Review Article

The use of tranexamic acid in spine surgery

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Abstract: Patients undergoing surgical procedures of the spine with associated large volume blood loss often require perioperative blood conservation strategies. Synthetic antifibrinolytic medications such as tranexamic acid (TXA) may reduce blood transfusion requirements and postoperative complications following spinal procedures. Studies investigating the role of TXA in spine surgery have presented promising results and have proven its safety and efficacy. However, further investigation is needed to determine the optimal dosing regimen of TXA. In this article, we provide an overview of the basic science and pharmacology of TXA. A comprehensive summary of the findings from clinical trials and a review of the literature that demonstrate the risks and benefits of TXA in spine surgery are also presented.

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

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Introduction

Complex surgical cases of the spine have been associated with significant perioperative blood loss (1,2). Postoperative clinical outcomes may be negatively impacted by the anemia, hematoma formation, and increased propensity for coagulation stemming from massive blood loss (3). The ensuing need for blood transfusions may give rise to associated risks including infections, increased long-term mortality, and transfusion reactions such as graft-host rejection and immunomodulation (4). Greater healthcare costs are associated with intra- and postoperative hemorrhage due to the cost of blood products, utilization of intraoperative blood conservation technology, and increased hospital stay and complications (5). As such, efforts have focused on maintaining red blood cell mass through the perioperative provision of antifibrinolytic agents, such as intravenous administration of tranexamic acid (TXA) (6,7). TXA is increasingly being used in spine surgery, especially in cases with expected large volume blood loss. Prior investigations have evaluated the role of TXA in reducing perioperative and postoperative blood loss, as well as reducing transfusion requirements. As such, the purpose of this narrative review is to provide a summary of the evidence pertaining to the safety and efficacy of TXA in spine surgery.

Methods and materials

Published articles in the scientific literature regarding the use of TXA in spine surgery were identified and reviewed. Relevant publications including case series studies, retrospective cohort studies, prospective studies, randomized controlled trials (RCTs), systematic reviews, and meta-analyses were searched using PubMed, Ovid MEDLINE, and CENTRAL (Cochrane Library). Results of the literature search germane to the present topic were screened by title, keywords, abstract, and then the whole publication. Articles were not restricted by the date of publication or region of origin.

History and background

First introduced to clinical practice in the 1960s, TXA has proven to be effective in reducing perioperative and traumatic bleeding, and decreasing blood transfusion requirements in various specialties including obstetric, urologic, and cardiac surgery (8). In the field of orthopedic surgery, TXA has also demonstrated its efficacy in total knee and hip arthroplasty procedures (9). Spine surgery has also seen the increasing use of TXA. Early studies evaluating its utility consisted mostly of retrospective cohort and case series studies with heterogeneous patient populations (10,11). More recent investigations have included prospective clinical trials assessing its efficacy in adolescent and adult populations undergoing various spinal procedures of differing complexity (12,13). One of the initial meta-analyses performed in 2008 on the use of TXA in spine surgery did not demonstrate a clear benefit partly due to limitations in the methodology utilized in the investigations (14). TXA was being used off-label for spinal procedures because of the lack of approved indications for the product in spine surgery. Additional systematic reviews and meta-analyses of the available literature have emphasized the need for higher-powered studies with more consistency in terms of the procedure, dosage, and regimen utilized (15,16).

Clinical pharmacology of TXA

TXA is a synthetic lysine analogue that was demonstrated to be more potent and superior to the previously used antifibrinolytic agent, epsilon-aminocaproic acid (EACA) (17). Included on the list of the World Health Organization (WHO) List of Essential Medicines, TXA has taken its place as a widely used hemostatic agent in the clinical setting (18). TXA works by interfering with the fibrinolysis through the reversible binding and competitive inhibition of the lysine moieties on the structural proteins plasminogen, plasmin, and tissue plasminogen activator (tPA) (19). It diminishes the binding ability of plasminogen and tPA to fibrin, which subsequently inhibits the activation of the zymogen plasminogen to the serine protease plasmin that would otherwise lead to the breakdown of fibrin clots (20). TXA can be administered through several routes—orally, topically, or intravenously—and has a 100% bioavailability. A 10 mg/kg intravenous administration of TXA has a half-life of approximately 80 minutes and reaches peak concentration within 1 hour after administration (21). TXA is cleared through the renal system, which means its dosage needs to be adjusted appropriately for patients who are suffering from chronic kidney disease.

Dosing regimen of TXA

The optimal dosing regimen for IV administration of TXA is unclear. Previous studies have demonstrated the clinically effective dose to be 10–15 mg/kg of body weight, with higher dosages providing diminishing benefits (16). IV administration of TXA has been shown to have systemic penetrance and absorption, with 10 mg/kg doses able to achieve as much as 80% inhibition of the fibrinolytic process in tissues (22). The IV administration of TXA in spine surgery is typically provided as a bolus with a dose range of 10 to 20 mg/kg preoperatively and with a maintenance infusion of 1 to 10 mg/kg per hour of surgical duration (19). The ideal dosing regimen of TXA in spinal surgery remains an area of continued research, with a wide variation in the protocols utilized in different institutions and practice settings.

While low doses of TXA have been determined to provide efficacy, the dose-efficacy relationship of TXA still remains a poorly understood area of research (23). Moreover, special consideration must be given for select spinal procedures such as the correction of adult spinal deformity, which has been associated with major blood loss defined as 60 mL/kg in 24 hours, or greater than 40% of a patient's total blood volume (24). In fact, close to 10% of intraoperative adverse events have been reported to be due to blood loss exceeding 5 liters (25). Therefore, the determination of a dosage regimen that retains its efficacy throughout the entirety of the perioperative period becomes even more important in complex surgical cases (26). Given that the elimination of TXA after a single-dose IV administration may take place over 2 to 3 hours, complex spine procedures may necessitate a second bolus dose given after the initial infusion. The efficacy of this regimen was studied by Raksakietisak *et al.* in their evaluation of 39 patients who received an initial bolus dose of 15 mg/kg bolus at the beginning of the procedure and an additional bolus 3 hours later. The experimental group, when compared with placebo, demonstrated less perioperative blood loss and decreased need for transfusions (27). Moving forward, investigations that further evaluate the repeated dose administration of TXA should be performed. Comparison studies of the regimen to other strategies such as the initial loading dose combined with a maintenance

infusion throughout the duration of the operation are warranted.

TXA in spine surgery

Increasing numbers of meta-analyses of RCTs in recent years are contributing to our body of knowledge regarding the hemostatic benefits of TXA in spinal surgery. Wong *et al.* administered TXA intravenously with an initial bolus dosage of 10 mg/kg and 1 mg/kg per hour of maintenance infusion until skin closure for 147 patients who underwent elective posterior instrumented spinal fusion (12). Estimated blood loss from the procedure was reduced by as much as 30% in patients who were given IV administration of TXA as measured by higher postoperative hemoglobin levels and decreased need for red blood cell saver use. Yang *et al.* conducted a meta-analysis of 9 studies comprising of 581 patients and demonstrated that patients receiving TXA perioperatively had a reduction of blood loss along with a statistically significant decrease in the need for blood transfusion (16). Raksakietisak *et al.* showed a statistically significant decrease in blood loss in patients receiving TXA following a complex laminectomy procedure. Patients who received two doses of TXA at 15 mg/kg compared to those who received placebo demonstrated decreased blood loss and decreased use of IV crystalloid fluids including packed red blood cells (27).

TXA can also be utilized for spinal procedures involving the pediatric and adolescent patient population. A prospective, randomized study by Verma *et al.* evaluated the use of TXA in 125 adolescent patients undergoing surgery for idiopathic scoliosis. TXA reduced blood but not transfusion rates (28). Schouten *et al.* indicated the superiority of TXA for patients undergoing scoliosis surgery by demonstrating an almost two-fold decrease in blood loss through TXA versus placebo (29). Yagi *et al.* concluded that patients receiving a 1 g loading dose of TXA followed by a maintenance dose of 100 mg per hour intraoperatively in scoliosis cases resulted in decreased blood loss and no greater risk of complications compared to control (11). Lastly, a single surgeon study by Lykissas *et al.* confirmed these findings with a 100 mg loading dose and 10 mg/hour infusion rate of TXA in adolescent patients undergoing surgery for scoliosis (30).

TXA has been used to achieve greater rates of hemostasis in the cervical spine and in cases of spinal oncology (31). Elwatidy *et al.* conducted an RCT of 64 patients undergoing complex spinal cases involving multiple vertebral levels who were administered high doses of IV TXA (2 grams of loading dose followed by a maintenance dose of 100 mg per hour up to 5 hours postoperatively) (13). The authors reported a reduction of blood loss by 48% intraoperatively and 55% postoperatively in terms of drain output. These clinical trials help to establish the key role that TXA can play in helping to achieve hemostasis in spinal surgery and suggests its safety and efficacy in consistently decreasing perioperative blood loss and the consequent need for blood transfusions.

While our review of published literature uncovered mostly published articles that supported the use and efficacy of TXA, there were a few studies that presented opposing findings. Peters *et al.* conducted a prospective, randomized trial that used a TXA dosage of 10 mg/kg for induction with 1 mg/kg per hour for infusion. The reduction of bleeding in the experimental group was not statistically different from the control group (32). Farrokhi *et al.* demonstrated that patients undergoing posterior instrumentation and fusion of the thoracic or lumbar spine did not experience a difference of intraoperative blood loss or the need for blood products (33). Nevertheless, it is evident that increasing numbers of clinical trials and investigations are proving TXA to be an effective solution in the perioperative control of blood loss for spine surgeons.

Possible adverse effects arising from the systemic absorption and distribution of TXA must also be taken into consideration. Circulation within the central nervous system (CNS) after crossing the blood-brain barrier can lead to concentrations as high as 10% by volume in the cerebrospinal fluid (CSF) (19). Prior literature has reported on the incidence of postoperative epileptic seizures in patients predisposed to convulsive activity (34). Other investigations have reported the potential neurotoxicity of TXA on CNS tissue through the interference of the inhibitory GABAA and glycine receptors. Rare but serious side effects afflicting other organ systems, such as changes in the visual perception of color or necrosis of the renal cortex have also been described (35,36).

Perhaps the most significant concern regarding the use of TXA is the potential for increased thrombogenesis and its related adverse events such as venous thromboembolism (VTE) (37). A review of the available meta-analyses demonstrates there is still inconclusive evidence for increased risk of developing thromboembolic complications due to TXA. Previous RCTs have been limited by small

sample sizes and flaws in the methodology, such as the lack of control for reporting bias (38).

Conclusions

A growing body of meta-analyses and clinical trials are demonstrating that the use of TXA in spine surgery can lead to significant reduction of intraoperative blood loss and the need for blood transfusions. TXA has been confirmed to reduce healthcare costs associated with the use of blood products and decrease the risk of adverse events arising from transfusions. Although the increased potential for thrombogenesis remains an area of continued research, the general consensus is that TXA is associated with relatively few unfavorable outcomes and complications following peri- and postoperative administration in spinal procedures. With increasing evidence for its safety and efficacy, TXA is proving to be an essential tool in the spine surgeon's armamentarium.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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