Safety, Efficacy, and Cost-effectiveness of Tranexamic Acid in Orthopedic Surgery

ZILAN X. LIN, MD; SHANE K. WOOLF, MD

**abstract**

Perioperative bleeding and postsurgical hemorrhage are common in invasive surgical procedures, including orthopedic surgery. Tranexamic acid (TXA) is a pharmacologic agent that acts through an antifibrinolytic mechanism to stabilize formed clots and reduce active bleeding. It has been used successfully in orthopedics to reduce perioperative blood loss, particularly in total hip and knee arthroplasty and spine surgery. Numerous research studies have reported favorable safety and efficacy in orthopedic cases, although there is no universal standard on its administration and its use has not yet become the standard of practice. Reported administration methods often depend on the surgeon’s preference, with both topical and intravenous routes showing efficacy. The type and anatomic site of the surgery seem to influence the decision making but also result in conflicting opinions. Reported complication rates with TXA use are low. The incidence of both arterial and venous thromboembolic events, particularly deep venous thrombosis and pulmonary embolism, has not been found to be significantly different with TXA use for healthy patients. The route of administration and dosage do not appear to affect complication rates either. However, data on patients with higher-risk conditions are deficient. In addition, TXA has shown potential to reduce blood loss, transfusion rates and volumes, perioperative hemoglobin change, and hospital-related costs at various degrees among the published studies. Conservation of blood products, reduced laboratory costs, and shorter hospital stays are likely the major factors driving the cost savings associated with TXA use. This article reviews current data supporting the safety, efficacy, and cost-effectiveness of TXA in orthopedic surgery. [Orthopedics. 2016; 39(2):119-130.]

Numerous studies have been conducted on the development and use of pharmaceutical agents and other methods to reduce perioperative surgical bleeding. Among the most common complications, severe perioperative bleeding and postsurgical hemorrhage can lead to significant consequences, including hematomata, acute anemia, need for transfusion, and prolonged hospital stay with greater costs. With a growing geriatric population, increased activity levels, and the development of more advanced surgical techniques, the volume of orthopedic surgeries and procedures—ranging from simple fracture and soft tissue repair to prosthetic replacement and revision reconstructive surgery—has been rising.

Thus, minimizing peri- and postoperative complications, especially bleeding, is imperative to contain health care costs.

In orthopedic cases, controlled hypotensive anesthesia and tourniquets with pressure-controlled pumps have been used along with other methods to control intraoperative bleeding. However, these extrinsic methods do not eliminate blood loss completely and are not without issues. For example, in total knee arthroplasty (TKA), tourniquet-related isch-
emia can inadvertently cause a rebound effect when the tourniquet is released at the end of the procedure. This can lead to increased fibrinolytic activity, resulting in up to 2 L of ongoing blood loss even after wound closure, sometimes necessitating transfusion.\(^1\)\(^,\)\(^2\) Furthermore, transfusions can cause complications, including anaphylactic and allergic reactions to blood products, infections, and even death.\(^2\)\(^,\)\(^8\)\(^,\)\(^9\) Current medical standard of care advocates a conservative and limited use of blood products,\(^1\)\(^,\)\(^10\) which further emphasizes the need for better control of bleeding. For this purpose, antifibrinolytic drugs such as epsilon-aminocaproic acid and since-discontinued aprotinin have been investigated.\(^5\)\(^,\)\(^11\) Tranexamic acid (TXA) is another such agent shown to be safe and effective in orthopedic surgery.

Tranexamic acid has shown efficacy in reducing bleeding and possibly other surgical complications. It was initially introduced more than 40 years ago in cardiothoracic surgery and has shown application in controlling gynecologic hemorrhage and providing life-saving hemostasis in acute trauma. In addition to cardiothoracic\(^1\)^,\(^2\); trauma\(^1\);\(^3\); gynecological and obstetric\(^1\)^,\(^4\)^,\(^15\); gastrointestinal\(^1\)^,\(^6\); hepatic\(^1\)^,\(^2\); urologic\(^1\)^,\(^7\); and ear, nose, and throat surgeries,\(^1\)^,\(^2\)^,\(^8\)^,\(^9\) TXA has also been studied and used for diseases such as von Willebrand–factor deficiencies,\(^19\) hemophilia,\(^20\) and thrombocytopenia.\(^1\)^,\(^5\)^,\(^21\) However, use in orthopedic surgery is not universal and remains subject to research. The current article reviews details of TXA in orthopedic surgery, including possible benefits beyond reduced blood loss and transfusion requirements, such as treatment cost savings and decreased length of hospital stay.

**MECHANISM OF ACTION AND PHARMACOLOGY**

Tranexamic acid is a synthetic derivative of the amino acid lysine and carries out its effects through an antifibrinolytic action. It stabilizes formed clots and prevents the degradation of fibrin by reversibly inhibiting the lysine binding site on plasminogen. This impairs plasminogen’s linkage with fibrin to become plasmin, which normally creates a fibrinolytic effect and dissolves clots.\(^1\)^,\(^12\)^,\(^18\) The capacity of TXA to bind to plasminogen appears to be 6 to 10 times more potent than epsilon-aminocaproic acid.\(^5\)^,\(^12\) Its half-life is approximately 2 hours,\(^1\)^,\(^5\)^,\(^15\)^,\(^18\) and it is eliminated via the kidneys.

**SAFETY AND COMPLICATIONS**

Contraindications of TXA use are controversial. It is generally well tolerated but can cause uncommon dose-dependent side effects, including nausea, vomiting, diarrhea, headache, orthostatic reactions, blurred vision, and vertigo.\(^1\)^,\(^2\)^,\(^8\)^,\(^9\)^,\(^12\)^,\(^18\)^,\(^22\) Of particular concern is the drug’s antifibrinolytic action, which could theoretically lead to a hypercoagulable state and induce thrombosis. However, multiple primary studies and reviews have suggested no significant differences between TXA and placebo in the incidence of both arterial and venous thromboembolic events, particularly deep venous thrombosis and pulmonary embolism.\(^2\)^,\(^5\)^,\(^9\)^,\(^12\)^,\(^23\)^,\(^34\) Reported complications with TXA use in orthopedic surgery from published meta-analyses are shown in Table 1. No reported data have shown a correlation between TXA and any significant major complication, thromboembolic or nonthromboembolic, including numerous recent studies of topical and intravenous (IV) administration not included in previously published meta-analyses.\(^25\)^,\(^26\)^,\(^32\)^,\(^34\)^,\(^52\) According to Tuttle et al,\(^35\) readmissions within 30 days with topical TXA use was not statistically significant after total hip arthroplasty (THA) and TKA. A meta-analysis by Yang et al\(^27\) concluded that the addition of TXA did not affect prothrombin time and activated partial thromboplastin time after TKA. Two randomized, controlled trials (RCTs) on scoliosis surgery showed no statistically significant difference in prothrombin time, international normalization ratio, partial thromboplastin time, fibrinogen, or d-dimer with TXA use,\(^53\)^,\(^54\) whereas Mut-suzuki and Ikeda\(^36\) reported that d-dimer was lower on postoperative day 7 after cementless TKA in their cohort study. Thus, in terms of thrombotic complications, TXA has been shown to be a relatively safe agent for control of perioperative bleeding in orthopedic surgery.

Although most studies do not suggest that TXA lowers thromboembolic and other complication rates, some have reported intriguing results. A retrospective cohort study by Lozano et al\(^37\) suggests a tendency toward fewer thromboembolic events with TXA use. Poeran et al\(^34\) reported that the rate of admission to the intensive care unit was decreased significantly from 7.5% to 3.1% with TXA use in their cohort study. According to Wong et al,\(^30\) the percent of patients who required discharge to rehabilitation facilities was shown to be lower with 3 g of topical TXA, compared with 1.5 g or placebo. To clarify whether TXA has the potential to reduce complication rates or facilitate recovery, larger controlled studies are necessary.

Different routes of administration and dosages do not appear to cause a significant rise in adverse outcomes. No study has shown a significant correlation between TXA use, regardless of route of administration, and complications. By comparing the effects of TXA administered topically and intravenously, Hegde et al\(^18\) concluded that both routes are equally safe in simultaneous bilateral computer-assisted TKA. Hourlier and Fennema\(^26\) found in an RCT that administration of TXA by a single shot or a loading dose and followed 2 hours later by a continuous infusion was equally safe in THA. In general, TXA appears to be a safe agent for use in healthy patients undergoing orthopedic surgery.

However, most studies excluded patients with significant risk factors, such as a history of cardiovascular disease, thromboembolic events, and renal failure.\(^2\)^,\(^7\)^,\(^23\)^,\(^29\) Thus, most of the available data would likely support TXA’s safety in healthy patients.
rather than those with higher risk. Furthermore, there are proposed contraindications for TXA use, including arterial and venous thrombosis, cerebral thrombosis, myocardial infarct, and acute renal failure. For example, a case report by Bruce-Brand et al revealed that a 65-year-old man with a previously undiagnosed patent foramen ovale suffered pulmonary emboli and cerebrovascular infarction after synchronous bilateral TKA, during which TXA was administered intravenously. With current evidence, the safety of TXA in patients with higher-risk conditions is still uncertain. Prudence would suggest withholding TXA in higher-risk individuals, including those with a history of venous thromboembolic disease, cardiac disease, cerebrovascular disease, or significant risk factors for blood clots.

**ADMINISTRATION IN ORTHOPEDIC SURGERY**

In orthopedics, numerous studies and reviews have focused on TXA use in TKA, hip arthroplasty, and spine surgery. Topical injections can range from 0.5 mg/kg to 5 g TXA/100 mL normal saline and may provide benefits in reducing postoperative blood loss and transfusion rates. Topical TXA treatment has been shown to significantly reduce blood transfusion rate compared to IV TXA in TKA. Furthermore, the dosage of TXA administered varies widely among studies, with some reporting better efficacy with higher doses, while others suggest a dose-response effect. The choice of topical or IV TXA is dependent on the type and site of the surgery, the surgeon’s preference, and other factors such as the type of blood disease and risk factors for blood transfusions.

First, route of administration has been an area of specific research interest. Often TXA is administered intravenously, and by doing so, TXA is directly loaded into the vascular system and could reach the body systemically. Intravenous administration seems to be the most effective because TXA can penetrate into large joints relatively quickly. In their comparison of topical TXA vs placebo, Alshryda et al reviewed previous studies of topical and IV TXA. Their meta-analysis of this group showed that topical administration was significantly less effective than intravenous TXA in TKA, with a transfusion risk difference of 30%. However, when Wang et al compared topical and intravenous TXA use in TKA, they concluded that there was no statistically significant difference in blood loss and transfusion rates. One meta-analysis indicated that topical TXA provides a greater benefit in reducing postoperative blood loss and transfusion rates than IV TXA in arthroplasty. Moreover, in TKA, intravenous TXA may decrease external blood loss only, meaning blood loss that could be observed or measured intraoperatively or in the drain but not potentiate ongoing postoperative blood loss, which likely contributes to hematoma formation.

It may be useful to apply TXA locally at the conclusion of surgery. Sarzaeem et al reported that injection through the drain was more effective at decreasing postoperative drainage after TKA, although IV TXA injection seemed to reduce the number of transfused units and magnitude of the drop in hemoglobin more effectively. Two studies also examined oral TXA use and suggested efficacy. Therefore, it may be the surgeon’s preference as to what route of administration to use, and consideration of expected postoperative ongoing blood losses should be made.

Second, surgical location seems to make a difference in terms of route of administration. Table 1 illustrates the choice of topical or IV TXA in various orthopedic specialties. Consistency is noted in spine surgery but not THA and TKA. The reason for popularity of IV administration in spine cases may be due to multiple spinal levels involved and large exposure, resulting in the practical need for systematic distribution. However, it seems to matter less in THA and TKA. This is most likely associated with the previously mentioned benefits of local and IV TXA use and depends on the surgeon’s preference. Of note, a feature specific to TKA is the common use of a tourniquet. The tourniquet would help reduce local bleeding before TXA administration and likely impair TXA delivery to the surgical site intraoperatively.

Third, the dosage of TXA administered has not been standardized. Often TXA is administered intravenously with a loading dose of 10 or 15 mg/kg, followed by an infusion of 100 mg during surgery. However, a meta-analysis of 6 RCTs by Zhao-Yu et al. proposed that topical injections can range from 0.5 g TXA/100 mL normal saline to 3 g/100 mL in TKA. Some studies have suggested a dose-response effect with TXA use. In their meta-analysis, Alshryda et al reported that 3 g TXA/100 mL normal saline was more effective in reducing total blood loss than 1.5 g in TKA, although similar efficacy was found in transfusion rates. Panteli et al reported in their meta-analysis that a higher dose (>2 g) of topical TXA in TKA significantly reduced blood transfusion requirements compared with a lower dose (≤2 g). Alshryda et al also concluded in their meta-analysis that higher doses (>4 mg) of TXA may provide a larger, homogeneous treatment effect in TKA, whereas lower doses may provide a smaller, heterogeneous effect. Poeran et al. found that 2 g of IV TXA seemed to have the best effectiveness and safety profile in arthroplasty compared with ≤1 or ≥3 g of IV TXA. All of these data illustrate that the dosage of TXA matters within a certain range. However, a meta-analysis by Sukeik et al. found that a higher dose of IV TXA did not necessarily reduce intraoperative and total blood loss or transfu-

**Table 1**

<table>
<thead>
<tr>
<th>Specialties</th>
<th>Topical TXA</th>
<th>IV TXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine surgery</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>THA</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>TKA</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

This table illustrates the choice of topical or IV TXA in various orthopedic specialties.
Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgery</th>
<th>Administration Route</th>
<th>Included Studies (No. of Patients)</th>
<th>Mean TBL Reduction With TXA, mL</th>
<th>Mean IBL Reduction With TXA, mL</th>
<th>Mean PBL Reduction With TXA, mL</th>
<th>Blood Transfusion Relative Risk of TXA</th>
<th>No. of Reported VTE Complications: Non-TXA/TXA</th>
<th>No. of Other Reported Complications: Non-TXA/TXA</th>
<th>Other Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alshryda et al</td>
<td>TKA</td>
<td>IV, topical, oral</td>
<td>19 RCTs</td>
<td>591 (P&lt;.001)</td>
<td>n/a</td>
<td>245 (P&lt;.001)</td>
<td>0.39 (P&lt;.001)</td>
<td>DVT: NS; PE: 4/1 (P=.5)</td>
<td>n/a</td>
<td>DVT risk difference: 0.00 (P=.98)</td>
</tr>
<tr>
<td>Alshryda et al</td>
<td>THA, TKA</td>
<td>Topical</td>
<td>14 RCTs; 11 TKA/2 THA/2 both</td>
<td>TKA: 461.8 (P&lt;.001); THA: 364 (P=.02)</td>
<td>n/a</td>
<td>TKA: 314.5 (P&lt;.001)</td>
<td>TKA: 0.22 (P&lt;.001); THA: 0.39 (P=.004)</td>
<td>DVT: NS; PE: 4/2</td>
<td>n/a</td>
<td>DVT risk difference: -0.01 (P=.24)</td>
</tr>
<tr>
<td>Fu et al</td>
<td>TKA</td>
<td>IV</td>
<td>22 RCTs (1361)</td>
<td>435.41 (P&lt;.01)</td>
<td>10.28 (P=.62)</td>
<td>406.69 (P&lt;.001)</td>
<td>n/a</td>
<td>DVT: 27/47 (P=.77); PE: 3.0 (P=.44)</td>
<td>n/a</td>
<td>Mean reduction in blood transfusion units: 0.95 unit (P&lt;.01); transfusion rate risk difference: -0.30 (P&lt;.01)</td>
</tr>
<tr>
<td>Huang et al</td>
<td>Orthopedic surgery</td>
<td>n/a</td>
<td>46 RCTs (2925)</td>
<td>408.33 (P&lt;.00001)</td>
<td>125.65 (P&lt;.0001)</td>
<td>214.58 (P&lt;.00001)</td>
<td>0.51 (P&lt;.00001)</td>
<td>DVT: 26/30 (P=.66)</td>
<td>n/a</td>
<td>Mean reduction in blood transfusion rate: 49% (P&lt;.00001); mean reduction in blood transfusion units per patient: 0.78 unit (P&lt;.0002); mean reduction in blood transfusion volume per patient: 205.33 mL (P&lt;.0001); DVT relative risk: 1.11 (P=.66)</td>
</tr>
<tr>
<td>Li et al</td>
<td>Spine surgery</td>
<td>IV</td>
<td>6 RCTs (411)</td>
<td>285.35 (P=.01)</td>
<td>n/a</td>
<td>n/a</td>
<td>0.71 (P=.01)</td>
<td>DVT: 1/0</td>
<td>n/a</td>
<td>Mean reduction in blood transfusion volume per patient: 198.12 mL (P=.08)</td>
</tr>
<tr>
<td>Panteli et al</td>
<td>TKA</td>
<td>Topical</td>
<td>7 studies</td>
<td>220.08 (P&lt;.00001)</td>
<td>n/a</td>
<td>268.36 (P=.02)</td>
<td>0.47 (P=.01)</td>
<td>DVT: 1/3 (P=0.66); PE: 1/1 (P=.67)</td>
<td>n/a</td>
<td>Mean reduction in maximum postoperative Hb drop: 0.94 g/dL (P&lt;.00001)</td>
</tr>
<tr>
<td>Sukeik et al</td>
<td>THA</td>
<td>IV</td>
<td>11 RCTs</td>
<td>289 (P&lt;.0002)</td>
<td>104 (P=.0006)</td>
<td>172 (P=.0002)</td>
<td>n/a</td>
<td>DVT: NS; PE: 1/2 (P=.76)</td>
<td>Infections: 2/2 (P=.97)</td>
<td>Transfusion rate risk difference: -0.20 (P&lt;.00001)</td>
</tr>
<tr>
<td>Tan et al</td>
<td>TKA</td>
<td>IV</td>
<td>19 RCTs (1114)</td>
<td>570 (P&lt;.00001)</td>
<td>n/a</td>
<td>290 (P&lt;.00001)</td>
<td>0.39 (P&lt;.00001)</td>
<td>NS</td>
<td>Hematoma: 13/11; superficial infections: 2/3; deep infections: 0/1; cardiac events: 0/1; pulmonary infection: 1/1; respiratory insufficiency: 0/1</td>
<td>Mean reduction in blood transfusion units per patient: 0.96 unit (P&lt;.00001); mean reduction in blood transfusion volume per patient: 440 mL (P&lt;.00001)</td>
</tr>
</tbody>
</table>
Table 1 (cont'd)

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgery</th>
<th>Administration Route</th>
<th>Included Studies (No. of Patients)</th>
<th>Mean TBL Reduction With TXA, mL</th>
<th>Mean IBL Reduction With TXA, mL</th>
<th>Mean PBL Reduction With TXA, mL</th>
<th>Blood Transfusion Relative Risk of TXA</th>
<th>No. of Reported VTE Complications: Non-TXA/TXA</th>
<th>No. of Other Reported Complications: Non-TXA/TXA</th>
<th>Other Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al.24</td>
<td>Spine surgery</td>
<td>IV</td>
<td>9 studies (581)</td>
<td>389.21 (P&lt;.0003)</td>
<td>128.28 (P&lt;.008)</td>
<td>98.49 (P&lt;.0001)</td>
<td>0.65 (P&lt;.0001)</td>
<td>DVT: 1/0</td>
<td>n/a</td>
<td>Mean reduction in blood transfusion volume: 134.55 mL (P=0.001); DVT relative risk: 0.34 (P&lt;0.50)</td>
</tr>
<tr>
<td>Yang et al.25</td>
<td>TKA</td>
<td>n/a</td>
<td>15 RCTs (837)</td>
<td>504.9 (P&lt;.00001)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>NS</td>
<td>n/a</td>
<td>Mean reduction in blood transfusion units: 1.43 units (P&lt;0.001); transfusion odds ratio: 0.16 (P=0.001); odds ratio on DVT: 0.75 (P=.48); odds ratio on PE: 0.65 (P=.50); no significant changes on PT, aPTT</td>
</tr>
<tr>
<td>Zhang et al.25</td>
<td>TKA</td>
<td>n/a</td>
<td>15 RCTs (842)</td>
<td>486.7 (P&lt;0.0001)</td>
<td>126.75 (P=.18)</td>
<td>245.0 (P=.004)</td>
<td>n/a</td>
<td>DVT: 12/12 (NS); PE: 3/2 (NS)</td>
<td>Hematoma: 4/7; drain secretions: 2/3; death: 1/1; MI: 10; infections: 2/6</td>
<td>Mean reduction in blood transfusion units per patient: 1.3 units (P&lt;0.001); transfusion rate risk difference: 0.4 (P&lt;0.001); DVT risk difference: 0.00 (P=.85)</td>
</tr>
<tr>
<td>Zhao-Yu et al.26</td>
<td>TKA</td>
<td>Topical</td>
<td>6 RCTs (647)</td>
<td>320.44 (P&lt;.01)</td>
<td>n/a</td>
<td>206.09 (P&lt;.01)</td>
<td>0.28 (P&lt;.01)</td>
<td>PE: 2/1</td>
<td>n/a</td>
<td>Mean reduction in Hb drop: 0.63 g/dL (P&lt;.02); DVT relative risk: 1.75 (P=.82)</td>
</tr>
<tr>
<td>Zhou et al.27</td>
<td>THA</td>
<td>IV</td>
<td>19 RCTs (1030)</td>
<td>305.27 (P&lt;.001)</td>
<td>86.33 (P&lt;.01)</td>
<td>176.79 (P&lt;.001)</td>
<td>n/a</td>
<td>DVT: 19/15 (NS); PE: 1/3 (NS)</td>
<td>n/a</td>
<td>Transfusion odds ratio: 0.28 (P&lt;.01); mean reduction in Hb drop: 0.603 g/dL (P&lt;.001); mean reduction in Hct drop: 2.29% (P&lt;.001)</td>
</tr>
</tbody>
</table>

Abbreviations: aPTT, activated partial thromboplastin time; DVT, deep venous thrombosis; Hb, hemoglobin; Hct, hematocrit; IBL, intraoperative blood loss; IV, intravenous; MI, myocardial infarction; n/a, not available; NS, nonsignificant; PBL, postoperative blood loss; PE, pulmonary embolism; PT, prothrombin time; RCTs, randomized, controlled trials; TBL, total blood loss; THA, total hip arthroplasty; TKA, total knee arthroplasty; TXA, tranexamic acid; VTE, venous thromboembolism.
<table>
<thead>
<tr>
<th>Study</th>
<th>Level of Evidence</th>
<th>Surgery</th>
<th>TXA Dose</th>
<th>Administration Route</th>
<th>Total No. of Cases (Non-TXA/TXA)</th>
<th>Average Hospital Stay, d: Non-TXA/TXA</th>
<th>Mean Reduction in Combined Pharmacy and Transfusion Costs per Patient With TXA</th>
<th>Mean Cost of Hospital Stay per Patient: Non-TXA/TXA/% Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alshryda et al\textsuperscript{13}</td>
<td>I</td>
<td>THA</td>
<td>n/a</td>
<td>Topical</td>
<td>161 (81/80)</td>
<td>6.2/5.2 ((P) = .109)</td>
<td>n/a</td>
<td>£1526/£1221 ((P) = .05)/19.99%</td>
</tr>
<tr>
<td>Alshryda et al\textsuperscript{17}</td>
<td>I</td>
<td>TKA</td>
<td>1 g TXA/50 mL normal saline sprayed into wound at end of surgery before closure</td>
<td>Topical</td>
<td>157 (78/79)</td>
<td>6.1/4.8 ((P) = .041)</td>
<td>n/a</td>
<td>£1450/£1117 ((P) = .028)/22.97%</td>
</tr>
<tr>
<td>Bidolegui et al\textsuperscript{29}</td>
<td>I</td>
<td>TKA</td>
<td>15 mg/kg (diluted in 100 mL of normal saline) 10-min IV infusion twice, first dose during induction of anesthesia and second 3 h later</td>
<td>IV</td>
<td>50 (25/25)</td>
<td>3.8/4.1 ((P) = .271)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Elwatidy et al\textsuperscript{22}</td>
<td>I</td>
<td>Spine surgery</td>
<td>Loading dose of 2 g (adults) or 30 mg/kg (children) followed by continuous infusion of 100 mg/h (adults) or 1 mg/kg/h (children) intraoperatively and 5 h postoperatively</td>
<td>IV</td>
<td>64 (32/32)</td>
<td>10.69/8.45 ((P) = .21)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Georgiaidis et al\textsuperscript{17}</td>
<td>I</td>
<td>TKA</td>
<td>2 g TXA/75 mL normal saline applied to wound for 5 min under tourniquet before suctioning</td>
<td>Topical</td>
<td>101 (51/50)</td>
<td>2.8/2.7 ((P) = .495)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Gomez-Barrera et al\textsuperscript{30}</td>
<td>I</td>
<td>TKA</td>
<td>2 IV doses (15 mg/kg in 100 mL of physiological saline solution, 1 dose before tourniquet release and another 3 h postoperatively, or 3 g/100 mL physiological saline solution intra-articularly</td>
<td>IV or topical</td>
<td>78 (39 IV/ 39 topical)\textsuperscript{a}</td>
<td>3.9/3.5 ((P) = .316)\textsuperscript{a}</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Johanson et al\textsuperscript{166}</td>
<td>I</td>
<td>THA</td>
<td>Bolus infusion of 15 mg/kg mixed in 100 mL normal saline immediately preoperatively</td>
<td>IV</td>
<td>100 (53/47)</td>
<td>n/a</td>
<td>47 euros</td>
<td>n/a</td>
</tr>
<tr>
<td>Kazemi et al\textsuperscript{167}</td>
<td>I</td>
<td>Cementless THA</td>
<td>15 mg/kg administered 5 min preoperatively</td>
<td>IV</td>
<td>64 (32/32)</td>
<td>15.5/13 ((P) = .34)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Lin et al\textsuperscript{166}</td>
<td>I</td>
<td>Minimally invasive TKA</td>
<td>(1) Non-TXA; (2) 1 dose of 10 mg/kg at 5 min before tourniquet deflation; (3) 2 doses of 10 mg/kg at 5 min before incision and 5 min before tourniquet deflation</td>
<td>IV</td>
<td>151 (50 group 1/52 group 2/ 49 group 3)</td>
<td>5.5/5.3 ((P) = .175)\textsuperscript{b}</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
### Table 2 (cont’d)

**Length of Hospital Stay and Hospital Costs Associated With TXA Use in Orthopedic Surgery**

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of Evidence</th>
<th>Surgery</th>
<th>TXA Dose</th>
<th>Administration Route</th>
<th>Total No. of Cases (Non-TXA/TXA)</th>
<th>Average Hospital Stay, d: Non-TXA/TXA</th>
<th>Mean Reduction in Combined Pharmacy and Transfusion Costs per Patient With TXA</th>
<th>Mean Cost of Hospital Stay per Patient: Non-TXA/TXA/% Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al&lt;sup&gt;82&lt;/sup&gt;</td>
<td>I</td>
<td>TKA</td>
<td>1.5 g TXA/100 mL normal saline or 3.0 g TXA/100 mL normal saline applied into joint for 5 min at end of surgery</td>
<td>Topical</td>
<td>99 (35 non-TXA, 31 given 1.5 g dose, 33 given 3 g dose)</td>
<td>4.3/4.7/4.5</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Chen et al&lt;sup&gt;41&lt;/sup&gt;</td>
<td>II</td>
<td>Cemented TKA</td>
<td>1500 mg TXA/100 mL normal saline as a wash with 5-min contact time after cementing and before closure of retinaculum</td>
<td>Topical</td>
<td>100 (50/50)</td>
<td>5/5 (NS)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Vigna-Talianti et al&lt;sup&gt;62&lt;/sup&gt;</td>
<td>II</td>
<td>Arthroplasty</td>
<td>10 mg/kg in 30 min immediately preoperatively and 2 additional doses on postoperative d 1 and 2 in 6-h infusion period</td>
<td>IV</td>
<td>198 (100/98)</td>
<td>n/a</td>
<td>THA alone: 138 euros; both THA &amp; TKA: 135 euros</td>
<td>n/a</td>
</tr>
<tr>
<td>Chang et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td>III</td>
<td>THA</td>
<td>10 mL 5% TXA in topical cocktail solution with 1/3 injected intramuscularly and intra-capsularly and 2/3 intra-articularly after fasciae closure</td>
<td>Topical</td>
<td>388 (234/154)</td>
<td>5.2/5.7</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Chimento et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>III</td>
<td>TKA</td>
<td>3 g TXA/100 mL normal saline used to irrigate wound following cementing</td>
<td>Topical</td>
<td>683 (373/310)</td>
<td>5.3/4.7 (P&lt;.001)</td>
<td>$187.63</td>
<td>$13,854.02/$12,333.72 (P&lt;.001)/10.97%</td>
</tr>
<tr>
<td>George et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td>III</td>
<td>THA &amp; TKA</td>
<td>1 g bolus</td>
<td>IV</td>
<td>Hip: 50 (20/30); knee: 60 (30/30); Hip: 6/6.43 (P=.70); knee: 5.23/5.62 (P=.68)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Gillette et al&lt;sup&gt;39&lt;/sup&gt;</td>
<td>III</td>
<td>THA &amp; TKA</td>
<td>1 g at incision and 1 g at closure</td>
<td>n/a</td>
<td>1018 (438/580)</td>
<td>n/a</td>
<td>n/a</td>
<td>$15,978/$15,099 (P&lt;.0002)/5.50%</td>
</tr>
<tr>
<td>Harris et al&lt;sup&gt;88&lt;/sup&gt;</td>
<td>III</td>
<td>THA</td>
<td>1 g IV infusion within 1 h of incision and again as wound closure began; topical TXA placed in wound before closure and hemovac drain clamped for 30 min postoperatively</td>
<td>IV or topical</td>
<td>1595 (1047 non-TXA/478 IV/70 topical)</td>
<td>n/a</td>
<td>IV: $163.52/topical: $154.49</td>
<td>n/a</td>
</tr>
<tr>
<td>Lozano et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>III</td>
<td>TKA</td>
<td>10 mg/kg infused over 10 min immediately before tourniquet inflation and immediately after release</td>
<td>IV</td>
<td>414 (215/199)</td>
<td>n/a</td>
<td>115.07 euros</td>
<td>n/a</td>
</tr>
<tr>
<td>Study</td>
<td>Level of Evidence</td>
<td>Surgery</td>
<td>TXA Dose</td>
<td>Administration Route</td>
<td>Total No. of Cases (Non-TXA/TXA)</td>
<td>Average Hospital Stay, d: Non-TXA/TXA</td>
<td>Average Hospital Stay, d: Non-TXA/TXA Mean</td>
<td>Mean Reduction in Combined Pharmacy and Transfusion Costs per Patient with TXA</td>
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<td>------------------------</td>
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<tr>
<td>Moskal et al&lt;sup&gt;89&lt;/sup&gt;</td>
<td>III</td>
<td>TKA</td>
<td>1 g IV infusion within 1 h of incision and again as wound closure began; topical TXA placed in wound before closure and he-movac drain clamped for 30 min postoperatively</td>
<td>IV or topical</td>
<td>2299 (1839 non-TXA/330 IV/130 topical)</td>
<td>n/a</td>
<td>IV: $2.31/topical: $45.76</td>
<td>n/a</td>
</tr>
<tr>
<td>Poeran et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>III</td>
<td>THA &amp; TKA</td>
<td>None, ≤1000 mg, 2000 mg, ≥3000 mg</td>
<td>IV</td>
<td>872,416 (852,365/20,051 ≤1000 mg: 7041; 2000 mg: 8992; ≥3000 mg: 4018)]</td>
<td>3 (3-4)/3 (2-4)&lt;sup&gt;6&lt;/sup&gt; (P&lt;.001)</td>
<td>n/a</td>
<td>$15,110/$14,980 (P&lt;.001)/0.86%&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Singh et al&lt;sup&gt;90&lt;/sup&gt;</td>
<td>III</td>
<td>THA</td>
<td>Single dose of 10 mg/kg administered 10 min prior to incision</td>
<td>IV</td>
<td>42 (21/21)</td>
<td>6.4/5.9 (P=.34)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Smit et al&lt;sup&gt;44&lt;/sup&gt;</td>
<td>III</td>
<td>Revision TKA</td>
<td>20 mg/kg given prior to tourniquet release</td>
<td>n/a</td>
<td>424 (178/246)</td>
<td>8.6/6.7 (P=.005)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Tuttle et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>III</td>
<td>THA &amp; TKA</td>
<td>In THA, 1 g TXA/10 mL normal saline injected in pericapsular and deep tissue spaces or intra-articularly following iliobial band or tensor fascia closure; in TKA, 1 g TXA/10 mL normal saline injected intra-articularly after capsular closure</td>
<td>Topical</td>
<td>591 (280/311)</td>
<td>3.16/3.15 (P=.84)</td>
<td>n/a</td>
<td>$83.73</td>
</tr>
<tr>
<td>Irisson et al&lt;sup&gt;39&lt;/sup&gt;</td>
<td>IV</td>
<td>THA &amp; TKA</td>
<td>1 g (15 mg/kg) at incision and wound closure then at 6-h intervals for 24 h</td>
<td>IV</td>
<td>451 (241/210)</td>
<td>n/a</td>
<td>41 euros</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; n/a, not available; NS, nonsignificant; THA, total hip arthroplasty; TKA, total knee arthroplasty; TXA, tranexamic acid.

<sup>a</sup>A study without a non-TXA group.

<sup>b</sup>P value calculated as compared with the non-TXA group.

<sup>c</sup>Transfusion costs included costs from autologous and homologous blood donations and autotransfusion from drainage.

<sup>d</sup>Median used instead of mean.

<sup>e</sup>Numbers listed: median (interquartile range).
would work most effectively in the early phase of the fibrinolytic cascade.\textsuperscript{64,71}
Likely due to the same reason, continuous IV infusion appears to be somewhat more popular in spine surgery. The majority of recently published spine studies chose to use continuous IV infusion.\textsuperscript{43,47,48,65} Furthermore, in Table 1, 3 meta-analyses addressed TXA in spine surgery and included a total of 10 studies.\textsuperscript{9,24,74} Half of them chose continuous IV infusion,\textsuperscript{53,54,75-77} 3 bolus,\textsuperscript{22,78,79} and 2 unknown.\textsuperscript{80,81} However, there is also counterevidence. According to a cohort study by George et al,\textsuperscript{40} no significant difference in total blood loss was noticed with TXA administration within or after 30 minutes of the anesthetic induction. Furthermore, topical TXA could be administered after fascia closure to prevent leakage\textsuperscript{6-29} or before closure to ensure adequate contact time.\textsuperscript{7,41}

In short, the optimal dose and route of administration of TXA is still unclear. Although studies with different doses and routes of administration have shown statistical significance for using TXA, few have actually compared and concluded a correlation between efficacy and administration method or between efficacy and dosage. Further data are needed to define the optimal practices for dosing and administration.

**Potential Advantages of Tranexamic Acid in Clinical Pathways**

Many researchers agree that TXA decreases peri- and postoperative blood loss volume and transfusion rates and minimizes hemoglobin change. Studies and reviews in TKA,\textsuperscript{2,6,7,9,23,25-27,31,34,36,37,39-41,51,56-58,60-62} THA,\textsuperscript{9,26,32,34,40,42,62-64} and spine surgery\textsuperscript{9,22,43,53,54,65} have supported TXA's ability to lower blood loss and transfusion requirements.\textsuperscript{1,5} Data were also obtained with similar results in revision,\textsuperscript{44,56} bilateral,\textsuperscript{38} and computer-assisted TKA\textsuperscript{2,29} and cementless THA.\textsuperscript{32} A meta-analysis by Huang et al\textsuperscript{9} included 46 RCTs of 2925 patients in major orthopedic surgery and concluded that, on average, TXA use reduced the number of blood transfusions per patient by 0.78 units; the volume of blood transfusion per patient by 205 mL; and total, intraoperative, and postoperative blood loss by 408, 125, and 214 mL, respectively.\textsuperscript{9} Similar trends were demonstrated by a meta-analysis of 22 RCTs exclusively in TKA\textsuperscript{28} and a meta-analysis of 6 RCTs in spine surgery.\textsuperscript{24} Table 1 summarizes details of blood loss and transfusion rate differences in published reports. Both transfusion rates and transfusion volume are decreased by TXA. In 2 level I studies, the transfusion rates were significantly decreased from 47.5% to 25% in TKA and from 22.4% to 5.7% in THA after TXA administration.\textsuperscript{52,82} In addition, TXA further reduced blood transfusions in TKA when a blood conservation program was applied.\textsuperscript{58} Other evidence shows significant decreases in drain output,\textsuperscript{49,61} hemoglobin loss,\textsuperscript{25,35,37,44,49} and hematocrit reduction\textsuperscript{42,49,61,64} with TXA use, although the control group with placebo had a higher rate of transfusion.

The efficacy of TXA may vary with timing. In a nonrandomized, controlled trial of cementless THA, Yamashiki et al\textsuperscript{32} noted the greatest reduction in blood loss during the first 4 hours. Mutsuzaki and Ike-dâ\textsuperscript{36} reported that the hemoglobin level was higher with TXA use on postoperative day 7 but not on days 1 and 14. Overall, there is ample agreement on TXA's efficacy in reducing surgical blood loss and transfusion requirements in orthopedic surgery.

The efficacy of TXA seems to vary by location. Zufferey et al\textsuperscript{70} suggested that the efficacy of TXA is higher in TKA than THA, whereas Vigna-Taglianti et al\textsuperscript{65} reported that the reduction in blood transfusions was greater in THA than in TKA. The efficacy of TXA in spine surgery seems to be somewhat less potent and more inconsistent. For example, in pediatric scoliosis surgery, Sethna et al\textsuperscript{64} concluded that TXA significantly reduced blood loss but not transfusion requirements, whereas Neilipovitz et al\textsuperscript{53} reported no significant difference in blood loss, although perioperative blood transfusion was reduced. An RCT by ElWatidy et al\textsuperscript{22} showed significant reduction in both blood loss and transfusion need. Although TXA does not seem to always affect multiple hematologic metrics in spine surgery, as seen more commonly in TKA and THA, most studies still show significant effects of TXA in 1 or more ways. Therefore, most researchers still argue that the effect of TXA on hemostasis would support routine administration in orthopedic spine surgery.

Other than decreasing blood loss and transfusion requirements, TXA use may have other benefits as well. Swelling after surgery is inversely linked to postoperative recovery. An RCT by Ishida et al\textsuperscript{6} suggested that topical injection of TXA could reduce knee joint swelling after TKA because it was most evident in suprapatellar girth at 1 week postoperatively and in calf girth at 2 weeks. This observation suggests that TXA may have an effect on hidden blood loss related to hematoma or hematrophis formation. Zhou et al\textsuperscript{83} reported in their meta-analysis that topical TXA in TKA could reduce hidden blood loss by a mean of 152.70 mL, whereas another study showed that IV TXA was able to decrease external but not hidden blood loss in TKA.\textsuperscript{60} In addition, other studies report that no difference in postoperative joint function exists with TXA use according to hip or knee scores, generic quality of life scores, visual analog scale pain scores, active range of motion, or osteoarthritis index.\textsuperscript{7,29,30,33,57} Controlled, prospective studies are still needed to examine TXA's correlation with patient functional outcomes.

Shorter hospital stays are a significant economic benefit of using TXA. Among the studies listed in Table 2 re-
porting hospital stay or economic data, 11 of 24 illustrate shorter stays. Three of these show statistical significance. Smit et al demonstrated that the TXA group was associated with a hospital stay shortened by approximately 2 days after revision TKA. Interestingly, all 3 studies involved TKA or revision TKA, whereas no THA studies show any significant difference in length of hospital stay. The other significant finding in Table 2 is that there was no change in the median length of hospital stay in one study; however, the interquartile range for length of stay was lower with TXA use. The shorter hospital stay could be attributed to reduced bleeding and transfusion requirements, which can lead to quicker recovery time.

The effect of TXA on operative time seems to be minimal but not fully clear. Some studies have shown a decrease and others an increase, although few have shown any statistical significance. A possible factor for this difference may be that some of these data were collected from TKA surgeries where TXA was administered at the end of the procedure and thus did not affect operative time.

The advantages of using TXA can lead to better economic outcomes. Tranexamic acid is relatively inexpensive and widely available. Currently, hospital cost is roughly $100 per 2000-mg infusion. Although adding TXA will increase pharmacy costs, evidence shows that operating room, blood bank and laboratory, room and board, and total direct hospital costs could be reduced.

Table 2 shows the percentages saved on total hospital cost per patient stay with TXA use in 5 studies that report these data, ranging from 1% to 23%. Considering pharmacy and transfusion costs alone, the combined expense is typically reduced with TXA use as well. According to a cohort study by Gillette et al, pharmacy expenses were the only increased component, from an average of $781 to $921 (an increase equivalent to $140), in TKA and THA, whereas the savings in blood bank and laboratory, operating room, room and board, and hospital total costs were $139, $222, $457, and $870 per patient, respectively. Smit et al calculated a potential average savings of $22,300 in revision TKA with TXA. Chimento et al computed an average savings of $1500 per patient after TKA. Interestingly, Slover and Bosco suggested that the cost-effectiveness of TXA in arthroplasty was correlated with transfusion rates and was more noticeable when baseline blood transfusion rates at an institution were above 25% and the reduction in transfusion rates with TXA use was at least 12%. Although many factors, such as calculation method for costs, market fluctuation, and regional or national variation in health care expenses, can lead to discrepancies, the majority of studies reporting costs offer strong evidence that TXA use is cost-effective.

**CONCLUSION**

Tranexamic acid has shown safety and efficacy in orthopedic surgery, especially TKA, THA, and spine surgery, for controlling peri- and postoperative bleeding. Although universal agreement has not been reached on its administration, it is capable of reducing blood loss and transfusion requirements. By lowering various hospital-related costs, including blood bank, operating room, and room and board, TXA is cost-effective in certain orthopedic procedures. Further study is needed to learn more about TXA’s cost-saving potential and to examine the drug’s safety and complication rates in high-risk patients; the correlation of TXA’s efficacy with different administration methods, dosages, and timing; and the correlation of TXA use with postoperative joint functional outcomes.

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