by cerebral ischemia as result of treatment with antifibrinolytics (20).

Adverse events of lysine analogues

Allergic reaction

EACA and TA being synthetic analogues of lysine, there is no risk of anaphylactic reactions.

Thrombotic events

The inhibition of fibrinolysis without reduction in thrombin generation raises questions about a possible pro-thrombotic profile in cardiac surgery. The Cochrane review however did not show an increase in the incidence of myocardial infarction (3). The same is true for the incidence of deep venous thrombosis as well as cerebrovascular accidents. Pulmonary embolism (5 trials, 541 patients) also is not increased by the use of TA; but some case reports exist on massive pulmonary embolism during liver transplantation (3).

Renal insufficiency

Only 2 trials reported data on renal function in randomized clinical trials (240 patients). The relative risk of developing renal failure was not increased (3).

CONCLUSIONS (FROM 3)

Antifibrinolytic drugs are effective in reducing blood loss, the need for allogeneic red cell transfusion and, in cardiac surgery the need for reoperation due to continued post-operative bleeding.

The drugs appear to be acceptably safe, and the benefits are likely to outweigh the harms. Most information exists for aprotinin, which has been studied in a large number of small randomized trials. The benefits are likely to be greatest in those participants with a high probability of requiring a red cell transfusion, for instance major cardiac surgery. The applicability of these drugs outside of such settings is presently unclear. The comparative clinical performance of the drugs has not been adequately assessed. Limited data indicate that they may have comparable efficacy and safety. Aprotinin is extremely expensive, and the cost-effectiveness of the drug is uncertain.

The use of antifibrinolytic drugs is justified in cardiac surgery, particularly in situations where there is doubt about the safety of the blood supply. Tranexamic acid is cheaper and may be as effective as aprotinin, although the data are sparse.

The principal need is for large comparative trials to assess the relative efficacy, safety and cost-effectiveness of anti-fibrinolytic drugs in different surgical procedures.

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