

Tranexamic Acid and Major Spine Surgery: Trends and Controversies

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Abstract

The beneficial role and efficacy of Tranexamic Acid in reducing perioperative blood loss and blood transfusion requirements in spine surgery is being established. Tranexamic Acid is an antifibrinolytic agent traditionally used to lessen perioperative blood loss. Tranexamic Acid can be administered orally, intramuscularly, intravenously or topically. Tranexamic Acid studies in spine surgery have limited patient enrolment. Most of the reported studies have mixed results and difficult to interpret. The efficacy of antifibrinolytic agents is evident in a wide variety of surgical procedures: liver transplantation, obstetrics and gynaecology, trauma and orthopaedic surgical procedures. The effect of Tranexamic Acid on the occurrence of thromboembolic events, strokes, myocardial ischemia, seizures and mortality has not been adequately assessed and remains uncertain. A number of possible complications reported. In this review, we analyze the efficacy and safety profile of perioperative Tranexamic Acid with the exclusion of cardiac surgery and a focus on major spinal surgery.

Introduction

Excessive bleeding often complicates spine surgery. This may result in increased morbidity and mortality [1,2]. The amount of blood loss depends on many factors. The extent of a surgical procedure is the principal cause of a blood loss during spine surgery. Perioperative coagulation dysfunction is also an important factor leading to an excessive blood loss during lengthy spinal surgeries. Tranexamic Acid (TA) is safely used for the prevention of blood transfusion for major joint replacement procedures [3,4]. The benefit and safety of tranexamic TA in patients undergoing major spinal fusion is not completely established. Nevertheless, TA appears to have a potential role in the management of spinal surgery. Identifying patients at risk plays paramount importance in preventing excessive blood loss [5,6]. The role of a surgeon cannot be overestimated. Optimal positioning to minimize epidural venous bleeding, including intraoperative normovolemic hemodilution, cell salvaging, minimization of a surgical invasiveness, staging of a procedure and administration of various antifibrinolytic agents is utilized with various success to lessen perioperative blood loss in patients undergoing spine surgery. What method is the most effective, safest or advantageous remains unclear [7,8].

Surgical hemostasis is obviously the most crucial blood loss-preventing factor [9]. Nevertheless, topical and systemic pharmacological agents are evidently of an additional merit [10,11]. Judicious surgical hemostasis and procoagulants agents are complementary in managing perioperative hemorrhage [5,12]. Systemic procoagulants agents, such as aprotinin, ε-aminocaproic acid (EACA) and TA are being used. These agents are proved to be effective in prophylaxis of perioperative blood loss and its treatment [13]. Efficacy of Desmopressin and Recombinant VIIa factor classically used perioperatively in patients with pre-existing coagulopathy is also controversial [14,15]. Overall the efficacy of antifibrinolytic agents was evident in a wide variety of surgical procedures: liver transplantation [16], obstetrics and gynecology [17], trauma [7,18] and orthopedic surgical procedures [19].

Though TA studies in spine surgery have limited patient enrolment, the beneficial role and efficacy of TA in reducing perioperative blood loss and blood transfusion requirements in spine surgery is continuously evolving. The safety of TA is still unclear and remains inadequately investigated [20,21]. The incidence of side effects and complications of TA use in spinal surgery needs to be further explored. The effective dosage of TA in spine surgery is not completely established. Reported data supports a wide range of different TA regimens [20]. There is still a need for a standard peri-operative administration of antifibrinolytic agents. It is ultimately important to identify patients with active history of thromboembolic disease (DVT, PE and etc.) and those at risk for thrombosis (like those with thrombophilia, immobility, atrial fibrillation, mechanical valve prostheses, hyperhomocysteinaemia, increased plasma level of coagulation factors, chronic inflammatory diseases, chronic hormone therapy, pregnancy, smoking, oral contraceptives intake and Factor C and Factor S deficiency) and advanced age [22]. Each patient's risks and benefits assessment needs to be established individually as TA use advocated in a wide range of conditions (such as spinal fusions, spinal stenosis correction, and trauma) or discouraged (such as tumor cases). In this review, we analyze the efficacy and safety profile of perioperative TA with the exclusion of cardiac surgery and a focus on major spinal surgery.

What is Tranexamic Acid?

TA is an antifibrinolytic agent traditionally used to lessen perioperative blood loss. TA can be administered orally, intramuscularly, intravenously or topically [23,24]. TA is a synthetic analog of the amino acid lysine. It is in a way similar to EACA, which is a synthetic lysine analog. EACA competitively inhibits the conversion of plasminogen to plasmin and directly inhibits the activity of plasmin, integral to fibrin lysis. TA affects fibrinolysis in the same manner as EACA but is significantly more active. TA competitively inhibits plasminogen activation to plasmin by binding to plasminogen specific sites. This prevents fibrin degradation [25] and clot breakdown. TA

also improves the impaired platelet function, which contributes to the blood-saving effect [26].

Question of a Perioperative TA Dosage

The peri-operative dosage of TA poorly established and not well standardized. It varies considerably for different surgeries and medical conditions. The original manufacturer of TA, Pfizer, recommends different dosages. As per insert, the dosage is different for variety surgical interventions. For dental surgery in patients with (hemophilia A) coagulopathy it is recommended that immediately before surgery 10 mg per kg of body weight should be given intravenously followed by 25 mg per kg of body weight is given orally three to four times daily for six to eight days after surgery. For adult cardiac surgery: after induction of anesthesia and prior to skin incision, the manufacturer recommends the administration of a loading dose of 15 mg/kg of TA, followed by an infusion of 4.5 mg/kg/hour for the duration of the surgery; up to 0.6 mg/kg of this dose may be added to the priming volume of the heart-lung machine. For adult knee arthroplasty, the administration of 15 mg/kg TA is recommended prior to the release of the tourniquet, followed by two repeat bolus injections of 15 mg/kg at 8 h intervals; the last bolus dose should be administered 16 hours after the initial dose. For adult hip arthroplasty, the administration of 15 mg/kg of TA is recommended immediately prior to skin incision, followed by 2 repeat boluses of 15 mg/kg at 8 hour intervals. The last bolus dose is to be administered 16 hours after the initial dose [27].

There is evolving evidence about the comparable efficacy of a topical TA to the intravenous route. Topical route may potentially minimize the chances of possible perioperative adverse effects of the intravenous TA administration (like thromboembolic, renal or neurological adverse events). A randomized controlled trial exhibit comparable efficacy of a topical TA in decreasing blood loss in total hip and knee arthroplasty and heart surgery [28-30].

Controversy of TA efficacy in blood loss and blood transfusion reduction

Spinal surgery is often bloody. Blood transfusions are not uncommon. Antifibrinolytic agents, including TA, could be valuable adjuncts to perioperative hemorrhage management. Evidence suggests that TA reduces the need for transfusion. The efficacy of TA varies. It depends on the type of surgery and many other factors. The evidence that TA reduces blood transfusion in surgical patients is available. TA may reduce overall blood loss by up to one-third [31]. TA was compared to placebo in randomized clinical studies. Reduced perioperative blood loss was established in a variety of surgical procedures, including intracranial surgery [32], trauma [7,20], cardiac surgery with or without cardiopulmonary bypass [33], total hip and knee replacement [34], craniotomies [35], gastrointestinal endoscopy procedures [36], ear-nose-and-throat procedures [37], prostatectomy [38], and spinal surgeries [39-42], caesarean sections and vaginal deliveries [43]. Oral TA has been used with success as a treatment for heavy menstrual bleeding [17].

TA was proved to be effective in trauma care. In a multi center study TA decreased the need to massive blood transfusion and improved survival rate in bleeding injury patients [44]. TA is incorporated into US Military practice guidelines for tactical combat casualty care [21]. Army forces' experience showed TA's efficacy in the pre-hospital setting without evacuation delays [45]. Retrospective analysis 896 injured personnel database in Afghanistan, reported significant mortality

reduction with the use of TA [46]. CRASH-2 trial established that TA administration reduces death, vascular occlusive events and blood transfusion in trauma patients with significant blood loss [47,48].

The majority of research on this topic has significant limitations. The present role of TA in reducing perioperative loss and blood transfusion requirements in spine surgery is still not fully elucidated. Insufficient patient enrollment and mixed results are common [49]. TA reduces the percentage of spinal surgery patients' blood transfusion need [50-52]. It reduces transfusion requirements at a higher degree than desmopressin [22] and proved to be equally effective as EACA in intraoperative hemorrhage reduction [53]. TA was compared to aprotinin for blood loss control during spinal surgery and was found to be equally effective [54].

Spinal deformity surgery involves almost unavoidable and sometimes significant perioperative blood loss risk [55]. Intraoperative antifibrinolytic agents reduce this risk [41,42,45,56-62]. Aprotinin, TA and EACA are effective in reducing bleeding and blood transfusion reduction during spinal surgery [53,63,64]. Nevertheless, one study reported that EACA had a greater effect on reducing blood transfusions as the complexity of surgery increased [65], another one reported aprotinin being more effective than EACA [64]. A 2009 systematic review of the literature and meta-analysis conducted to identify all randomized controlled trials of aprotinin, TA, and EACA involving children undergoing cardiac or scoliosis surgery failed to show evidence that compared with aprotinin, TA was more effective in reducing blood loss in major pediatric surgery [66]. In retrospective review of 230 patients undergoing single stage posterior spinal fusion for idiopathic scoliosis TA administration reduced the percentage of patients with idiopathic scoliosis received blood transfusion [67]. In another study TA reduced blood loss by 41% compared with placebo in pediatric patients undergoing elective scoliosis surgery [56]. TA decreased intraoperative blood loss in the study of intraoperative blood loss and transfusion requirements in adolescent idiopathic scoliosis patients undergoing posterior spinal fusion by a single surgeon [68]. In 2012, a retrospective review of prospectively collected data of 84 pediatric scoliosis corrections, TA significantly reduced intraoperative blood loss associated with posterior spinal fusion [57]. Recently published randomized trial showed a 33.4% reduction in the intraoperative estimated blood loss and a 41% reduction in total blood loss when TA was used intraoperatively for posterior lumbar surgery for spondylolisthesis [69].

The hemostatic effect of TA is a dose-dependent. A prospective dose-ranging study is required to determine the optimal dose for pediatric patients with idiopathic scoliosis [70]. TA showed to reduce blood loss and hemotransfusion requirements during thoracolumbar trauma surgery [71] and during posterior lumbar surgeries [72]. The prophylactic efficacy of TA in spinal surgery is neither well studied nor established. The administration of a prophylactic low dose of TA failed to have a significant effect on transfusion requirements in patients undergoing spinal fixation surgery [73].

TA failed to improve hemostasis during surgical treatment of metastatic spine tumors [74]. It showed to be effective in perioperative blood loss reduction, primarily through a reduction in postoperative blood loss, in cervical laminoplasty [75]. Interestingly, TA may also influence inflammatory pathways. This could be TA's additional benefit. Studies on this role of TA are controversial and indecisive [76]. TA was shown to reduce overall hospital stay after knee replacement surgery [77]. Intraoperative Viscoelastic Hemostatic Assay (VHA) may be a useful tool to assess the need for TA. A recently published

systematic review and meta-analysis [78] showed a significant reduction of allogenic blood products transfusion rates when VHA was used. Targeted administration of TA in those with proved hyperfibrinolysis could allow a more effective approach to reduce perioperative blood loss.

Questions and Controversy of Complications Associated with TA Usage

The effect of TA on the occurrence of thromboembolic events, strokes, myocardial ischemia, seizures and mortality has not been adequately assessed and remains uncertain (39). A number of possible complications and events were reported (summarized in a Table 1).

Thromboembolic events

Intraoperatively, when antifibrinolytics agents are given, postoperatively fibrinogen levels tend to be increasingly higher [79]. It brings a concern, that TA may cause a higher incidence of postoperative thromboembolic events. In the UK, Japan and EU TA is not advised in patients with a history of thromboembolic disease or extreme vigilance is strongly recommended. Active thromboembolic disease is a contraindication for TA use in the EU and the UK [80]. Pulmonary embolism (PE) [81] and deep venous thrombosis (DVT) [82] has been reported with TA use. Though prospective controlled trials, retrospective studies and case-series in children and adults [57,83-86] including those targeted at spine surgeries [65,72,87] showed low incidence of vascular thrombosis, these trials and studies were not designed specifically to evaluate the incidence of thrombosis. Majority of these clinical trials and randomized studies were done on patients undergoing joint replacements. There are no targeted retrospective spinal surgery database studies, which could possibly explain this issue. Most of the clinical trials analyzing thromboembolic complications of TA in surgery are either conflicting or inadequately powered to make a definitive conclusion [21,50]. A number of randomized studies showed that compared to placebo, ant fibrinolytic agents reducing bleeding and need for transfusion in joint replacement orthopaedic surgery [34,88] and spine surgery without increased risk of myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism. 2016 meta-analysis of TA use in bilateral total knee arthroplasty did not show an increase in occurrence of DVT [88]. Though, Claeys et al. reported an increase in the rate of DVT when TA was used [89]. Ker et al. assessed 129 trials done between 1972 and 2011, totalling 10488 patients. Their data source was the Cochrane central register of controlled trials, Medline, and Embase, the World Health Organization International Clinical Trials Registry Platform, and the reference lists of relevant articles. While reducing the probability of receiving a blood transfusion by a third, the effect of TA on myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism was uncertain [36]. Gillette et al. retrospectively reviewed 2046 patients from 2007 to 2009 and who underwent primary total hip arthroplasty or total knee arthroplasty and received TA, comparing three chemical regimens (aspirin alone, warfarin and dalteparin). The primary outcome measures were venous TE events, including symptomatic deep vein thrombosis and pulmonary embolism, and arterioocclusive events, including myocardial infarction and cerebrovascular accident. For aspirin, warfarin, and dalteparin, the

rates of symptomatic deep venous thrombosis and nonfatal pulmonary embolism were similar. Authors saw a low complication rate when using TA as a blood conservation modality during primary THA and TKA with less aggressive thromboprophylactic regimens such as aspirin alone and dose-adjusted warfarin [90]. Duncan et al. [91] retrospectively reviewed 13,262 cases of elective total knee arthroplasty and total hip arthroplasty, and found that the odds of postoperative venous thromboembolism and 30-day mortality were unchanged with TA administration. Alshryda et al. conducted a systematic review and meta-analysis of 19 randomized controlled trials analyzing TA usage complications in total knee replacement. Considerable patient heterogeneity slights the interpretation of the study with no sufficient evidence indicating an increased risk of deep-vein thrombosis or pulmonary embolism caused by TA [92]. In Baldus et al. study of aprotinin and TA in controlling blood loss during lumbar pedicle subtraction osteotomy in adults, no major intraoperative complications like postoperative cases of seizures, myocardial infarction, stroke, deep venous thrombosis or pulmonary embolism were identified [52]. Currently there is no strong evidence that TA leads to increased rate of thromboembolic events. Future studies multicenter randomized studies are needed to clarify the exact role and safety of TA in spine surgery.

Seizures and Renal Complications

TA is associated with postoperative seizures in patients with renal disease [93,94]. Cases of acute renal cortical necrosis after TA use have been described [95,96].

Perhaps, doses of TA should be reduced in patients with mild to moderate renal insufficiency [93] or may be TA needs to be avoided in these patients [64]. In patients with renal insufficiencies or at a high risk for developing TA related adverse events, a VHA-guided administration of TA may be a wise approach [64]. TA is contraindicated in the EU in patients with severe renal failure because of the risk of accumulation. Multifocal myoclonus was reported after TA infusion [97]. TA is known to lower the seizure threshold in animals [98]. A nationwide data base study in japan 2016, Maeda et al retrospective cohort study showed a significant increase in seizures risk with use of TA in pediatric patients who underwent cardiac surgery [99]. The use of high-dose TA in older patients in conjunction with cardiopulmonary bypass and open-chamber cardiac surgery [100-103] was associated with clinical seizures, which could be due to ischemic brain injury [104]. These seizures are more pronounced in those with perioperative renal disease [105]. A one-year follow up of 1188 cardiac surgery patients found a significantly higher incidence of seizures among those who received TA [13]. Another multivariate analysis of 11 529 cardiac surgery patients revealed a strong association between postoperative seizures and TA. TA was also reported as an independent predictor of postoperative seizures [106]. TA is structurally similar to the inhibitory neurotransmitter glycine. Since reduced function of glycine receptors causes seizures, TA may possibly inhibit the activity of glycine receptors [96,107] and may have intrinsic proconvulsive properties. When compared to EACA in a clinical retrospective study, TA was found to cause seizures more often [108]. High dose TA appears to be an independent seizure predictor [109]. Seizures may also develop as a result of TA overdose [110].

Table 1. Adverse Events associated with Tranexamic Acid

Adverse Events	Reference	Characteristics of Events
Thrombo-embolic events		
Pulmonary Embolism	[81]	Reported case of a pulmonary embolism in a patient with an acquired Factor VIII inhibitor, who was on a prophylactic TA
Deep Vein Thrombosis	[82]	Multiple reports of deep venous thrombosis sited
	[88]	Authors report that TA did not increase the occurrence of deep vein thrombosis in bilateral total knee arthroplasty patients
	[89]	In this prospective, placebo-controlled, double blind, randomized clinical trial, authors investigated the effect of a single preoperative bolus dose of tranexamic acid (15 mg/kg) on perioperative blood losses and packed cell transfusion requirements in patients scheduled for primary unilateral total hip replacement surgery. Compression ultrasonography on the 10th postoperative day was positive for deep venous thrombosis in 3 patients who were on TA group (17 patients were screened) and negative in all patients of the placebo group (18 patients screened). The rate was 3/17 or about 17%.
Unclear evidence to support the increased risk of Stroke & MI		
	[36]	Seven double-blind randomized trials on tranexamic acid vs. placebo were analyzed. Data from three of the included trials suggested that tranexamic acid did not significantly increase the risk of thromboembolic disease. Authors reported Incidence that Myocardial infarction rate was 2 out of 522 patients in TA group vs 2 out of 526 in placebo group. Stroke was reported in 1 out of 522 on TA and in 2 out of 526 patients on placebo.
	[52]	Though the primary concern with the use of TXA is the potential for an increased risk of thromboembolic complications such as peri-operative myocardial infarction, stroke, deep vein thrombosis, and pulmonary meta-analysis demonstrates that TXA was not associated with increased incidence of such thromboembolic complications.
Neurologic events		
a. Seizures	[13]	Retrospective analysis of 1188 consecutive patients, which showed an incidence of seizure of 4.6% in patients receiving tranexamic acid vs 1.2% in the aprotinin group ($P < 0.001$).
	[102]	The study aimed to examine the association between TA use and adverse events as seizures, thromboembolism, and renal dysfunction) in a pediatric cardiac surgery population using Japan's national inpatient database. Propensity-matched analysis showed that the proportion of seizures was significantly higher in those on TA (1.6% versus. Authors concluded that TA is associated with a significantly increased risk of seizures.
	[103]	In this case series, 7 patients receiving TA described over the course of 18-month period who had open-chamber cardiac surgery and developed seizures in the postoperative period. There was an increased incidence in a group compared to those who did not receive TA (0.66% versus 0%; $P < .05$).
	[27,28,109]	Authors report that the use of higher doses of TXA has been associated with a higher incidence of seizures (2.7% versus 7.6%)
Multifocal Myoclonus	[100]	Myoclonus reported in a patient on chronic ambulatory peritoneal dialysis for adult polycystic kidney disease who was transfused with two units of packed cells and started on oral tranexamic acid 500 mg four times daily.
Renal events		
Acute cortical Necrosis.	[97]	The author reported a case of acute cortical necrosis associated with TA use.
	[98]	The author reports one case of renal acute cortical necrosis induced by TA in a patient with Hemophilia A.
Ophthalmic events		
Central retinal artery occlusion & disturbance in color vision	[112]	A case of central retinal occlusion with a color vision disturbance reported
b. Central venous stasis retinopathy	[113]	Report on central venous stasis retinopathy observed in two young women following the administration of oral TA for the treatment of menorrhagia.
c. Ligneous conjunctivitis	[114]	A case report of Ligneous Conjunctivitis

Other complications

Adverse allergic reactions may also occur with a TA infusion [111]. Ligneous conjunctivitis [112], toxic epidermal necrolysis, central venous stasis retinopathy [113], disturbances of color vision as well as central retinal artery occlusion may also result from TA infusion [112]. Though never reported in clinical trials, retinal degeneration with a high dose TA infusion was described in dogs. Ophthalmological examinations probably guarded if patient is to be receive TA.

Conclusion

Antifibrinolytic agents, including TA, could be valuable adjuncts to perioperative hemorrhage management. TA is a widely used antifibrinolytic agent. The beneficial role and efficacy of TA in reducing perioperative blood loss and need for blood transfusion is evident. TA is administered orally, intramuscularly, intravenously or topically for a wide variety of surgical procedures. The efficacy of antifibrinolytic agents is described in a wide variety of surgical procedures: liver transplantation, obstetrics and gynecology, trauma and orthopedic surgical procedures. Bleeding often complicates spine surgery. This results in increased morbidity and mortality. The extent of a surgical procedure is the principal cause of a blood loss. Perioperative coagulation dysfunction is also a factor leading to an excessive blood loss during lengthy spinal surgeries. TA efficacy in spine surgery is noticeable but most of the studies have either limited patient enrolment, mixed results or difficult to interpret. The effect of TA on the occurrence of thromboembolic events, strokes, myocardial ischemia, seizures and mortality has not been adequately assessed and needs to be elucidated. There is evidence that TA reduces the need for transfusion. The efficacy varies from study to study, depending on the type of surgery and many other factors. The benefit and safety of tranexamic TA in patients undergoing major spinal fusion is not completely established. Identifying patients at risk still plays paramount importance in preventing excessive blood loss and the role of a surgeon cannot be overestimated. Surgical hemostasis is obviously the most important. Topical and systemic pharmacological agents are of an additional merit. Judicious surgical hemostasis and procoagulant agents are complementary in managing hemorrhage.

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