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Review Article

Tranexamic Acid and Total Knee Arthroplasty

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Abstract

Total knee arthroplasty (TKA) is one of the most commonly performed elective orthopaedic procedures in the United States. TKA provides significant pain relief and improvement in quality of life. However, TKA surgery has been shown to have significant blood loss that sometimes requires blood transfusions. Transfusion of blood products is not a benign procedure and is associated with many risks such as; periprosthetic joint infection, lengthen hospital stay, and increased cost for the patient and payers. Tranexamic acid (TXA), an inhibitor of fibrinolysis, has been used in TKA to control blood loss. Because of the TXA's mode of action, there have been longstanding concerns about the possibilities of adverse effects, such as thrombosis, pulmonary embolism, and renal failure. Multiple studies and review articles have shown that tranexamic acid is efficacious and does not significantly increase the risk of stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism, and renal failure. Intravenous and intra-articular (topical) TXA injection has been shown to be efficacious in controlling blood loss and transfusion requirement, with increasing concentration being more efficacious. Common dosage of IV TXA is 10mg/kg prior to tourniquet inflation and during closure. Common dosage for intra-articular TXA is 1.5g/100ml of normal saline during closure or through a drain. This article presents a review of literature on intravenous and intra-articular (topical) use of TXA in TKA.

BACKGROUND

Total knee arthroplasty (TKA) is one of the most commonly performed elective orthopaedic procedures in the United States [1]. By 2030, the number is estimated to grow by 673% to 3.48 million TKAs performed a year [1]. TKA provides significant pain relief and improvement in quality of life [2]. However TKA surgery is not without complications. Of note is the risk of bleeding and requirement for transfusion. TKA surgery has been shown to have significant blood loss that sometimes requires blood transfusions [3-5]. Bleeding during total knee arthroplasty can be from different factors such as patient characteristics (hemophiliac, anticoagulation, cirrhosis, etc.) and surgical technique (bone cuts, soft tissues dissection, blood vessel injury). In some studies, transfusion rate after TKA has been as high as 30% [4]. Transfusion of blood products is not a benign procedure and is associated with many possible risks such as infection, acute systemic reactions, and death [6]. Transfusions also increase rehabilitation time and lengthen hospital stay and cost for the patient and payers [7,8]. Therefore, controlling blood loss during and after surgery is an important goal in order to achieve good results in TKA. One such method is to use tranexamic acid during TKA surgery.

Tranexamic acid has been available for more than 20 years, with its medical uses ranging from dental extractions, tonsillectomy, cardiac surgery, prostate surgery, menstrual bleeding control, and treatment for patients with hemophilia [9,10,11].The US Food and Drug Administration (FDA) first approved intravenous tranexamic acid in 1986 for the short-term use in hemophiliac patients undergoing tooth extraction. Recently, the FDA approved the oral form of TXA for the treatment of menorrhagia [9,10,11]. Tranexamic acid used in trauma and orthopaedic surgery are considered "off-label". Primary fibrinolysis occurs in many trauma patients and is integral in the pathogenesis of the acute coagulopathy of trauma (ACOT) [12,13]. Presence of hyperfibrinolysis is associated with high mortality rates [12,13]. Use of antifibrinolytic agents such as tranexamic acid (TXA) has been shown to improve mortality rate in trauma patients with hyperfibrinolysis [12]. Furthermore tranexamic acid has been extensively studied in trauma patients and other major surgical sub-specialties (such as thoracic surgery) to decrease blood loss and mortality. In orthopaedics, tranexamic acid has recently been gaining favor due to its efficacy and ease of use, both in IV and topical usage. Cost, bioavailability, efficacy and low complications have helped to increase the common use of TXA in TKA [14,15].

PATHOPHYSIOLOGY

Tranexamic acid, a lysine analog, is an inhibitor of fibrinolysis

(Figure 1). Tranexamic acid functions by inhibiting plasminogen activation. With trauma or surgery, damage occurs to the endothelium of blood vessels that results in the exposure of collagen and release of tissue factors. These tissue factors and exposed collagen will activate the extrinsic and intrinsic coagulation cascade and allow for formation of thrombin and the creation of clot with the assistance of platelets (Figure 2) [16]. This in turn will allow for blood to clot and prevent excessive blood loss. Plasminogen, which is a zymogen that is made in the liver and released into the bloodstream, binds to clots and cell surfaces. Plasminogen is converted to its active form plasmin via enzymes such as tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), kallikrein, and factor XII (Hageman factor) [17]. Plasmin in turn cleaves the fibrin clots into fibrin degradation products, allowing clots to dissolve. Therefore by competitively inhibiting the conversion of plasminogen to plasmin, tranexamic acid allows mature fibrin clots to be maintained and coagulation to continue uninhibited.

The structure of tranexamic acid is composed of C8H15N02 (Figure 1). At room temperature, tranexamic acid has a solid form but is freely soluble in water. After ingestion or injected intravenously, tranexamic acid has a short half-life of about 2-3 hours and is rapidly excreted via the kidneys. In adults, tranexamic acid is typically administered with a loading dose of 10mg/kg, followed by infusion of 1mg/kg/h [18]. The values were primarily based on studies of antifibrinolytic uses during cardiac surgery [18]. In those studies, tranexamic acid has been shown to be effective in reducing blood loss and transfusion without a significant risks for increased mortality, stroke, myocardial infarction, or renal failure [18-20]. However, because of the TXA's mode of action to prevent plasminogen activation, there have been longstanding concerns about the possibilities of adverse effects, with the most attention directed at the risk of thrombosis and renal failure. There are few case reports which showed that tranexamic acid is associated with a higher rate of pulmonary embolism [21,22,23,24]. To address those concerns, a recent Cochrane review showed that tranexamic acid does not significantly increase the risk of stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism, and renal failure [25]. Similarly, the CRASH-2 study did not show any statistically significant increase in vascular occlusive events in over 20,000 trauma patients with significant hemorrhage treated with TXA [26]. Multiple studies and systemic reviews have shown that intravenous injection of TXA in TKA do not increase the risk of DVT or PE [27-30]. In a systematic review of RCTs, Alshryda et al showed that intravenous TXA does not increase the risk of DVT or PE compared control groups (treated with normal saline) [27]. The authors' treatment dosage of TXA ranged from 500mg-3g or 10-20mg/kg. In 13 RCTs, deep vein thrombosis was found in 44 of 409 patients receiving TXA and 22 of 392 patients receiving normal saline (p=0.98). In 18 RCTs with a combined 971 patients, 1 patient was found to have a PE in the TXA group compared to 4 patients in the control group (p=0.5).

For bilateral total knee arthroplasty, Karam et al showed that intravenous injection of TXA reduced the need for blood products without any significant effect on venous thromboembolic events [30]. In their retrospective study, 37 of 87 patients (37 treatment group, 50 control group) received one dose of TAX (20mg/kg) prior to incision. No patient, in both the control and experiment group, suffered from a venous thromboembolic event. Karam et al concluded that TXA is a safe and efficacious in reducing blood loss in bilateral total knee arthroplasty procedures [30].

Similarly, intra-articular topical application of TXA has not been shown to increase DVT or PE occurrence in total knee arthroplasty [32,38]. In a recent prospective double-blinded RCT of 101 patients, Georgiadis et al evaluated the effects of topical TXA application in total knee arthroplasty [36]. Two grams of TXA in 75ml of normal saline versus 75ml of normal saline alone as a control were topically placed in the arthrotomy after cementation of the components. Four patients in the TXA group developed a DVT and 1 patient developed a PE compared with 9 and 2 in the control group (p = 0.234, p = 1.00, respectively). Like many other studies, they conclude that TXA does not significantly increase the rate of DVT or PE while effectively decreasing blood loss.

Even so, the use of tranexamic acid is not without risks. There are case reports which showe that accidental application of tranexamic acid in spinal anesthesia may cause convulsions [39]. High-dose tranexamic acid (61-259mg/kg) is also shown to be associated with non-ischemic clinical seizures in cardiac surgical patients [40].This is likely due to the fact that tranexamic acid has a direct effect on CNS cells by inhibiting GABA receptor [41].

CLINICAL RESULTS

Drawing on the experience gained from the cardiac surgery cases, Capdevila et al were among the first to use aprotinin, an antifibrinolytic, in orthopaedic surgery [42]. They showed that aprotinin was effective in reducing blood loss and transfusion requirements in patients undergoing major orthopaedic surgery of the hip or pelvis [42]. In 1997, Hiippala et al showed that intravenous tranexamic acid significantly reduces blood loss and transfusion units compared to placebo [43]. In their randomized study, 75 patients were randomized to receive either intravenous tranexamic acid or saline placebo. Tranexamic acid group showed reduction in blood loss (689+/-289 ml) compared to placebo (1,509+/-643 ml). Mean transfused units was similarly reduced, from 3.1 +/-1.6 in placebo compare to 1.0+/-1.2 in tranexamic group. Subsequent studies, systemic reviews, and meta-analysis in total knee arthroplasty have confirmed these results for intravenous tranexamic acid [44,47]. In a recent meta-analysis in 2013, Tan et al confirmed the effectiveness of intravenous tranexamic acid in reducing blood loss and transfusion units while having no significant risk of deep vein thrombosis or pulmonary embolism [48]. Dosage of intravenous tranexamic acid was shown to vary for different studies; however, optimal dose ranges from 10-20mg/kg before deflation of tourniquet and 10-20mg/kg 3 hours after first IV dose [48]. Studies have shown that repeat-doses of intravenous tranexamic acid further decrease blood loss in total knee arthroplasty [49,50]. Additionally, intravenous tranexamic acid is effective in mini-

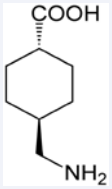

Figure 1 Chemical structure of tranexamic acid.

incision total knee arthroplasty, revision total knee arthroplasty, and bilateral total knee arthroplasty in reducing blood loss. In a randomized control trial of 151 patients, Lin et al randomly assigned patients who underwent unilateral minimally invasive total knee arthroplasty to one of 3 groups: 1) a placebo group (50 patients); 2) a one-dose tranexamic acid group (52 patients), who received one injection of tranexamic acid (10 mg/kg) intra-operatively on deflation of the tourniquet; and 3) a two-dose tranexamic acid group (49 patients), who received two injections of tranexamic acid (10 mg/kg) given pre-operatively and intra-operatively [51]. They demonstrated that one intra-operative dose of tranexamic acid was as effective as two doses for blood conservation during mini incision total knee arthroplasty.

In a study by Aguilera et al, the effect of intravenous tranexamic acid in reducing blood loss and blood transfusion in revision total knee arthroplasty was evaluated [52]. In this study, patients who received tranexamic acid had significantly lower amounts of blood loss (p=0.015); however, the rate of transfusion was not statistically lower in the tranexamic acid group (p=0.057). No adverse events were observed in the studied patients. Similarly, MacGillivray et al evaluated the effects of 2-dosage regimen of tranexamic acid (10mg/kg and 15mg/kg) versus placebo on blood loss and transfusion requirement among 60 patients undergoing bilateral total knee arthroplasty [53]. They found an increased blood loss amendable to auto-transfusion in the control group compared to the 10mg/kg and 15mg/kg case groups (918ml, 678ml, and 462ml, respectively).

Topical vs. Intravenous

Due to safety concerns with intravenous administration of tranexamic acid, there has been a growing interest in the topical use of tranexamic acid for prevention of bleeding in orthopaedics. Since topical application of tranexamic acid can directly target the source of bleeding, it can be considered to be a safer method of delivery while decreasing potential systemic effects. Similar to intravenous tranexamic acid, multiple studies and meta-analysis confirm the safety and efficacy of topical intraarticular administration of tranexamic acid [32-38,54-56]. In a recent meta-analysis, Panteli et al examined the safety and efficacy of topical application of tranexamic acid in total knee arthroplasty in 7 studies, mainly consisting of RCT and one prospective case control study [37]. The authors' topical application of tranexamic acid ranges from 500mg to 3g mixed with normal saline solution

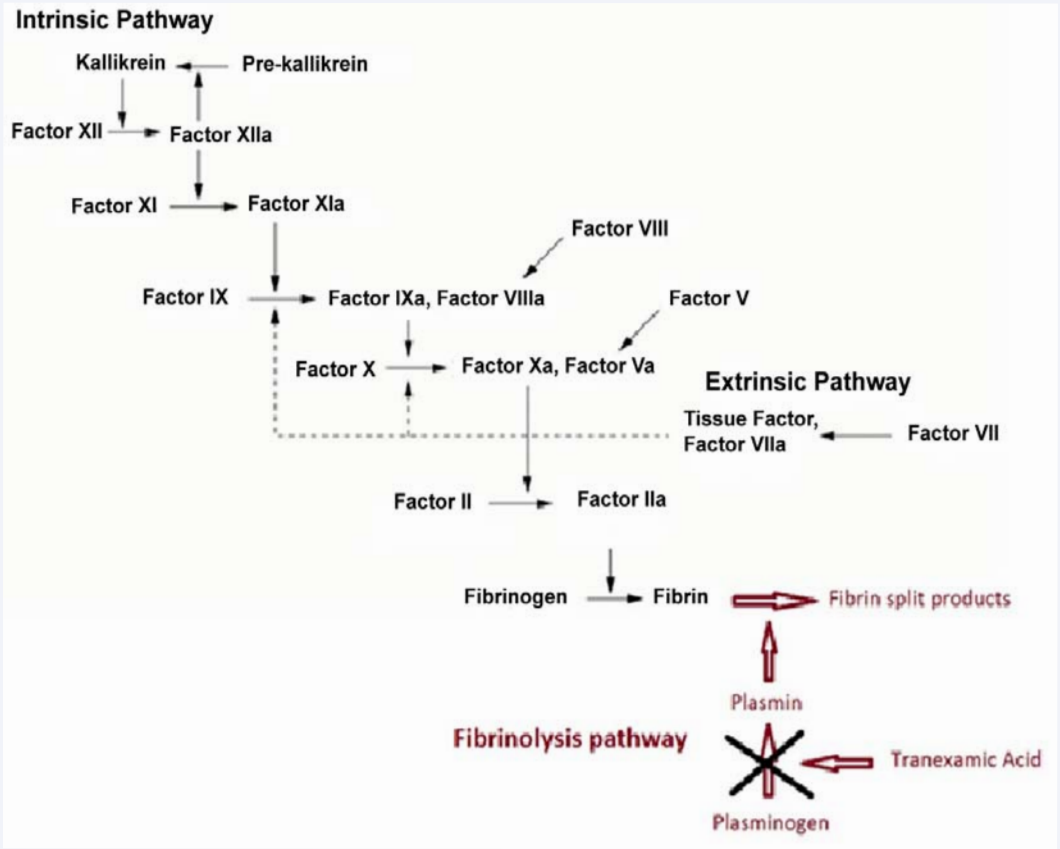

Figure 2 Tranexamic acid mechanism of action in the coagulation pathways.

Table 1: Data from multiple studies on methods of topical tranexamic acid application.

Authors	Year	Type of Study	Intervention	Method of Administration
Roy SP	2012	RCT	500mg TAX/ 5ml NS	Intra-articular administration through drain
Ishida K	2011	Quasi	2gr TAX/ 20ml NS	Intra-articular administration through drain and 30 min clamp
Maniar RN	2012	Prospective Case-Control	3gr TAX/ 100ml NS	Local application 5 min before tourniquet release
Sa-Ngasoongsong	2011	RCT	250mg TAX/ 25ml NS	Intra-articular injection after fascia closure and 2 hour clamp
Wong J	2010	RCT	1.5gr TAX/ 100ml NS	Local application for 5 min at end of procedure
Wind TC	2013	Retrospective Review	1gr TAX then 1gr TAX at closure	Local application one dose during initial incision, another at closure
Mutsuzaki H	2012	Retrospective	1gr TAX/ 100ml NS	Intra-articular administration through drain and 60 min clamp
Seo JG	2013	RCT	1.5gr TAX/ 100 ml NS	Local application vs intravenous while suturing/after closure

* Clamp = Drainage tubing clamped and suction inactive

of 5ml to 100ml. Application methods vary the most common being injection of the solution into the drain after capsule closure and clamping the drain for 30 minutes to 2 hours. Other methods include local application for 5-minutes before tourniquet release, and local application for 3-5 minutes at the conclusion of the operation. Their result showed that topical application of tranexamic acid significantly lowers blood loss and transfusion requirements after total knee arthroplasty. Sub-group analysis indicated that a higher dose of topical tranexamic acid (>2) is more efficient in reducing transfusion requirements after TKA.

Author's experience

In our institution, our tranexamic acid application protocol includes; 1gram of tranexamic acid delivered intravenously prior to inflation of the tourniquet at the start of the case and an additional 1gram of tranexamic acid during closure of the knee fascia after the tourniquet was deflated. The administration prior to inflation allows the tranexamic to distribute into the knee and help with intraoperative hemostasis. Due to the short half-life of tranexamic acid, we administer an additional dose to help with postoperative hemostasis. Additional postoperative dose has been shown to improve hemostasis after surgery [49,50]. Our administration method is similar to the other authors' reported methods in the meta-analysis by Tan et al. [48] (Table 1).

SUMMARY

From the multitude of studies and reviews on tranexamic acid use in trauma, orthopaedics, and total joint surgeries, we can assume that tranexamic acid is safe and efficacious for decreasing blood loss [27-38,42-46]. Intravenous use in total knee arthroplasty has been extensively studied and has shown good results [27-31,42-50]. Reported uses in min-incision, bilateral and revision total knee arthroplasty are few, but are also promising [51-53]. Topical use on the other hand is still up and coming, although early results are promising [32-38,52-56]. In a direct comparison between intravenous and intra-articular topical tranexamic acid application during unilateral total knee arthroplasty, Seo et al showed better efficacy with intra-articular administration [38]. In their study, 150 patients were prospectively allocated to 3 groups (intravenous, intra-articular, and placebo). During closure, 1.5g/100ml saline was administered intra-articularly or intravenously, and an equivalent volume was administered intravenously or intra-articularly in the placebo group. Their results showed mean blood loss in placebo, intravenous, and intra-articular to be 833 +/-412ml, 528 +/-227, and 426 +/- 197, respectively. About 80% of the intra-articular group, 66% of the intravenous group, and 6% in the placebo group did not require transfusion for any reason, and the mean transfusion amount was 129.6ml, 273.6ml, and 920.8ml, respectively. Topical use of tranexamic acid may have the potential of directly inhibiting fibrinolysis at the injured site and limit systemic effects of tranexamic acid; however, this benefit has not been proven yet. A study by Ishida et al showed that intraarticular tranexamic acid application not only reduces blood loss but also decreases knee joint swelling after total knee arthroplasty [56]. Although topical tranexamic acid has shown good results, further studies are needed to find the optimal application dose, timing, and frequency of administration. Furthermore, since intra-articular tranexamic acid directly bathes polyethylene, its effects on wear needs further investigation. On a systemic level, high dose tranexamic acid (61-259mg/kg) has been shown to be associated with seizures during cardiac procedures [40]. It is unlikely for orthopaedic surgeons to use such high dosages, however further studies need to determine optimal dosing to minimize potential risks.

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