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REVIEW

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Tranexamic acid for major spinal surgery

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Abstract Patients who undergo major spinal surgery often require multiple blood transfusions. The antifibrinolytics are medications that can reduce blood-transfusion requirements in cardiac surgery and total knee arthroplasty. The present role of synthetic antifibrinolytics, especially tranexamic acid, in reducing peri-operative blood-transfusion requirements in spine surgery is still unclear. The majority of studies exploring the role of these drugs in spine surgery have limited patient enrolment and report mixed results. The goal of the present review is to discuss the pharmacology of tranexamic acid briefly. A brief synopsis of the studies using the synthetic antifibrinolytics for spine surgery is presented. Finally, the potential risks and the benefits of antifibrinolytics are discussed.

Keywords Blood transfusion · Coagulation · Tranexamic acid · Antifbrinolytics · Spine surgery · Scoliosis

Introduction

Major spinal surgery has the potential for massive blood loss [20]. Concerns surrounding the accompanying blood transfusions have spawned considerable interest in reducing peri-operative blood loss. Improved surgical techniques and peri-operative management may reduce blood requirements, but the majority of patients are still subjected to blood transfusions [26]. The prophylactic administration of synthetic antifibrinolytics, including tranexamic acid, has therefore been investigated for improving haemostasis for orthopaedic surgery. The goal of this review is to discuss synthetic antifibrinolytics briefly and explore their role in major spinal surgery.

Review of haemostasis

A discussion of antifibrinolytics requires a brief synopsis of the normal haemostatic process. Injury to blood vessels initiates the four components of haemostasis. First, the blood vessel attempts to vasoconstrict to reduce blood loss. Subsequent to this, exposure of the injured endothelium initiates platelet adhesion. The glycoprotein-Ia platelet receptors adhere to the damaged vessel wall with von Willebrand factor serving as a bridge. Platelet degranulation, which follows adhesion, liberates substances which in turn further augment platelet aggregation and vessel vasoconstriction. The third phase of haemostasis is the contact phase of coagulation, which includes the intrinsic and extrinsic coagulation cascades. The consequence of the third phase is fibrin clot formation and activation of the fibrinolytic system. Fibrinolysis, the fourth stage of haemostasis, results in dissolution of fibrin clots mediated by plasmin. Evidence suggests that plasmin also inhibits haemostasis at other levels, including inhibition of platelet aggregation through cleavage of the glycoprotein-Ia receptors on platelets and inactivation of fibrinogen [7]. Thus, a patient who develops a relative excess of fibrinolysis will be more likely to experience considerable blood loss during surgery.

A relative increase in fibrinolysis occurs in cardiac surgery primarily owing to the use of the cardiopulmonary

bypass machine. The use of a tourniquet in total knee arthroplasty has been implicated as the cause of increased fibrinolysis [13, 19]. Enhanced fibrinolysis has also been suggested to be a contributing factor to blood loss during spinal surgery [15, 16]. Drugs that counter fibrinolysis, including tranexamic acid, would therefore have a potential beneficial role in these procedures.

Antifibrinolytics

Tranexamic acid (TXA) is a synthetic antifibrinolytic drug released in the 1970s. Although it is similar to the prototypical synthetic antifibrinolytic drug, Σ-amino-caproic acid (EACA), TXA is considered to have ten times the potency of EACA [7]. The mechanism of action for synthetic antifibrinolytics is competitive blockade of the lysine-binding sites of plasminogen, plasmin, and tissue plasminogen activator [7]. The reversible blockade impedes fibrinolysis and blood-clot degradation [7]. Plasmin inhibition by TXA may also help prevent platelet degradation. Relative to EACA, TXA has higher and more sustained antifibrinolytic activity in tissues, but both have a similar toxicity profile [7]. Although TXA would appear to be the synthetic antifibrinolytic drug of choice, both drugs may be beneficial in states where there is an excess of fibrinolysis relative to the coagulation cascade.

The half life of TXA is approximately 80 min, provided there is normal renal function. A wide range of TXA dosing has been advocated, depending on the indication. Oral and topical applications of TXA have been used peri-operatively, but the majority of studies use intravenous TXA. Bolus and infusion dosing again vary, but pharmacokinetic evidence would suggest the use of 10–15 mg/kg loading dose, followed by an infusion dose of 1 mg/kg per h or repeated bolus dosing [10]. Dosage adjustments are recommended in patients with renal insufficiency.

TXA has been safely used in many different situations where it has beneficial effects. Nonsurgical uses of TXA include the management of bleeding associated with leukaemia, ocular bleeding, recurrent haemoptysis, menorrhagia, hereditary angioneurotic angio-oedema and numerous other medical problems. The prophylactic administration of TXA reduces both blood-transfusion requirements and the financial cost of cardiac surgery [6, 14]. Interest in TXA for orthopaedic surgery was rekindled in part by the work of Hiippala et al. who explored the use of the drug for total knee arthroplasty [8]. In this prospective double-blind study, 75 patients scheduled for 77 total knee arthroplasty were randomized to receive either TXA or saline. A TXA bolus dose of 15 mg/kg was given intravenously before deflation of the tourniquet, followed by two 10 mg/kg additional doses given postoperatively. Blood transfusions were used to keep haemoglobin levels above 10 g/dl. The results from Hiipala et al. demonstrate a significant reduction in estimated total blood loss (689±289 ml versus 1509±643 ml). The use of TXA reduced the mean number of transfused red cell units in the TXA group (1.0±1.2) compared to the placebo group (3.1±1.6), which was significantly different ($P<0.0001$). Subsequent to this study, numerous other studies support the premise that TXA reduces blood loss and, more importantly, significantly reduces transfusion rates [2, 11, 25]. A meta-analysis of studies using TXA for total knee arthroplasty supports the premise that it reduces total blood loss and reduces both the proportion of patients requiring allogeneic blood transfusion and the total number of units of allogeneic blood transfused [9]. The use of TXA does not increase the risk of thromboembolic complications such as deep-vein thrombosis, pulmonary embolism, thrombotic cerebral vascular accident, or myocardial infarction [9, 11, 25]. Intravenous TXA thus appears to be both safe and effective in reducing allogeneic blood transfusion and blood loss in total knee arthroplasty. In contrast to the substantial evidence supporting the use of TXA for total knee arthroplasty, there have been a limited number of studies that have investigated the role of TXA and the other antifibrinolytics for major spinal surgery.

Urban et al. assessed the efficacy of two different antifibrinolytics to reduce peri-operative blood loss for adult patients undergoing complex spine reconstructive surgery [24]. Sixty patients undergoing anteroposterior spinal fusion were randomly assigned to EACA, aprotinin, the natural antifibrinolytic, or placebo. A 5-g load of EACA was administered, followed by an infusion of 15 mg/kg per h. Patients received scavenged blood once they were processed. Stored blood products, both autologous and allogeneic blood units, were transfused to maintain haemoglobin above 8 g/dl. Although both drugs reduced total blood loss and transfusion requirements, only aprotinin reached significance levels. There was no increase in thrombotic complications in either of the treatment groups.

Florentino-Pineda et al. evaluated the use of EACA for paediatric patients undergoing posterior spinal fusion surgery for idiopathic scoliosis [5]. Twenty-nine patients were consecutively assigned to EACA at a dose of 100 mg/kg (up to 5 g) intravenous load, followed by 10 mg/kg per h for the duration of surgery. Thirty-one consecutive patients formed the control group. Transfusions were performed to maintain a haemoglobin above 7 g/dl or in response to several predefined clinical criteria. The EACA patients had significantly lower intra-operative and postoperative blood loss than the control group. The total number of units of blood transfused was also significantly lower in the EACA group. There were no complications associated with the use of EACA. Unfortunately, the results of the study are limited by the use of a historical control.

Adult patients with malignancies undergoing surgery for pelvic, extremity, or spine surgery were randomly assigned to aprotinin, EACA, or placebo [1]. The patients assigned to EACA received an intravenous loading dose of 150 mg/kg, followed by 15 mg/kg per h for the duration of surgery. Transfusions were administered to keep the haemoglobin above 8 g/dl. The study by Amar et al. found

Table 1 Demographics values. Values are expressed as mean ±SD unless stated otherwise (*TXA* tranexamic acid)

Characteristics	Control (*n*=18)	TXA (*n*=22)	*P* value
Weight (kg)	50.6±20.2	41.8±16.7	0.15
Cobb angle (degrees)	59±16.6	68±21.6	0.15
Scoliosis form (1:2)	8:10	7:15	0.62
Median levels fused (range)	15 (7–18)	14 (8–17)	0.96
Intra-operative blood loss (ml)	2703±1292	2453±1526	0.58
Total blood transfused (ml)	1784±733	1253±884	0.045
Transfused packed cells[a] (ml)	1254±542	874±790	0.08

[a]Transfused packed cells include predonated autologous units, directed donation units, and allogeneic units

no benefit from the use of either drug in regard to blood loss or transfusion requirements [1]. The overall incidence of deep venous thrombosis and pulmonary embolism was not different among the groups. Unfortunately, only 17 of the total number of patients in this study underwent spinal surgery, with 7 receiving EACA, 3 placebo, and 7 receiving aprotinin.

Two studies have investigated the use of TXA for paediatric patients undergoing spinal surgery for scoliosis. An abstract from Dell et al. reported on the use of TXA for idiopathic scoliosis surgery [3]. The preliminary results of 20 patients did not report any differences in intra-operative blood loss or intra-operative transfusion [3]. The second study, conducted by our group, investigated the role of TXA in 40 paediatric patients undergoing posterior spinal fusion for primary and secondary scoliosis [17]. Management was standardized, including the anaesthetic approach, fluid guidelines, and patient positioning. Since the primary outcome was blood transfusion, the most critical component of the study was a uniform transfusion policy for the intra-operative period and the first 24 h after surgery. Transfusions of stored blood, autologous or allogeneic, were given to keep haemoglobin levels above 7 g/dl. The treatment group received a 10 mg/kg intravenous loading dose of TXA, followed by an infusion of 1 mg/kg per h for the duration of the operative period. The control group received a saline placebo.

The TXA group had significantly lower blood transfusion requirements in the peri-operative period (Table 1). The intra-operative blood loss in the TXA group (2453± 1526 ml) was however not significantly different (*P*=0.58) than the control group (2703±1292 ml). Since the haemoglobin levels measured at the end of surgery and on the first postoperative day were similar, transfusion practice was similar in both groups. Transfusion violations were the same in both groups. TXA was well tolerated with no cases of haemodynamic instability, clinically overt thrombotic complications, or other adverse effects associated with its use.

Although the demographic data of the two groups was not significantly different, the groups were not identical. Generally, the differences put the TXA group at increased risk for peri-operative blood transfusions. Most notably, the greater proportion of patients with secondary scoliosis and lower weight in the TXA group would predispose this group to more peri-operative blood transfusions [1, 13, 26]. Despite these discrepancies, the TXA group still had less blood transfused. Further tests to assess the impact of these potential confounders were conducted with a multivariate analysis. Weight was not significant (*P*=0.11), but treatment group (*P*=0.028) and scoliosis form (*P*=0.001) were significant predictors for total blood transfused.

The lack of difference in operative blood loss should not lessen the significance of the study. Blood loss is often used as a surrogate outcome for transfusion requirements, but the use of surrogate endpoints is not recommended [4, 21]. Also, despite considerable effort, estimating blood loss has been demonstrated to be highly imprecise [18]. The described study was however primarily designed to determine the effect of TXA on the requirement for blood transfusion. Indeed, while studies that use blood loss as the primary outcome are helpful, they may not answer the more clinically important question regarding effects on blood transfusion. The design of future studies should therefore focus upon the effects of antifibrinolytics on blood transfusion rather than blood loss.

The major concern surrounding the use of TXA and other antifibrinolytics is the potential for an increase risk of thrombotic events. No patient in our study experienced a complication from the use of TXA, although no investigations beyond a physical examination and history taking were indicated [17]. No increased thrombo-embolic events occurred in the other spinal fusion studies [1, 5, 24]. The studies examining the use of TXA in patients undergoing total knee arthroplasty also did not experience an increased incidence of deep venous thrombosis [2, 8, 9]. Reports of thrombo-embolic events attributed to TXA are uncommon, occur in the non-operative setting, and are primarily anecdotal in nature. A common misconception is that these drugs are procoagulants and that they will increase blood clotting. The drugs do not alter blood clotting, but instead slow dissolution of blood clots. Sites where clots have formed will therefore remain or enlarge, but spontaneous formulation of clots should not occur. Benoni et al. suggested that TXA was not associated with thrombo-embolic events because the effects of TXA are more pronounced in operative wounds than in the peripheral venous blood [2]. The beneficial effects are believed to probably be due to inhibition of local fibrinolytic activity in the surgical field. TXA has no significant effects on peripheral fibrinolysis or other coagulation variables [2]. Although topical application of TXA theoretically could reduce widespread thrombotic complications, its efficacy and safety for this application are unknown. Although the majority of evidence suggests that TXA can be safely used

in patients undergoing posterior spinal fusion, constant vigilance for deep venous thrombosis is recommended.

Although the prevention of complete exposure to allogeneic blood products was not the primary outcome of the aforementioned studies, a beneficial reduction in blood transfusion would suggest that patients would be exposed to less allogeneic blood. Although the infectious and immune-suppressing risks of blood transfusions have been reduced in recent years, risks still remain [12]. Reduced allo-immunization to foreign antigens is important in paediatric patients and especially so in female patients [22]. These risks, along with recurrent shortages of allogeneic blood products, warrant the consideration of using of TXA for major spinal surgery. The cost of TXA ($CAN 29) is considerably less than the cost of one allogeneic unit ($CAN 210) or an autologous unit ($CAN 338) [23]. The potential advantages of TXA for posterior spinal fusion are considerable even if complete prevention of allogeneic exposure does not occur.

In conclusion, emerging evidence supports the safe use of tranexamic acid and other antifibrinolytics for the prevention of blood transfusion for major orthopaedic procedures. Although the benefit and safety of tranexamic acid in patients undergoing major spinal fusion have yet to be thoroughly established, tranexamic acid appears to have a potential beneficial role in the management of such procedures. Hopefully, future studies will clarify the exact role tranexamic acid has in spine surgery.

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