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REVIEW

Utilization of Tranexamic Acid in Surgical Orthopaedic Practice: Indications and Current Considerations

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Aryan Haratian
Tara Shelby
Laith K Hasan
Ioanna K Bolia
Alexander E Weber
Frank A Petrigliano

USC Epstein Family Center for Sports Medicine at Keck Medicine of USC, Los Angeles, CA, USA

Abstract: Tranexamic acid (TXA) is a lysine analog that exhibits an anti-fibrinolytic effect by directly preventing the activation of plasminogen as well as inhibiting activated plasmin from degrading fibrin clots, thereby promoting hemostasis and reducing the duration and quantity of blood loss. The aims of this study were to summarize the indications, routes of administration, safety, and clinical outcomes of TXA use throughout the different subspecialities in orthopedic surgery. Given that orthopedic procedures such as TKA, THA, fracture fixation, and various spine surgeries involve significant intraoperative blood loss, TXA is indicated in providing effective perioperative hemostasis. Additionally, use of TXA in orthopedic trauma has been indicated as a measure to reduce blood loss especially in a group with potential for hemodynamic compromise. TXA has been implicated in reducing the risk of blood transfusions in orthopedic trauma, joint surgery, and spine surgery, although this effect is not seen as prominently in sports medicine procedures. There remains disagreement in literature as to whether TXA via any route of administration can improve other clinically significant outcomes such as hospital length of stay and total operative time. Procedures that rely extensively on clarity on visualization of the surgical field such as knee and shoulder arthroscopies can greatly benefit from the use of TXA, thereby leading to less intraoperative bleeding, with better visual clarity of the surgical field. While most studies agree thrombosis due to TXA is unlikely, new research in cells and animal models are evaluating whether TXA can negatively impact other aspects of musculoskeletal physiology, however with conflicting results thus far. As of now, TXA remains a safe and effective means of promoting hemostasis and reducing intraoperative blood loss in orthopedic surgery.

Keywords: tranexamic acid, TXA, orthopaedic surgery, operative blood loss, transfusion rate, outcomes

Introduction

Tranexamic acid (TXA) is a lysine analog that exhibits an anti-fibrinolytic effect by directly preventing the activation of plasminogen as well as inhibiting activated plasmin from degrading fibrin clots.[1] These properties of TXA promote hemostasis and thereby can reduce the duration and quantity of blood loss.[1,2] As such, TXA has been listed on the World Health Organization's (WHO) List of Essential Medicines and has been utilized in various fields of medicine including Obstetrics, General Surgery, and Orthopedic Surgery.[3–7] Given the nature of surgical procedures, with the need to maximize hemostasis for patient stability as well as for adequate visualization of the surgical field, the use of adjunctive TXA perioperatively has become more widely

Correspondence: Frank A Petrigliano
USC Epstein Family Center for Sports Medicine at Keck Medicine of USC, Los Angeles, CA, USA
Tel +1 323 442-5822
Email Frank.Petrigliano@med.usc.edu

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implemented in recent years. The CRASH-2 trial was the first large scale randomized controlled trial (RCT) that evaluated the use of TXA in over 20,000 trauma patients.[8] A similar study explored the use of intravenous TXA in military personnel with combat injuries (MATTERs study) and noted that those receiving TXA had lower mortality particularly in patients that necessitated large quantities of blood transfusions.[9] The promising results from these studies have prompted greater utilization of the drug and stimulated further investigations to better elucidate the role of TXA in surgical practice.

Multiple routes of TXA administration have been described in current surgical practice including intravenous (IV) most commonly; however, topical and intra-articular (IA) administration in the case of joint surgery have also described. Various dosing regimens have also been used including bolus vs continuous, and single vs multiple doses, as well as variations in the timing of dose administration in the preoperative, intraoperative, or postoperative period. This review intends to summarize current evidence on the use of TXA in surgical orthopedic practice, evaluating indications, routes of administration, safety, and patient outcomes. The results of our review are summarized in Table 1.

Joint Replacement Surgery

Hip and Knee Arthroplasty

Outside of General Surgery, the use of TXA has been well documented in Orthopedic Surgery, most predominantly in total hip arthroplasty (THA) and total knee arthroplasty (TKA). Both procedures are linked to substantial blood loss, influencing procedure outcomes such as hospital stay length and the need for costly allogenic blood transfusions that can lead to both transfusion reactions and secondary infections further putting strain on hospital resources as well as the cost of patient care.[10–13] Various routes of TXA administration in arthroplasty have been discussed in literature, with the most prominent being intravenous (IV), topical, and oral.

While optimal route of delivery remains controversial, IV remains the most common route of TXA administration. Various regimens of IV dosages and timings have been offered, with studies showing multiple administrations to be more effective than a single dose.[14–17] Lei et al in a RCT of 132 patients undergoing TKA demonstrated a reduction in blood loss, postoperative pain, and markers of inflammation such as C-Reactive Protein (CRP) and interleukin-6 (IL-6) using a relatively high dosage bolus of 60 mg/kg preoperatively, followed by five subsequent administrations of TXA intraoperatively.[15] Zhang et al conducted a RCT of 175 TKA patients receiving a total of six doses of IV TXA also demonstrated decreased hidden blood loss all without a significant increase in incidence of thromboembolic events as compared to the placebo and single-dose TXA groups.[18]

Several studies and meta-analyses have shown that IV and topical use have similar safety and efficacy during both TKA and THA.[12,19,20] A meta-analysis of 32 randomized control trials conducted by Zhao et al showed IV TXA use in THA as superior in decreasing transfusion need and topical TXA as superior in reducing total blood loss.[20] A direct comparison resulted in no significant differences between the two deliveries, which is consistent with previous meta-analyses in delivery of TXA in THA procedures.[20–22] The authors recognized short follow-up times of the RCTs potentially confounded the number of postoperative complications. Alternatively, while Wei et al also found the two delivery methods to show no significant differences in blood loss or postoperative differences in thromboembolic events in TKA, the topical group showed a significantly lower pain score than the IV group which the authors believe warrant further investigation.[12] These results were further validated in a study by Laoruengthana et al that demonstrated a reduction in postoperative morphine requirement as well as subjective visual analog scale (VAS) pain scores after the use of IA TXA intraoperatively with the proposed mechanism of pain reduction speculated to be a decrease in postoperative inflammation and surgical site swelling.[23] A meta-analysis conducted by Xie et al of 18 RCTs of TXA on TKA and THA found IV to be associated with smaller decreases in hemoglobin before and after subgroup analysis.[24]

Other routes of administration, such as combined and oral, are gaining prominence. Combined administration of topical and IV have been shown to not only match but possibly exceed the efficacy of the administration individually.[25–27] Zhang et al conducted a meta-analysis of seven studies showed lower transfusion rates, hemoglobin decline and total blood loss in the combined group compared to the individual administrations.[25] Authors cite the need for higher quality RCTs to support recommendations of combined delivery.

Multiple studies have also cited the clinical efficacy (lower total blood loss, transfusion rates, limited thromboembolic events, and positive clinical outcomes) for oral

Table 1 Summary of Current Evidence on Use of TXA in Orthopedic Surgery

	Name of Study	OP	Type	Population	Methods	Conclusion
Arthroplasty	Lei et al, 2020[14]	TKA	RCT	132 patients	Patients groups: (A) no TXA (B) before incision, 3, 6, and 12 h later (C) before incision, 3, 6, 12, and 18 h later (D) before incision, 3, 6, 12, 18, and 24 h later	- A high initial-dose (60 mg/kg) IV-TXA before surgery followed by five doses is an effective approach to reduce blood loss, provide additional fibrinolysis and inflammation control, and ameliorate postoperative pain following TKA. - This will not increase the risk of treatment-related complications.
	Zhang et al, 2021[18]	TKA	RCT	175 patients	Patients groups (A) placebo (B) a single preoperative dose of 20 mg/kg IV-TXA (C) six-dose IV-TXA from the beginning of the procedure to subsequent 24 hours with the total dosage more than 6 g	The administration of six-dose IV-TXA during the first 24 hours resulted in reduced HBL following TKA without a measured increase in thromboembolic events.
	Zhao et al, 2019[20]	THA	Meta analysis	32 RCTs 2476 patients		Intravenous TXA may be the best way to reduce the need for transfusion and total blood loss.
	Xie et al, 2017[24]	TKA THA	RCT	18 RCTs involving TKA and 4 RCTs involving THA 2260 patients		- Topical and intravenous tranexamic acid have similar transfusion requirements and safety in THA and TKA. - Intravenous injection is associated with a smaller maximum drop in hemoglobin.
	Zhang et al, 2017[25]	THA	Meta analysis	7 RCTs 1762 patients	Combined application versus individual topical and intravenous application of tranexamic acid	The combined application showed lower transfusion rates, hemoglobin decline and total blood loss compared to the individual administrations.
	Yu et al 2017[38]	SA	Meta analysis	Two RCTs and 2 non-RCTs 580 patients		TXA in SA decreases postoperative hemoglobin reduction, drainage volume, and total blood loss and does not increase the risk of complications
	Rojas et al, 2021[37]	SA	Meta analysis	4 RCTs 375 patients		There was no conclusive evidence for a positive effect of tranexamic acid upon transfusion rate, infection rates or hematoma formation in patients undergoing primary shoulder arthroplasty.
	Abildgaard et al, 2016[36]	SA	Retrospective comparison	77 TSAs and 94 RTSAs performed in 168 patients.		Use of TXA perioperatively in patients undergoing primary shoulder arthroplasty can decrease perioperative blood loss, change in Hgb and Hct, and postoperative drain output

(*Continued*)

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Table 1 (Continued).

	Name of Study	OP	Type	Population	Methods	Conclusion
Trauma	Zhu et al, 2018[40]	ITF	Meta analysis	7 RCTs 746 patients		- Administration of TXA in Intertrochanteric Fracture Surgery significantly reduced surgical blood loss and total blood loss - It had no significant effect on transfusion rate, postoperative drainage, and the risk of thromboembolic events
	Ma et al, 2021[41]	ITF	RCT	125 patients		Early IV TXA intervention was shown to reduce post-traumatic HBL and pre-operative transfusion rate in elderly patients with intertrochanteric fractures without increasing the risk of venous thrombosis.
	Zhang et al, 2018[42]	FF	Meta analysis	12 RCTs, and one was a retrospective cohort study. Approximately 1063 patients		IV and topical routes of TXA administration in patients undergoing surgical fixation for unspecified femoral fractures were both very useful in reducing the rate of blood transfusions
	Qi et al, 2019[43]	HF	Meta analysis	10 RCTs Approximately 854 patients		The use of TXA in hip fracture surgery showed a significant decrease in transfusion rates without a concurrent increase in the incidence of thromboembolic events
	Xiao et al, 2019[44]	HF	Meta analysis	11 RCTs 892 patients		Significant decrease in transfusion rates in the TXA group without a concurrent increase in the incidence of thromboembolic events
	Gausden et al, 2017[45]	TRAUMA	Meta analysis	12 studies 1333 patients		TXA reduces the risk of blood transfusion, reduces perioperative blood loss, and has no significant effect on the risk of symptomatic thromboembolic events when used in patients with orthopedic trauma surgery

Spine	Bai et al, 2019[46]	SPINE	Meta analysis	9 studies with 713 total patients		- TXA can decrease the Hb loss, TBL, IBL, PBL, and without increasing the risk of thrombotic event in patients with degenerative lumbar disc herniation, stenosis or instability who underwent PLF surgery. - There was no significant difference in blood transfusion rates between the two groups.
	He et al, 2020[47]	SPINE	RCT prospective randomized, double-blind, placebo-controlled trial	40 patients	Patients groups (A) TXA group (B) control group (placebo)	In patients undergoing transforaminal lumbar interbody fusion (TLIF), the TXA group have significantly showed reduced intraoperative hemorrhage and time to ambulation after surgery but showed similar hospital stay, postoperative drainage, time for drainage removal, postoperative Hb one day after surgery, and adverse events.
	Zhang et al, 2019[52]	SPINE	Meta analysis	11 studies (6 RCTs and 5 retrospective studies)		The use of TXA can effectively reduce intraoperative blood loss and perioperative blood transfusion in patients undergoing multiple-level spine surgery, and it can also restore hemoglobin levels after surgery.
Sports Medicine	Ersin et al, 2020[54]	SPORT SHOULDER ROTATOR CUFF	RCT	60 patients	Patients groups (A) control (Saline) (B) IV TXA	Preoperative IV TRX administration in patients undergoing arthroscopic rotator cuff repair had improved visual clarity and reduced need for high pressure and amount of irrigation fluid during the surgery
	Bayram et al, 2021[55]	SHOULDER ROTATOR CUFF	RCT	90 patients	Patients groups (A) TXA infused irrigation fluid (B) epinephrine infused irrigation fluid	Adding TXA to the irrigation fluid during arthroscopic rotator cuff repair can provide similar visual quality to the EPN infused irrigation method.
	Liu et al, 2020[57]	SHOULDER	RCT	72 patients	Patients groups (A) preoperative 1 g of IV TXA (B) preoperative placebo	- IV administration of TXA is an alternative way to improve visual clarity in arthroscopic shoulder surgery. - It also reduces subjective pain and analgesic consumption in the early postoperative period without significant side effects.
	Hartland et al, 2021[58]	SHOULDER	Meta analysis	7 RCT Approximately 708 patients	Examined the use of intraoperative TXA use in various shoulder surgery procedures including, TSA, rTSA, open Latarjet, and arthroscopic rotator cuff repair	Patients given TXA had reduced blood loss as measured by drain output
	Gao et al, 2020[59]	SHOULDER	RCT	60 patients	Observation group and control group, 30 cases in each group	- There was no significant difference in hemoglobin levels between patients given TXA and those given placebo. - The TXA group had a significant smaller shoulder circumference indicating relatively reduced swelling.

(*Continued*)

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Table 1 (Continued).

	Name of Study	OP	Type	Population	Methods	Conclusion
	Chiang et al, 2019[63]	KNEE ACL	RCT	304 patients	Patients groups (A) received a 10-mL intra-articular injection of TXA (100 mg/mL) (B) No TXA	- TXA use could significantly reduce postoperative intra-articular bleeding in the first 24 hours in patients receiving arthroscopic ACLR. - TXA may also decrease pain and the grade of hemarthrosis in the early postoperative period. - No systemic side effects or need for aspiration was noted during the follow-up period.
	Felli et al, 2019[64]	KNEE ACL	RCT	80 patients	Patients groups (A) intravenous infusion of 15 mg/kg of TXA (B) No TXA	In patients undergoing ACLR, the use of TXA can reduce hemarthrosis as well as reduce volume of blood suctioned during the operation
	Fried et al, 2021[65]	KNEE ACL	RCT	110 patients	Patients groups (A) received two 1-g boluses of IV TXA, one prior to tourniquet inflation and one prior to wound closure (B) No TXA	TXA had no significant impact on perioperative blood loss, postoperative pain, and incidence of hemarthrosis
	Ma et al, 2021[66]	KNEE ACL	RCT	120 patients	Patients groups (A) IV group, received (15 mg/kg in 100 mL of saline solution) 10 min before tourniquet release (B) IA group, received intra-articular TXA (15 mg/kg in 100 mL of saline solution) injected via the drainage tube (C) placebo group, received an equivalent volume of normal saline administered into the knee joint cavity and intravenously	- In ACL reconstruction, both intravenous administration and intra-articular injection can reduce intra-articular hemarthrosis, joint pain and swelling. - No significant difference in the efficacies of reducing hemarthrosis, joint pain and swelling was found between intravenous administration and intra-articular injection.
	Ma et al, 2021[74]	HTO	Meta analysis	5 studies 532 patients		In high tibial osteotomy, the use of TXA demonstrated reduced incidence of wound complications and smaller decreases of postoperative hemoglobin.
	Li et al, 2020[72]	HTO	Retrospective case control study	24 patients in the combined group and 21 in the solo group.	Patients groups (A) combined group, 100 mL saline containing 1 g TXA was intravenously administered before application of a tourniquet, and 20 mL saline containing 2 g TXA was injected through a drainage tube after closure of the incision (B) solo group, 100 mL of saline containing 1 g TXA was intravenously administered before application of a tourniquet	Combined use of Intravenous and topical TXA in HTO is superior to intravenous administration alone for reducing postoperative blood loss and drainage volume without thromboembolic complications.
	Yao et al, 2019[73]	HTO	Meta analysis	6 studies 665 patients	665 patients. Three studies were Peri-acetabulum (PAO), and the other three were High Tibia (HTO0	There was no difference in wound complication rates in patients receiving TXA versus placebo during HTO

Abbreviations: TKA, total knee arthroplasty; THA, total hip arthroplasty; SA, shoulder arthroplasty; ITF, intertrochanteric fracture; FF, femoral fracture; HF, hip fracture; HTO, high tibial osteotomy.

administration compared to no-TXA use for both TKA and THA.[28–32] In addition, comparisons have been made directly to intravenous administration.[30,33] Han et al and Chen et al found similar outcomes when conducting meta-analyses comparing oral to IV administration in both THA and TKA patients, with.[33,34] There were no significant differences in total blood loss, Hb loss, DVT rate, and total blood loss.[33,34] These findings are promising as the oral TXA dosage is a cheaper option, costing 70–90% less than the equivalent IV dose, however further research is needed given the relatively low frequency of oral TXA use.[35]

Shoulder Arthroplasty

In addition to hip and knee arthroplasty, a few studies have explored the use of TXA in shoulder arthroplasty.[36–38] Patients receiving shoulder arthroplasty are susceptible to large quantities of blood loss, with one study estimating a blood transfusion rate of over 7% postoperatively, and thus supplemental TXA is viewed as an attractive option for support of intraoperative hemostasis.[39] An early retrospective study reported on the outcomes of patients given IV TXA during total shoulder arthroplasty (TSA) and reverse total shoulder arthroplasty (rTSA) and reported a reduction of total blood loss and total drop in hemoglobin in patients given TXA.[36] A meta-analysis of 4 studies evaluating TXA use in shoulder arthroplasty found that TXA reduced total blood loss and hemoglobin reduction postoperative, with no increased risk of complications.[38] However, the authors also noted that TXA did not reduce the risk of blood transfusions, operation time, or hospital length of stay.[38] A more recent meta-analysis supported this claim and emphasized the lack of reduction in the risk of blood transfusions among patients receiving TXA for shoulder arthroplasty.[37] Both studies, however, were limited by the relatively low number of primary studies included and may have been potentially underpowered in detecting a significant difference in blood transfusion rates in those receiving TXA versus placebo.[37,38] This further stresses the need for larger investigations to better elucidate whether TXA improves clinical outcomes such as risk of blood transfusions, wound infections, pain, and hematoma formation after shoulder arthroplasty.

Orthopedic Trauma

Orthopedic trauma patients, particularly those with multiple open fractures and significant blood loss preoperatively, are predisposed to hypotension, anemia, and often are at risk of necessitating one or more blood transfusions.[4] Given these constellation of risk factors, additional intraoperative blood loss during surgical fixation of fractures can potentially exacerbate the deficit and increase the likelihood of further patient complications, thus highlighting the need for effective intraoperative hemostasis. For these reasons, multiple studies have explored the use of supplemental TXA to provide promote hemostasis in orthopedic trauma surgery.[40–45] One such meta-analysis by Zhu et al aggregated data from 7 RCTs with a total of 746 patients who received either TXA (through either intravenous or intramuscular routes of administration), or placebo while undergoing operative fixation for an intertrochanteric fracture.[40] Patients receiving TXA had reduced blood loss during the operation and higher average hemoglobin levels, all without increased risk of thromboembolic events.[40] While some studies included in the meta-analysis demonstrated decreased risk of blood transfusion, the analysis overall concluded that TXA did not reduce the risk of a needing a transfusion.[40] These results contrasted with a meta-analysis of 13 RCTs consisting of either IV or topical routes of TXA administration in patients undergoing surgical fixation for unspecified femoral fractures which concluded that while those receiving IV TXA exhibited a significant reduction in postoperative transfusion, patients receiving topical TXA had no significant reduction in transfusion rates and postoperative hemoglobin levels.[42] A different study of 125 elderly patients with intertrochanteric fractures who received 1g of IV TXA instead reported on the degree of hidden posttraumatic blood loss and preoperative transfusion rates. The significant reduction in hidden blood loss, as determined by hemoglobin levels, as well as the reduction in preoperative transfusions in the TXA group highlights the potential of the drug in improving patient stability and reducing the likelihood of complications associated with acute trauma.[41] Two more meta-analyses reported on patients receiving TXA while undergoing surgical fixation for unspecified hip fractures, and both noted a significant decrease in transfusion rates in the TXA group without a concurrent increase in the incidence of thromboembolic events.[43,44] A meta-analysis by Gausden et al included studies with a variety of orthopedic trauma pathologies including femoral neck, hip, intertrochanteric, calcaneal, acetabular, and femoral shaft fractures.[45] Studies consisted of those giving purely IV TXA, purely topical TXA, or a combination of IV and topical, and patients given TXA in any form had a significantly decreased blood loss and risk of blood transfusion without increased risk of thromboembolic events relative to controls.[45]

Spine Surgery

Surgical procedures involving the spine have a high propensity to cause significant blood loss leading to both the increased risk of intraoperative and postoperative patient hypotension and anemia necessitating a blood transfusion, as well as the potential for significant loss of surgical field visibility thereby prolonging and complicating procedures. To this end, multiple studies have assessed the benefit of TXA for various procedures in spine surgery.[46–53] A meta-analysis consisting of 9 studies with 713 total patients examined the use of TXA in patients undergoing posterior lumbar fusion (PLF).[46] Those receiving TXA had a significant decrease in intraoperative and postoperative blood loss, and hemoglobin decline, without any increased risk of thromboembolic events. However, it is important to note that there were no significant differences between the rates of transfusions in those given TXA versus controls. A more recent randomized controlled trial specifically examined the outcomes in patients undergoing transforaminal lumbar interbody fusion (TLIF) treated with both an IV bolus of TXA preoperatively, followed by a continuous infusion of 6–8 mg/kg/hr intraoperatively up to a maximum allotted dose of 15 mg/kg.[47] Patients given TXA had less intraoperative blood loss and were able to resume ambulation quicker than the control group. However, the authors noted that there were no significant differences in terms of hospital length of stay, hemoglobin levels, and volume of postoperative drainage.[47] Postoperative complications were similar between the two groups as well. Even in more complex, multi-level spine procedures that are especially associated with significant blood loss and can often require blood transfusions, TXA can significantly reduce blood loss and the risk of transfusions in patients undergoing these procedures.[52,53] More recent meta-analyses have aggregated RCTs, most prominently those giving IV TXA, in patients undergoing some form of spine surgery, and have further demonstrated that TXA can reduce the risk of blood transfusions in a dose-dependent manner without significantly increasing thrombosis in any circumstance.[48,51] However, these results were not observed in a similar meta-analysis including only studies where TXA was given topically, potentially indicating that the route of TXA administration can play a role in the drug's effectiveness in reducing the risk of transfusions, which contrasts with similar studies in joint surgery.[20–22,49]

Orthopedic Sports Medicine

Shoulder, Knee, and Hip Arthroscopy

Continuous and adequate visualization of the surgical field is a necessity for efficiently conducting many Sports Medicine operations such as shoulder, knee, and hip arthroscopy, as excessive bleeding can prolong and complicate procedures. TXA has been utilized via both intra-articular (IA) and IV routes of administration in shoulder surgery to promote hemostasis. A randomized controlled trial by Ersin et al involved 60 patients undergoing arthroscopic rotator cuff repair who were given either a bolus of IV TXA or saline, with attending surgeons rating the visual clarity of the field on a scale of 1–10 at the end of the procedure.[54] Those given intravenous TXA had significantly higher visual clarity scores and required lower volumes of high-pressure irrigation as compared to those given saline.[54] Another study did a comparison of TXA versus epinephrine infused irrigation fluid on visual clarity during arthroscopic rotator cuff repair.[55] Visual clarity was quantified using a VAS given to the operating surgeon, and no significant differences were noted between the TXA and epinephrine groups in VAS scores.[55,56] Liu et al conducted a randomized controlled trial involving a total of 72 patients who were received either 1 g of IV TXA or placebo preoperatively.[57] Visual clarity was measured through a Numeric Rating Scale given to the operating surgeon that ranged from 1 to 3 (poor-clear) every 15 minutes during the procedure and patient pain was quantified through subjective pain scores and postoperative analgesic consumption measured in morphine equivalents.[57] The authors noted a significantly higher visual clarity score as measured by percent of grade 3 scores and lower postoperative analgesic use, however there was no significant difference in degree of shoulder swelling, operative time, and perioperative blood loss.[57] A meta-analysis conducted by Hartland et al included a total of 7 studies with examined the use of intraoperative TXA use in various shoulder surgery procedures including, TSA, rTSA, open Latarjet, and arthroscopic rotator cuff repair, and concluded that patients given TXA had reduced blood loss as measured by drain output.[58] However, there was no significant change in hemoglobin levels between those treated with TXA and those without.[58] Another study in shoulder arthroscopy had similar findings indicating no significant difference in hemoglobin levels between patients given TXA and those given placebo, however the TXA group had a significantly smaller shoulder circumference indicating relatively reduced swelling.[59] Similar results were seen in patients given IV TXA while undergoing knee arthroscopy leading to decreased knee

swelling and pain as well as quicker return to functionality.[60,61] Patients undergoing hip arthroscopy for treatment of femoroacetabular impingement who were given TXA had decreased total blood loss, but no differences were noted in postoperative pain and operation time.[62] The effect of TXA on total blood loss and hemoglobin is less appreciated and pronounced in arthroscopy, as evidenced by the mixed results in studies, however it is possible that this might be due to the nature of arthroscopic procedures, which generally have much less blood loss on average as compared to trauma and spine procedures. That said, all studies reviewed agreed that TXA vastly improved surgical field clarity in arthroscopic procedures. Future research should also explore the link between postoperative complications due to hematoma and overall pain scores as decreased hematoma formation through the use of TXA may influence pain.

Knee Surgery

The use of TXA has been documented in patients undergoing anterior cruciate ligament reconstruction (ACLR), with studies seeking to compare both intravenous and IA routes of administration.[63–69] Chiang et al carried out a RCT evaluating IA administration of TXA in patients undergoing arthroscopic ACLR.[63] Postoperative bleeding was significantly reduced in the TXA group thereby decreasing the grade of hemarthrosis, and patients in the TXA group reported decreased pain.[63] A different study utilized an IV route of TXA administration in patients undergoing ACLR and noted reduced hemarthrosis as well as reduced volume of blood suctioned during the operation.[64] The patients who received intravenous TXA had better range of motion (ROM) and quadriceps strength postoperatively.[64] However, a more recent study by Fried et al examining use of IV TXA in patients receiving ACLR concluded that TXA had no significant impact on perioperative blood loss, postoperative pain, and incidence of hemarthrosis.[65] Furthermore, these two studies further disagreed on whether IV TXA improves ROM or quadriceps reactivation.[64,65] A recent RCT directly compared the efficacy of IV versus IA TXA in ACLR and concluded that both routes were equally effective in terms of reducing hemarthrosis, knee swelling, and knee pain.[66] These results are further backed by other studies that have consistently reported decreased postoperative blood loss, decreased incidence of knee aspiration postoperatively, as well as improved pain scores with administration of TXA during ACLR.[67–69] Similar to ACLR, high tibial osteotomies (HTO) carry a risk of hemorrhage given the necessity to expose cancellous bone during the procedure.[70–72] In addition to risk of anemia necessitating blood transfusions, the resulting hemorrhage can potentially lead to the creation of hematomas and thereby delaying postoperative healing.[70,72] In an effort to avoid these complications, TXA has been utilized both preoperatively and intraoperatively in patients receiving HTO.[72–75] While all studies reported decreased operative blood loss without increased incidence of thromboembolic events in patients receiving TXA, they also agreed that the use of TXA was not associated with a decreased risk of blood transfusion.[72–75] The most recent of these studies, a meta-analysis by Ma et al, also demonstrated reduced incidence of wound complications and smaller decreases of postoperative hemoglobin in patients receiving TXA, however these results contrasted from an earlier meta-analysis by Yao et al that indicated no difference in wound complication rates in patients receiving TXA versus placebo during HTO.[73,74] This observed contrast in results highlights the need for larger and more robust studies to evaluate the true impact of TXA in patient outcomes in sports medicine procedures such as ACLR and HTO.

Dosage and Optimal Timing of TXA Administration

Previous studies have explored differences in dosages and optimal timing of TXA administration in the perioperative period. A large multicenter RCT reported on multiple different dosing regimens for TXA in patients receiving THA including (1) single 1 g IV TXA given prior to incision, (2) 1 g IV TXA given both prior to incision and after wound closure, (3) 1 g of IV TXA preoperatively, followed by 1 g of intraoperative topical TXA, and (4) 3 doses of oral TXA with a total dose of 1.95g given.[76] All regimens were noted to be equivalent in regard to transfusion rates, postoperative hemoglobin reduction, and complication rates implying a similar hemostatic effect among the different routes of administration.[76] A prospective cohort study by Balachandar and Abuzakuk explored the use of preoperative versus intraoperative single dose of IV TXA in patients undergoing bilateral TKA and noted that while patients in the intraoperative group had a significantly lesser decrease in hemoglobin on the first day postoperatively, no significant difference was appreciated with respect to transfusion rates and drain blood loss volume.[77]

Risk of Thrombosis and Contraindications of TXA

Although TXA promotes coagulation, nearly all studies agree that there are no appreciable adverse effects in terms of pathological coagulation.[12,18,40–53,63–69] This

finding has been consistent with all routes of TXA administration including IV, topical/intra-articular, oral, and even in cases where patients were given TXA through more than one route.[20–22,25–27,63–69] The most frequently described contraindications to TXA administration include patients with histories of allergic reactions to TXA, seizures, and patients with immediate acute renal failure and chronic kidney disease.[78] Although most studies have shown no increased risk of thromboembolic events with administration of TXA, patient history of venous or arterial thrombosis continues to remain a contraindication.[78] A large-scale meta-analysis of 9067 patients involving a variety of orthopedic procedures including THA, TKA, and those involving the lower extremity showed no significant difference in incidence of thromboembolic events when compared across all orthopedic surgical procedures included, and when analyzed by individual procedure further substantiating the claim that clinical use of TXA is not associated with an increased risk of thrombosis.[79] However, a retrospective study by Myers et al conducted in a single Level I trauma center retrospective study noted threefold increased odds of venous thromboembolism in patients receiving without any benefit in survival.[80] While this study was not specifically done on patients necessitating orthopedic surgery, the contraindication displayed in the results relative to studies included in this review for orthopedic trauma surgery indicates the need for larger and more robust studies with longer follow-up times to better assess the safety of TXA in this patient group.

Other Safety Considerations and Recent Avenues in Research

While TXA is frequently implemented in current orthopedic practice and is generally considered safe, recent animal studies have yielded conflicting results regarding other previously unconsidered potential side effects from this drug. An in vitro study indicated increased cell death when human periarticular tissue was exposed to TXA at concentration of 100 mg/mL after an hour of exposure, however, there remains a question of how well these results translate to a single administration of TXA perioperatively.[81] Another in vitro study supported this conclusion and indicated that TXA has dose-dependent cytotoxicity to chondrocytes, with exposure to TXA above a dose of 20 mg/mL resulting in morphological changes promoting chondrocyte cell death.[82] However, a similar study involving in vitro assessment of clinical concentrations of TXA on osteochondral explants from an animal model concluded that there was no measurable cytotoxicity from the agent, although it is important to note that the highest concentration of TXA used in this study was 4 mg/mL.[83] An in vivo study using a rat model indicated poorer tendon healing when TXA was administered compared to placebo, although another similar study indicated that local and systemic TXA administration had no effect on healing of the Achilles tendon in rats.[84,85] Another study has examined whether TXA affects the rate of bone healing after fracture fixation in animal models and concluded that both IV and topical TXA exhibited no effect on fracture healing based on evaluation of imaging obtained 2–3 weeks postoperatively.[86] Given the mixed results and the implications that these potential musculoskeletal side effects can carry in the practice of orthopedic surgery, more studies, especially those in humans, are needed to clarify these results.

Most studies exploring the safety of TXA clinically often exclude high-risk patients prior to randomization, which in turn limits the generalizability of TXA to all orthopedic patients. Two studies have examined the use of TXA patients in high-risk patients. Porter et al conducted an institutional retrospective analysis of 38220 patients including 8877 that were classified as high risk for thrombotic complications based on their comorbidities that underwent TKA or THA and received TXA.[87] The authors reported no significant differences in both the odds of adverse outcomes and rates of thromboembolic complications between high and low risk patients. These results were supported by a similar study that noted no significant increase in thromboembolic events with TXA use in patients with severe predisposing comorbidities all while decreasing transfusion rates.[88] Although more research is needed to fully substantiate these results, these conclusions suggest that TXA may be safe to use even in patients with comorbidities that place them at a high baseline risk for thromboembolic complications.

Conclusion

TXA is widely utilized in nearly all Orthopedic Surgery subspecialties including trauma, joint, sports medicine, and spine. Many orthopedic procedures such as TKA, THA, fracture fixation, and various spine surgeries involve significant intraoperative blood loss highlighting the need for effective hemostasis, and TXA has been shown to decrease both total and/or intraoperative blood loss in all studies reviewed. Additionally, TXA has been implicated

in reducing the risk of blood transfusions in orthopedic trauma, joint surgery, and spine surgery although this effect is not seen as prominently in sports medicine procedures. Additionally, there is disagreement in literature as to whether TXA via any route of administration can improve other clinically significant outcomes such as hospital length of stay, and total operative time. Procedures that rely extensively on clarity in visualization of the surgical field such as knee and shoulder arthroscopies can greatly benefit from the use of TXA, thereby leading to less intraoperative bleeding, with multiple studies showing a significantly higher subjective rating of visual clarity by surgeons as well as a lower volume of irrigation required during these procedures. While most studies agree thrombosis due to TXA is unlikely, new research in cells and animal models is evaluating whether TXA can negatively impact other aspects of musculoskeletal physiology such as bone and tendon healing, however with conflicting results thus far. As of now, TXA continues to remain a safe and effective means of promoting hemostasis and reducing intraoperative blood loss in orthopedic surgery.

Disclosure

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