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The Efficacy and Safety of Tranexamic Acid in Total Hip and Knee Arthroplasty: A Literature Review

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Abstract

Historically, total hip arthroplasty (THA) and total knee arthroplasty (TKA) have been associated with significant perioperative blood loss and a relatively high rate of allogeneic blood transfusions. However, in recent years, tranexamic acid (TXA), a competitive inhibitor of tissue plasminogen activator, inhibiting fibrinolysis of existing thrombi, has substantially decreased the need for blood transfusion in THA and TKA. Various administration strategies have been studied, but there remains a lack of consensus on an optimal route and dosing regimen, with intravenous and topical regimens being widely used. A growing body of literature has demonstrated the safety and efficacy of TXA in primary and revision THA and TKA to reduce blood loss, allogeneic transfusions, and complications; it is associated with lowered lengths of stay, costs, and readmission rates.

Keywords

tranexamic acid, total hip arthroplasty, total knee arthroplasty, length of stay, transfusion

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Introduction

Primary and revision total hip arthroplasty (THA) and total knee arthroplasty (TKA) have historically been associated with significant perioperative blood loss, leading to the common use of allogeneic blood transfusion. Despite advances in perioperative patient optimization, neuraxial anesthesia, and restrictive transfusion thresholds, the increased use of tranexamic acid (TXA) in primary and revision THA and TKA has markedly influenced perioperative blood loss and transfusion rates [10]. With increased focus on value and perioperative outcomes, the impact of TXA use on transfusion rates, length of stay (LOS), readmissions, and overall costs has also gained increasing attention.

This article reviews the current evidence on the efficacy of TXA in decreasing blood loss and need for allogeneic transfusion, supporting its use as an integral component of THA and TKA blood management and perioperative rapid rehabilitation protocols.

Blood Loss and Transfusion Rates

In the 1980s, autologous and allogeneic transfusion rates following THA or TKA were as high as 60%, and more than 30% for allogeneic transfusions alone [5,36,65]. Gannon et al [24] evaluated blood salvage techniques in 239 patients undergoing either THA or TKA in 1989, reporting a homologous blood transfusion rate of 39% in their control group. Improvements in surgical technique and the use of hypotensive anesthesia significantly lowered these rates [3,77]. National Surgical Quality Improvement Program data from 2011 demonstrated a transfusion rate after THA of 22.2% and 18.3% after TKA [36]. Available data suggest that average blood loss following THA and TKA ranges from about 600 to 1800 mL [27,31,38]. Blood loss in contemporary THA and TKA can lead to an average decline in hemoglobin of 3 g/dL [72]. Several studies have examined risk factors for increased blood loss following THA and TKA, including preoperative anemia, older age, lower body mass index, multiple comorbidities, and increased operative time [9,57,69].

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Risks of Allogeneic Blood Transfusion

Blood management and avoidance of allogeneic transfusion following THA and TKA remain important considerations for orthopedic surgeons. The implications of allogeneic blood transfusions include impact on patient morbidity, periprosthetic joint infection (PJI) risk, LOS, and cost to the health care system [1]. Although rare, disease transmission has been reported with blood transfusions, including a 1 in 225,000 per unit risk of transmission of HIV, a 1 in 200,000 risk of hepatitis B, and a 1 in 30,000 to 150,000 risk of hepatitis C [6,15]. Allogeneic blood transfusions have also been associated with febrile reactions, reported in 1% to 3% of cases. Severe immune-mediated hemolytic reactions are more rare, at about 1 in 100,000, and these complications can be related to clerical error [6]. In general surgery literature, intraoperative blood transfusion has been associated with increased 30-day and composite mortality, highlighting the general health risk associated with blood transfusions [4]. Importantly, other complications related to transfusions include immunologic suppression or reactions, volume overload, lung injury, and transfusion-induced coagulopathy [35,77].

Multiple studies have identified blood transfusions as a risk factor for postoperative PJI for both THA and TKA [18,23,45,64]. A 2017 meta-analysis utilizing random-effect models demonstrated a significantly higher frequency of surgical-site infections in those receiving allogeneic blood transfusions, with a pooled odds ratio of 1.71 ($P = .002$) [45]. Post hoc analysis of more than 12,000 patients in the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism studies demonstrated that the rate of any infection (including postoperative wound infection, respiratory infections, urinary tract infections, and bone and joint infections) in those receiving allogeneic blood transfusion was significantly higher than in those not receiving an allogeneic transfusion (9.9% vs 7.9%, $P = .003$) [22]. However, specific analysis of bone or joint infection alone demonstrated no significant difference based on administration of allogeneic transfusion (0.4% in those receiving allogeneic transfusion vs 0.2% in the no allogeneic transfusion group; $P = .056$). Another retrospective analysis of 9245 THA and TKA patients identified allogeneic transfusion as an independent risk factor for PJI, along with higher American Society of Anesthesiologists (ASA) score, morbid obesity, bilateral arthroplasty, TKA, postoperative atrial fibrillation, myocardial infarction, urinary tract infection, and longer hospitalization [64]. This and other work highlight the complex and multifactorial risk associated with blood transfusion in patients undergoing THA and TKA.

The Cost of Blood Transfusions

Blood transfusions are associated with increased LOS and overall cost [5,7,68]. The estimated cost of resources related to obtaining, storing, testing, and administering a single unit of blood for transfusion ranges from $700 to $1130 [34]. Historically, when considering the total cost allocation for primary TKA, blood management has accounted for about 2.5% of the overall allocation [37,48]. A single institution case–control study from 2009 to 2013 on TXA use in THA found the institutional cost of a single unit of packed red blood cells to be $1130, with each additional unit being $291/unit [35]. They also note that if a reaction to the first unit was encountered, the cost was $1197/reaction. Another study with evaluation of Nationwide Inpatient Sample data from 2005 through 2008 demonstrated that the mean LOS after primary THA was longer by approximately 1 day for those who received a blood transfusion, translating to a 14% to 17% higher mean of associated hospital charges [7].

Tranexamic Acid

First introduced in the 1960s and gaining widespread use in gynecology, TXA is a synthetic analog of the amino acid lysine. Tranexamic acid inhibits plasminogen activation to plasmin through competitive inhibition of the 5 lysine-binding site on the surface of plasminogen [39,63]. It also acts as a competitive inhibitor of tissue plasminogen activator, leading to inhibition of fibrinolysis. The pharmacokinetics of TXA include a half-life of 120 minutes and distribution throughout all tissues in the body [19].

The ease of use and low cost associated with TXA make it an attractive approach to blood conservation, particularly in conjunction with hypotensive anesthesia and restrictive transfusion protocols [10,77]. Importantly, TXA is not a procoagulant; rather, it inhibits fibrinolysis of existing thrombi [10]. Jules-Elysee et al [40] performed a randomized controlled trial (RCT) of patients undergoing TKA, evaluating topical TXA versus 2-dose IV TXA, comparing plasmin-anti-plasmin (PAP, a measure of fibrinolysis) and prothrombin fragment 1.2 (PF1.2, a marker of thrombin generation). Systemic PAP levels were comparable between the topical and IV TXA groups 1 hour after the tourniquet was deflated, while lower PAP levels (indicative of higher antifibrinolytic activity) were noted in the IV TXA group 4 hours after the tourniquet was released (after patients had received a second IV TXA dose). The PF1.2 levels were similar between the 2 groups even after a second IV dose of TXA, which the authors propose suggests TXA does not increase the risk of thrombosis.

Impact of TXA in Primary Arthroplasty

With the increased use of TXA in total joint arthroplasty (TJA) in recent decades, there has been a significant decrease in blood loss and transfusion rates. Recent analyses suggest that following primary TKA, the transfusion rate ranges between 1% and 2%, a notable decrease from aforementioned reported rates prior to the use of TXA

[11,29]. A 2011 meta-analysis of available RCTs demonstrated that TXA use reduced total blood loss by a mean of 591 mL ($P < .001$) for patients undergoing TKA [2].

Gilbody et al [29] retrospectively reviewed the effect of topical TXA administration and found a decrease in the transfusion rate from 19.3% to 2.3% in THA patients and from 13.1% to 0% in TKA patients. Similarly, a meta-analysis of RCTs evaluating unilateral primary THA showed a decrease in intraoperative blood loss by a mean of 104 mL ($P = .0006$) and total blood loss by a mean of 289 mL ($P < .0002$) [70]. In addition, the number of patients requiring transfusion was lower in those receiving TXA.

A 2018 network meta-analysis evaluating efficacy of TXA in THA based on level-1 evidence studies showed mean differences of 295 to 432 mL lower blood loss for the different TXA treatments (compared with placebo, with the exception of low-dose topical TXA [<1.5 g]), which did not demonstrate superiority compared with placebo [19]. The corollary network analysis of TXA in TKA from the same group demonstrated similar significant decrease in blood loss and risk of transfusion compared with placebo in all TXA administration groups [20].

Tranexamic Acid and LOS

A number of studies have demonstrated an association between decreased LOS and TXA use in THA and TKA patients [2,28,29,34]. Gilbody et al [29] reported a mean LOS decrease of 1 day for THA and 1.2 days for TKA. Evaluation of more than 23,000 THA and TKA cases in the Michigan Arthroplasty Registry Collaborative Quality Initiative demonstrated a modestly decreased LOS for the TKA cases receiving TXA (incidence rate ratio [IRR] = 0.93; 95% confidence interval [CI], 0.92–0.95) but no significant difference for the THA cases [34]. Alternatively, this study demonstrated decreased readmissions (odds ratio [OR] = 0.77; 95% CI, 0.64–0.93) in the THA group receiving TXA, whereas no association was found for TKA cases receiving TXA (OR = 0.90; 95% CI, 0.79–1.04). Evaluation of the Mayo institutional total joint registry for patients undergoing simultaneous bilateral TKA from 2005 to 2013 demonstrated an association of TXA use with a 0.9-day reduction in hospital LOS ($P = .008$) and total decrease in hospital cost of care by 6.45% ($P < .001$) [16].

Tranexamic acid has demonstrated efficacy in revision arthroplasty, where postoperative blood loss generally exceeds that of primary arthroplasty [26,62,79]. A retrospective review of 100 revision THAs and TKAs from 2013 to 2016 found reduced hospital LOS for both revision cohorts—3 days shorter for THA patients receiving TXA and 2 days shorter for TKA patients receiving TXA, compared with the controls not receiving TXA [28]. Although these findings were significant, it is important to note that in their revision TKA cohort, the group receiving TXA tended to be younger (mean age 65.6 years vs 71.9 years, $P = .025$), with a lower ASA class (mean 2.3 vs 2.8, $P < .001$) than those not receiving TXA, both of which may have influenced LOS. Park et al [62] retrospectively reviewed 161 revision THA cases and found a mean LOS decrease of 1.3 days for those receiving TXA ($P = .0002$). As they note, three quarters of the patients who received TXA were discharged on postoperative day (POD) 1, whereas only 48% of those who did not were discharged on POD 1. Importantly, the joint-related 90-day readmission rate for those receiving TXA was also lower than for those who did not receive TXA (9% vs 29%, respectively, $P = .0013$).

Tranexamic Acid and Cost Savings

Due to its impact on blood transfusions and LOS, TXA has been proposed to provide value to TJA perioperative protocols. A single institution case–control study from 2009 to 2012 estimated the largest cost savings with topical TXA, which was estimated to have a facility cost of $39.14 per TKA and no employee hours consumed, compared with $84.90 per TKA for blood transfusion and 0.13 person-hours per TKA for the no-TXA group [58]. Evaluation of a single-institution cohort of 1018 patients with an ASA score of I or II undergoing THA or TKA showed a mean direct total cost of hospitalization with TXA of $15,099 compared with $15,978 ($P < .0002$) without TXA [30]. The authors posit that the reduced transfusion-related expenses likely had a direct impact on this observed difference in hospital costs, noting that when a transfusion occurred, the mean number of units transfused was 1.8.

Other proposed means for cost savings related to TXA use include discharge to home compared with rehabilitation and decreased readmission rates [53,56,71]. Tuttle et al [71] demonstrated that a significantly higher percentage of patients (71.4%) who received TXA were discharged home compared with a control cohort (62.1%, $P = .02$). This retrospective review of 591 consecutive patients also reported a reduced transfusion rate from 17.5% to 5.5% with TXA administration. The calculated cost savings after accounting for the price of TXA was $83.73 per patient. Topical TXA reduces costs in primary TKA and THA, reduces transfusion rates, reduces LOS, and increases home disposition.

Blood Conservation and Rapid Recovery

Due to its benefits, TXA use has become a part of blood management and rapid recovery protocols [14,73] that have evolved over several decades, including preoperative evaluation and treatment of anemia, intraoperative hypotensive anesthesia, use of electrocautery, and restrictive transfusion thresholds postoperatively [10]. There is increasing evidence to suggest that anemia is associated with increased

risk of overall complication following THA or TKA, including hospital LOS, infection, transfusion requirements, and mortality [32,33,36,52]. National Surgical Quality Improvement Program registry data for patients undergoing THA from 2006 to 2016 found that mild anemia (defined as hematocrit 27% to 36%) compared with normal hematocrit (>36%) was a significant risk factor for total complications (OR = 1.46, $P < .001$), as well as mortality, renal complications, respiratory complications, sepsis, wound infection, and urinary tract infection [33]. Therefore, patient optimization in the preoperative setting should also be a part of multimodal blood conservation programs. Hypotensive anesthesia, when safe to perform, also offers an approach to lower the intraoperative mean arterial pressure (MAP), which has been shown to correlate directly to intraoperative blood loss, with a 10 mm Hg rise in MAP, demonstrating an associated 40% increase in intraoperative blood loss [10,17].

Historical thresholds for transfusion in patients with hemoglobin value less than 10 g/dL or a hematocrit less than 30% have transitioned to more restrictive transfusion strategies (transfusion for hemoglobin less than 7 g/dL for those without cardiac history and without symptoms or less than 8 g/dL when symptomatic) [10]. With these restrictive transfusion protocols, the transfusion rate can be significantly decreased in patients undergoing TJA [10,44,61]; TXA is both easy to utilize and inexpensive, which makes it an attractive approach in rapid-recovery protocols.

TXA Route and Dosing

A variety of TXA route and dose administration strategies have demonstrated efficacy in blood conservation strategies in THA and TKA [21]. However, a single optimal dose and route has yet to be determined. Tranexamic acid can be administered through oral, IV, or topical routes and doses can range from 10 to 20 mg/kg or 1 to 2 g, although up to 3 g has been utilized topically. The doses utilized in arthroplasty are generally lower than those utilized in other applications, such as 3 to 4 g/day for 4 to 5 days for menstrual bleeding and 4 to 6 g/day for 20 days for subarachnoid hemorrhage [54,56]. Oral TXA has been promoted for its low cost and ease of administration; however, IV and topical regimens remain widely utilized, and there is not enough evidence to favor any method of TXA to reduce the risk of blood loss and need for transfusion during the perioperative period for TJA [21,74].

In 2017, Fillingham et al [21] published the endorsed clinical practice guides of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopedic Surgeons, Hip Society, and Knee Society. Based upon analysis of 82 high-quality studies, they report a strong recommendation that

> intravenous, topical, and oral TXA as well as combinations of individual formulations of TXA are all effective strategies when compared with placebo for reducing calculated blood loss and the need for transfusion during the perioperative episode of a primary [total joint arthroplasty].

Importantly, the network analysis supporting this statement in THA showed oral TXA did not reduce the risk of transfusion, compared with placebo, and low-dose (≤1.5 g) topical TXA resulted in a decreased risk of transfusion but did not significantly reduce blood loss, compared with placebo. However, these results are likely related to the relatively few published studies on these specific TXA dosing regimens.

Direct comparison of the multiple routes is further limited by variable dosage and timing strategies utilized. For example, a 2019 RCT of 200 THA patients compared 3 dosing strategies for oral TXA and found that a preoperative oral TXA bolus (2 g at 2 hours before surgery) combined with multiple postoperative doses of oral TXA (1 g 3 hours postoperatively; 1 g at 3 and 9 hours postoperatively; and 1 g at 3, 9, and 15 hours postoperatively) reduced perioperative blood loss, compared with a single preoperative bolus alone [74].

Sarzaeem et al [67] compared a control group with 3 TXA dosing strategies (1.5 g IV at wound closure, 3 g topical at wound closure, and 1.5 g topical injected through the surgical drain after closure) and found that IV TXA resulted in the largest decrease in hemoglobin loss and units of blood transfused. Another randomized comparison of 150 patients undergoing TKA with 1 g administered intra-articular, compared with 1 g IV and control, demonstrated intra-articular application reduced total blood loss more than IV administration ($P = .011$) [76]. Finally, a study from 2016 to 2019 of more than 13,000 THA and TKA patients found that a double dose of IV TXA (1 g administered within 30 minutes of the skin incision and 1-g dose within 3 hours postoperatively) and a single 1 g IV dose within 30 minutes of the skin incision in combination with topical TXA (3 g diluted in 45 mL normal saline) resulted in equal rates of blood transfusion [12]. Regardless of route, evidence supports the effectiveness of TXA in reducing blood loss in TJA when administered in the perioperative period [21,56]. Additional doses likely result in further decrease in postoperative blood loss; however, the added clinical benefit and weighted cost of additional doses need to be investigated further [50,74,75,80].

Contraindications and Complications

There is mounting evidence that TXA is safe in a broader group of patients than previously proposed, including those with a prior history of venous thromboembolism (VTE) or other cardiac comorbidities, although there are few high-quality randomized studies in these high-risk groups. Evaluation of 23,236 primary TKAs and 11,489 THAs from the Michigan Arthroplasty Registry Collaborative Quality Initiative demonstrated reduced risk of 90-day VTE in the

TKA cases, with no significant effect on risk of VTE in the THA cases [34]. Furthermore, this large study did not find an association between TXA use and an increased risk of myocardial infarction, stroke, or transient ischemic attack in either THA or TKA patients. A retrospective review of 1620 primary THA or TKA cases in patients with a history of VTE did not demonstrate an increased risk of VTE recurrence in cases receiving TXA (2.3%) compared with those who did not receive TXA (1.8%; P =.6) [66]. Further matched outcome study of those who experienced a recurrent VTE also found TXA was not associated with recurrent VTE. American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, the Hip Society, and the Knee Society have all endorsed clinical practice guidelines that give a moderate recommendation to the following statement: "existing high-quality literature regarding administration of TXA in patients of generally higher comorbidity burden does not suggest increased risk of adverse thromboembolic events during the perioperative episode of primary TJA" [21].

Importantly, TXA is renally cleared and therefore the dose must be adjusted for known renal disease [56]. In addition, TXA can cross the blood-brain barrier and when present in the cerebrospinal fluid can inhibit glycine receptors, leading to seizures [8,25,41,49]. Although there have been reports of postoperative seizures in the cardiac surgery literature, there is little evidence in the arthroplasty literature on this increased risk [42,43,46,56]. Therefore, caution with use in patients with a known seizure disorder is recommended and further work is necessary in this area to support clear guidelines. A single-surgeon retrospective study of topical TXA use in 382 THA patients reported increased early postoperative pain and opioid consumption in those receiving topical TXA [78]. Animal models suggesting an association between TXA and increased sensitivity to pain or potential toxicity to periarticular tissues in conjunction with this retrospective review warrant further study to understand the potential adverse consequences of TXA and translation to clinical outcomes [51,55,59,60,78]. Other reported complications of TXA include visual changes and impaired color vision in rare cases [13,47].

In conclusion, there is growing literature on the safety and efficacy of TXA in primary and revision THA and TKA to reduce blood loss, allogeneic transfusions and the complications thereof, LOS, costs, and readmissions. The implementation of multimodal rapid recovery protocols involving TXA has facilitated earlier recovery and discharge from the hospital. There remains a lack of consensus on route of administration and dosing of TXA, with IV and topical regimens being widely used. Overall, the current literature on TXA in THA and TKA supports its overall efficacy in perioperative blood conservation and appears safe for broad application with few contraindications.

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Declaration of Conflicting Interests

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Human/Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

Informed Consent

Informed consent was not required for this review article.

Required Author Forms

Disclosure forms provided by the authors are available with the online version of this article as supplemental material.

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