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Original Research Article

A meta-analysis evaluating tranexamic acid's effectiveness in reducing surgical bleeding during spine surgery

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Abstract

Background: Tranexamic acid (TXA) is a well-known antifibrinolytic drug that can be taken by mouth, injected into the muscle, or given through a vein. But there isn't much evidence that IV TXA helps reduce the need for blood transfusions during spinal surgery.
Method: We used electronic PubMed, Cochrane Central Register of Controlled Trials, and Embase databases to do a meta-analysis of randomized controlled trials (RCTs) and quasi-randomized trials (qi-RCTs) that included patients who had different spinal surgeries, such as adolescent scoliosis surgery given with perioperative IV TXA. Two independent researchers looked for more journal articles and conference proceedings by hand.
Results: There were a total of 9 studies, and 581 patients were used as samples. Mean blood loss was cut by 128.28 ml during surgery (range: 33.84-222.73 ml), 98.49 ml after surgery (range: 83.22–113.77 ml), and 389.21 ml all together in patients who were given perioperative IV TXA (ranging from 177.83 to 600.60 ml). The average amount of packed cells that were given as a transfusion was cut by 134.55 ml (range: 51.64-217.46 ml; 95% CI; P = 0.0001). Overall, 35% fewer patients treated with TXA needed blood transfusions than patients treated with the comparator (RR = 0.65; 95% CI = 0.53 to 0.85; P = 0.0001; I2 = 0%). It was seen that TXA had a positive effect and subgroup and sensitivity analyses confirmed this. Seven studies gave information about DVT. The study with only one DVT case was not added to the other ones.
Conclusions: With IV TXA treatment before and after spinal surgery, patients lost less blood. Also, there was a big drop in the number of spinal surgery patients who needed blood transfusions. Before TXA can be used safely on people having spine surgery, our findings need to be confirmed by more research.

Keywords: Tranexamic acid (TXA), spine surgery, anticoagulation, blood loss, transfusion

Introduction

Spine surgery usually causes a lot of blood loss during and after the surgery. This may be due, at least in part, to the large wound surfaces, long operating times and involvement of

cancellous bone, which has a lot of blood vessels. Even though the amount of blood loss during surgery can vary a lot from one procedure to the next, depending on both surgical and non-surgical factors, blood loss is still a big problem in spine surgery [1, 2]. When a lot of blood is lost, it can cause problems like low blood pressure, organ damage, or coagulopathy. Allogeneic blood transfusions come with extra risks, such as hemolytic transfusion reactions, acute lung injuries caused by the transfusion, infection transmission, and effects on the immune system. Because blood loss and allogenic transfusions come with a lot of risks and problems, it is very important to find safe and effective ways to reduce blood loss during spine surgery [3, 4]. Strategies for saving blood have been used successfully to cut down on surgical bleeding and the need for allogeneic transfusions during different types of surgery. Regional anaesthesia, hypotensive anaesthesia, intraoperative blood salvage, acute normovolemic hemodilution and giving medications intravenously, intramuscularly or orally are all examples of these techniques [5, 6]. Also, antifibrinolytics like tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) have been shown to reduce bleeding in many surgeries, including cardiac, trauma, hip, and knee arthroplasty, gynecological, and urologic procedures [7, 8]. Tranexamic acid works by competitively blocking the lysine-binding sites of plasminogen. This stops fibrinolysis and the breaking down of blood clots [9].
Recent research in spine surgery has shown that TXA works to reduce blood loss during surgery and the need for allogeneic blood transfusions in patients. However, it is still not clear what the best dose and length of treatment should be [10]. Antifibrinolytics are not usually used in spine surgery. Concerns have been raised about the safety of these drugs, including an increase in thromboembolic events like deep vein thromboses (DVTs), pulmonary embolisms (PEs), and myocardial infarctions (MIs), as well as an increase in seizures with moderate to high doses of TXA [11]. This meta-analysis looked at how well TXA works to prevent blood loss during spine surgery [12].

Methods and Materials

We found and read articles in the scientific literature that talked about the use of TXA in spine surgery. PubMed, Ovid MEDLINE, and CENTRAL were used to look for case series studies, retrospective cohort studies, prospective studies, randomized controlled trials (RCTs), systematic reviews, and meta-analyses (Cochrane Library). The results of the literature search that were relevant to this topic were sorted by title, keywords, abstract, and then the whole publication. Articles were not limited by when they were published or where they came from [13, 14].

History and Background

TXA was first used in clinical settings in the 1960s. Since then, it has been shown to be effective in reducing perioperative and trauma-related bleeding and the need for blood transfusions in obstetric, urologic, and cardiac surgery [15]. In the field of orthopedic surgery, total knee and hip arthroplasty procedures have shown that TXA works [16]. TXA is also being used more and more in spine surgery. Most of the early studies that looked at its usefulness were retrospective cohort and case series studies with different types of patients [17, 18]. In more recent research, prospective clinical trials have been done to see how well it works in adolescent and adult patients going through different spinal procedures with different levels of difficulty [19, 20]. One of the first meta-analyses, done in 2008, on the use of TXA in spine surgery did not show a clear benefit, in part because the way the studies were done was not perfect [21]. Because there were no approved uses for TXA in spinal surgery, it was being used for those procedures anyway. More systematic reviews and meta-analyses of the available research have shown that more powerful studies that are more consistent in how

they are done, how much they use and how often [22, 23].

Clinical pharmacology of TXA

TXA is a synthetic lysine analogue that was shown to be more effective and better than epsilon-aminocaproic acid (EACA), which was used before [24]. The World Health Organization's (WHO) List of Essential Medicines includes TXA as a hemostatic agent that is widely used in clinical settings [25]. TXA works by stopping fibrinolysis from happening. It does this by binding to the lysine moiety on the structural proteins plasminogen, plasmin and tissue plasminogen activator (tPA) and stopping them from competing with each other [26]. It makes it harder for plasminogen and tPA to stick to fibrin, which stops the zymogen plasminogen from activating the serine protease plasmin, which would otherwise break up fibrin clots [27]. TXA can be taken by mouth, put on the skin, or put into a vein. It is 100% bioavailable no matter how it is given. When TXA is given by IV at a dose of 10 mg/kg, it has a half-life of about 80 minutes and reaches its highest level in the body within an hour [28]. Since TXA is removed from the body through the kidneys, its dosage needs to be changed for people with chronic kidney disease [29].

Dosing regimen of TXA: It's not clear what the best way to give TXA through an IV is. Previous research has shown that the clinically effective dose is 10–15 mg/kg of body weight, and that higher doses have less of an effect [30]. It has been shown that TXA is absorbed and absorbed systemically when it is given by IV. Doses of 10 mg/kg can stop the fibrinolytic process in tissues by up to 80% [31]. In spine surgery, TXA is usually given through an IV as a bolus dose of 10 to 20 mg/kg before the surgery, followed by a maintenance infusion of 1 to 10 mg/kg per hour of surgery [32]. The best way to use TXA in spinal surgery is still being researched, and the protocols used in different institutions and practise settings are very different. Low doses of TXA have been shown to be effective, but the relationship between dose and effectiveness is still not well understood [33]. Also, some spinal procedures, like the correction of adult spinal deformity, have been linked to major blood loss, which is defined as 60 mL/kg in 24 hours or more than 40% of the patient's total blood volume [34]. In fact, close to 10% of bad things that happen during surgery are said to be caused by blood loss of more than 5 liters [35]. So, it's even more important in cases of complex surgery to find a dosage schedule that stays effective throughout the whole perioperative period [36]. Since the body can get rid of TXA over the course of 2 to 3 hours after a single IV dose, complicated spine procedures may need a second bolus dose after the first infusion. Raksakietisak *et al*. looked at 39 patients who were given a bolus dose of 15 mg/kg at the beginning of the procedure and another bolus dose 3 hours later to study how well this regimen worked. When compared to the placebo group, the experimental group lost less blood during surgery and needed less blood transfusions [37]. Moving forward, more research should be done to find out more about giving TXA in multiple doses. There needs to be a study comparing the regimen to other approaches, such as the initial loading dose plus a maintenance infusion given throughout the operation [38].

TXA in spine surgery: In recent years, more and more meta-analyses of RCTs are adding to what we know about how TXA can help stop bleeding during spinal surgery. Wong et al. gave TXA intravenously to 147 patients who had an elective posterior instrumented spinal fusion [39]. The first dose was 10 mg/kg, and the maintenance dose was 1 mg/kg per hour until the skin was closed. Estimated blood loss from the procedure was cut by up to 30% in patients who got TXA through an IV. This was shown by higher hemoglobin levels after surgery and less need for red blood cell savers. Yang et al. did a meta-analysis of 9 studies with 581 patients and found that patients who got TXA before surgery lost less blood and

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needed less blood transfusions [40].
Raksakietisak *et al*. found that patients who got TXA after a complicated laminectomy procedure lost less blood than those who didn't. Patients who got two doses of TXA at 15 mg/kg lost less blood and used less IV crystalloid fluids, including packed red blood cells, than those who got a placebo [41]. TXA can also be used for spinal procedures on children and teens. Verma *et al*. did a prospective, randomized study on the use of TXA in 125 teenagers who were getting surgery for idiopathic scoliosis. The number of blood transfusions did not go down because of TXA [42]. Schouten *et al*. showed that TXA is better for scoliosis surgery patients than placebo by showing that TXA cuts blood loss by almost twice as much as placebo (29). Yagi *et al*. came to the conclusion that patients with scoliosis who got a 1 g loading dose of TXA followed by a maintenance dose of 100 mg per hour during surgery lost less blood and had the same risk of complications as the control group [43]. Lastly, a single surgeon study by Lykissas *et al*. [44] confirmed these results with a 100 mg loading dose and 10 mg/hour infusion rate of TXA in adolescent patients getting surgery for scoliosis. TXA has been used to stop more bleeding in the cervical spine and in spinal oncology cases [45]. Elwatidy *et al*. did a randomised controlled trial (RCT) with 64 patients who were getting high doses of IV TXA (2 grammes of loading dose followed by a maintenance dose of 100 mg per hour for up to 5 hours after surgery) [46]. The authors said that the drain output showed a 48% decrease in blood loss during surgery and a 55% decrease in blood loss after surgery. These clinical trials show the important role that TXA can play in helping to stop bleeding during spinal surgery. They also show that TXA is safe and effective at reducing blood loss during surgery and the need for blood transfusions as a result. Even though most of the articles we found in the published literature supported the use and effectiveness of TXA, there were a few that showed the opposite. Peters et al. did a prospective, randomized trial in which 10 mg/kg of TXA was used to start the anaesthesia and 1 mg/kg per hour was given as an infusion. There was no statistical difference between the experimental group and the control group in how much bleeding stopped [47]. Farrokhi *et al*. showed that patients who had posterior instrumentation and fusion of the thoracic or lumbar spine did not lose more blood or need blood products during surgery [48]. Still, it is clear that more and more clinical trials and studies are showing that TXA is a good way for spine surgeons to control blood loss during surgery. It is also important to think about any bad effects that could come from the way TXA is absorbed and spread through the body. After crossing the blood-brain barrier and moving through the central nervous system (CNS), concentrations in the cerebrospinal fluid (CSF) can reach up to 10% by volume [49]. In the past, it has been written about how often epileptic seizures happen after surgery in people who were already likely to have them. Other studies have found that the inhibitory GABAA and glycine receptors could be blocked by TXA, which could cause damage to the CNS. Rare but serious side effects that affect other organ systems have also been reported, such as changes in how colors look or necrosis of the renal cortex [50]. The risk of increased thrombogenesis and the bad things that can happen as a result, such as venous thromboembolism, is probably the biggest worry about using TXA (VTE). Reviewing the meta-analyses that have been done so far shows that there is still no clear evidence that TXA increases the risk of thromboembolic complications. Previous RCTs were limited by their small sample sizes and methodological flaws, such as not being able to control for reporting bias [51].

Results

Inclusion of studies: During the first search, 990 articles were found in both electronic databases (PubMed: 276; Cochrane: 443; Em base: 269 and Orthopedics China Bio Med: 2). 585 studies were taken out because their data overlapped or they were in more than one database. This left 445 studies. After looking at the titles and abstracts, 397 studies that didn't

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meet the criteria for inclusion were thrown out, and 31 more studies that didn't have information about spinal surgery were also thrown out. Based on the criteria for excluding studies, 8 of the remaining 17 studies were ruled out. In the end, our study included 9 studies (5 RCTs and 2 qi-RCTs) that met all of the criteria for inclusion. Seven of the studies were written in English, one was written in Chinese, and one was written in Korean. There were a total of 581 patients in these 9 studies. Figure 1 shows a detailed flow chart for making a choice.

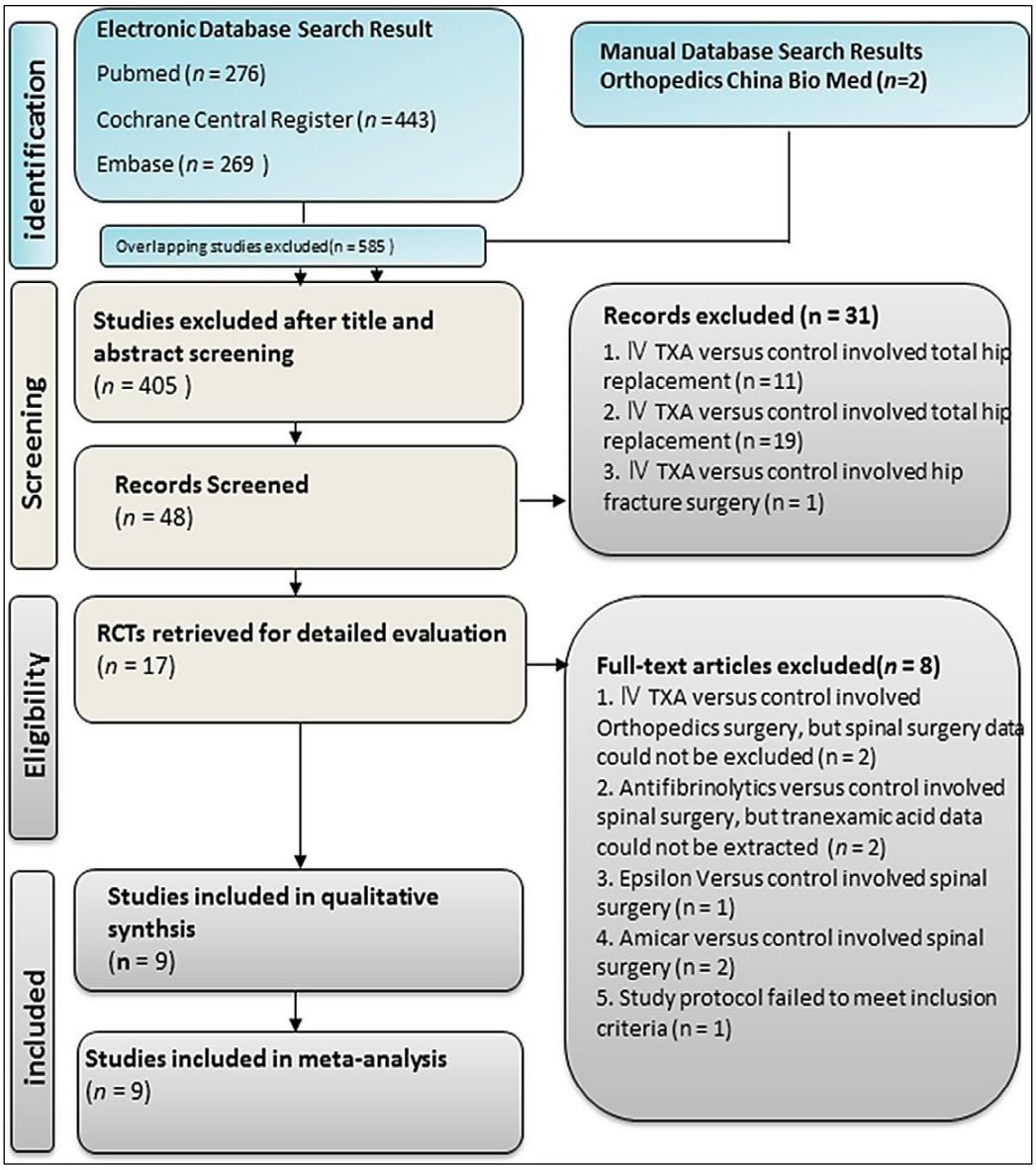

Fig 1: Method for study search and selection for inclusion

Quality assessment for included studies: For all of the studies that were included, the methodological quality meant that there was a small chance of error or uncertainty due to bias. All the studies gave detailed information about how the randomization was done, such as whether it was done by computer programs or by picking random numbers by hand [52]. All of the other 7 studies were fully random, except for the two studies by Elwatidy *et al*. and Tsutsumimoto *et al*. that used an odd and even numbering system. In one study [53], it wasn't clear how allocation concealment worked. Six studies used double-blind methods, and three studies used a single-blind study design, which suggests that there might be a selection bias [54].

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Study characteristics: All studies focused on the back, except for one that looked at both the front and back [55, 56]. The experimental and placebo groups had the same hemoglobin, age, gender, height, weight, and American Society of Anesthesiologists (ASA) grading before surgery. When it came to scoliosis surgeries, there wasn't a big difference between the experimental and placebo groups in terms of fusion ranges. In all studies, general anaesthesia was used during surgery and a placebo (normal saline) was always given. For each study, TXA was given through an IV, but different doses (10-100 mg/kg) and times of delivery were used. A single IV bolus was given before surgery in 2 studies [57]. In 2 studies, the drug was given through a slow infusion of 1 g every two hours. In the other five studies, boluses were given more than once. Either a clinical evaluation or a routine ultrasound was used to check for DVT. In five studies, a transfusion trigger was set off, which led to lower levels of hemoglobin or hematocrit [58].

Discussion

Blood loss during and after spinal surgery is a major concern. Because of this, patients often need transfusions, which may pose more risks. So, we need to learn more about how hemostatic techniques work in the real world. TXA, a synthetic antifibrinolytic agent, has been shown to reduce the need for blood transfusions, preventing problems like transfusion reactions and the formation of spinal epidural hematomas. Evaluation of the dose- and time-related effectiveness of current hemostatic techniques, as well as their wider use, could reduce the need for blood transfusions in clinical spinal surgery patients and improve patient outcomes overall.

When someone has surgery on their spine, they often need a blood transfusion. A lot of evidence shows that patients who have this kind of surgery and get a blood transfusion are at risk for a number of moderate and serious problems. So, there needs to be a safe and effective way to reduce the number of blood units these patients need during and right after surgery. TXA has been used to treat major bleeding after spinal surgery on adults [59]. Zufferey *et al*. did a meta-analysis of 23 trials with 1,268 participants to look at the safety and effectiveness of intravenous TXA and epsilon-aminocaproic acid. The results showed that these agents could reduce the risk of allogeneic erythrocyte transfusion during orthopedic surgeries by a large amount.

A lot of research has been done to show that these agents work, but some studies have questioned whether or not TXA is effective at stopping intraoperative blood loss [60]. Even though both TXA and aprotinin work, TXA has been thought to be a better choice because it can be used in clinical settings. So, there is still debate about whether or not TXA is the best way to reduce the need for blood transfusions in spinal surgery. TXA has been shown to work in many spinal surgeries on adults, teens and children.

This suggests that it could be used as a treatment for a variety of surgical procedures. When used with other ways to save blood during surgery to fix scoliosis, TXA was shown to be effective [61]. Both in adults and teenagers, surgeries for adolescent idiopathic scoliosis had the same effects [62].

Also, when TXA was given, the amount of hemoglobin in the blood after surgery was higher, and the amount of blood lost was less. This was seen in posterior lumbar surgery and pediatric vertebral column resection. Even though TXA has been used in a lot of surgeries, the methods for measuring the amount of TXA in plasma and blood were only made recently. More research on the effects of different types of spinal surgery is needed to come up with a better treatment plan with the best dose and time to give it.

A systematic review and meta-analysis showed that antifibrinolytic agents helped reduce blood loss and the number of blood transfusions in different spinal surgery patients. This suggests that surgeons and anesthesiologists should think about using these agents during

surgery. But there are some problems with that study, such as the use of old studies and a mix of different types of studies, which could make the results of a rigorous statistical review unclear. Only RCTs and qi-RCTs were used in our meta-analysis review.

This was done to improve the quality of the methods and reduce bias-based errors. Notably, our finding shows that patients who were treated with TXA before surgery lost less blood. Also, the number of patients who needed blood transfusions from a different person was 35% lower [63]. This positive effect of IV TXA was the same no matter how much or when it was given. So that the clinical effects of TXA could be fully studied, the included studies were chosen regardless of whether or not they supported its use. For example, two of the studies did not support the routine use of TXA in spinal surgery.

In a double-blind RCT of 76 patients having spinal fixation surgery, TXA was given for 10 minutes after the anaesthesia was started. This was followed by an IV infusion of TXA at a rate of 1 mg/kg/h in 38 patients, while normal saline was used as a control in the same number of patients [64]. There was no significant difference between the TXA-treated group (12,696,690 ml) and the control group in how much blood was lost during surgery (13366550 ml). In a single-blind RCT with 40 patients getting cervical laminoplasty, TXA was given based on body weight (15 mg/kg body weight) and given 15 minutes before the first surgical incision [65]. The results were the same. The TXA-treated group lost 49.1630.6 ml of blood during surgery, which was not much different from the control group (63.4653.0 ml; P = 0.30). The difference could be because TXA was only given once in these two studies, while it was given in multiple doses in other studies with positive results. To look at the effects of dosage in larger studies, more research will need to be done. A recent meta-analysis looked at the effects of TAX on blood transfusion, thromboembolic events, and death in surgical patients. It found strong evidence that TAX reduces bleeding and the need for blood transfusions in people who have thromboembolic events like myocardial infarction, stroke, DVT and pulmonary embolism. But it is still not clear what effect TAX has on thromboembolic events and death.

Ross *et al*. did a systematic review on the relationship between the number of thrombotic events and TAX after spontaneous bleeding. They found that the number of some events, like DVT, went down with TXA treatment. When TXA was used to save blood during primary total hip and knee arthroplasty, the number of DVT, PE and arterio occlusive events also went down [66]. Even though TXA has been shown to help prevent DVT in many types of surgery, the safety and effectiveness of TXA in spinal surgery is still up for debate. In some studies, it was suggested that TXA may raise the risk of DVT and other blood clots. Gulba *et al*. showed that TXA can actually stop heparin from working, which causes patients to constantly bleed seriously [67]. We didn't find any statistically significant increases in the risk of thromboembolic events when IV TXA was given before spinal surgery. But because the study only looked at a small number of patients and recorded a small number of events, bigger studies are needed to confirm the finding [68].

Conclusions

Meta-analyses and clinical trials are showing more and more that using TXA in spine surgery can significantly reduce the amount of blood lost during surgery and the need for blood transfusions. It has been proven that TXA lowers the costs of health care that come with using blood products and lowers the risk of bad things happening after a transfusion. Even though the increased chance of thrombogenesis is still being studied, most people agree that TXA is linked to few bad outcomes and complications when given during and after spinal procedures. With more and more evidence that it is safe and effective, TXA is becoming an important tool for spine surgeons.

In conclusion, perioperative IV TXA reduces blood loss and the need for blood transfusions

during spinal surgery by a large amount. Also, giving TXA was not linked to a significant rise in the number of complications, such as DVT. TXA reduces the total amount of blood lost during surgery, which leads to better outcomes after the surgery. Because the studies were very different and there weren't that many of them, more large studies are needed to confirm the findings and figure out the best TXA doses and times to give them to spinal surgery patients.

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