Safety and Efficacy of Intra-articular Injection of Tranexamic Acid in Total Knee Arthroplasty

YUAN ZHANG, MD; XIN FU, MD; WEN-XING LIU, MS; YAO-MIN LI, MD; XIN-LONG MA, MD; ZHI-JUN LI, PhD

abstract

Tranexamic acid was intra-articularly injected in total knee arthroplasty (TKA) to reduce blood loss and transfusion. However, no single study has been large enough to definitively determine whether it is safe and effective. To determine the safety and efficacy of intra-articular tranexamic acid in TKA, the authors searched various databases for relevant randomized controlled trials. Mean difference (MD) in total blood loss, risk ratio (RR) for transfusion, and complication rate in the tranexamic acid-treated group vs the placebo group were calculated. Seven randomized controlled trials, including 622 patients (174 men and 448 women), were identified. All 7 placebo-controlled randomized trials had a low risk of bias. The pooled results showed a positive effect of tranexamic acid in all treatment groups, with significant reduction in total blood loss (MD, -396.42 mL [95% confidence interval (CI), -629.64 to -163.20]; \( P = .0009 \)). However, there was significant heterogeneity in the finding (chi-square=27.16, \( df=3 \), \( P=89\% \), \( P<.00001 \)) among studies. The pooled results indicated that 5.8% (18 of 309) of tranexamic acid-treated patients required transfusion compared with 27.2% (85 of 313) of placebo-treated patients. This difference was significant (RR, 0.22; 95% CI, 0.14-0.35; \( P<.00001 \)). There was no significant difference between the groups in the incidence of deep venous thrombosis (RR, 0.83; 95% CI, 0.35-1.98; \( P=.68 \)) or pulmonary embolism (RR, 0.54; 95% CI, 0.10-2.85; \( P=.46 \)). In all, intra-articular tranexamic acid significantly reduced total blood loss, drainage, reduction of hemoglobin, and the need for transfusion without increasing the incidence of deep venous thrombosis and pulmonary embolism. Intra-articular tranexamic acid is safe and efficacious in TKA.

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With the aging of the population, the number of patients with osteoarthritis is expected to increase exponentially. Total knee arthroplasty (TKA) is widely used to relieve pain, correct deformity, restore function, and improve joint movement in patients with severe osteoarthritis of the knee. However, TKA is associated with considerable blood loss, as much as 1000 to 1790 mL, and up to 10% to 38% of patients undergoing TKA require allogeneic blood transfusion (1-2 units). This may lead to many complications, such as infection, graft-vs-host disease, transfusion-related acute lung injury, and hemolytic transfusion reactions.

Many methods have been developed to avoid excessive blood loss and transfusion-related complications, such as autologous blood transfusion by blood salvage, hypotensive anesthesia, tourniquet application, and fibrin tissue adhesives. Of these, pneumatic tourniquet compression can induce hypercoagulability and local fibrinolytic activity, resulting in blood loss, which mostly occurs after surgery. Intravenous administration of tranexamic acid, a fibrinolysis inhibitor and plasminogen activator, has long been used to reduce TKA-related blood loss and blood transfusion. Several meta-analyses have shown that intravenous administration of this antifibrinolytic agent reduced postoperative bleeding and the need for transfusion in cardiac, hip, and spine surgeries. However, it is generally agreed that only a small percentage of intravenously injected drug reaches the target location to inhibit tissue fibrinolysis and stabilize clots; the rest of the tranexamic acid enters the extravascular space and accumulates in tissue for up to 17 hours. It has also been reported that intravenous administration of tranexamic acid decreases external blood loss but not hidden blood loss after TKA.

The reduction of hidden blood loss in the joint by intra-articular injection of tranexamic acid has the same beneficial effect as the reduction of external blood loss. Therefore, recently, intra-articular application of tranexamic acid in TKA was introduced and significantly reduced postoperative bleeding and knee swelling. However, no single study has been large enough to definitively determine the safety and efficacy of intra-articular tranexamic acid in TKA. Therefore, the goal of the current meta-analysis was to evaluate the evidence from randomized controlled trials reporting the safety and efficacy of intra-articular tranexamic acid in TKA.

**Materials and Methods**

**Selection Criteria**

The authors identified all published placebo-controlled randomized trials that compared primary unilateral TKA involving intra-articular tranexamic acid vs those involving a placebo to reduce perioperative blood loss. The exclusion criteria were a retrospective trial design, lack of randomization of patients into 2 relevant groups, and focus on a special orthopedic subgroup of patients.

**Search Strategy**

Electronic databases, including MEDLINE, Embase, ScienceDirect, Ovid, and the Cochrane Central Register of Controlled Trials, were searched from the 1960s to July 2013. The following search terms were used to maximize search specificity and sensitivity: tranexamic acid, total knee arthroplasty, and total knee replacement. Broad MeSH terms and Boolean operators were selected for each database. In addition, using the

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**Figure 1:** PRISMA chart of literature search procedure according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (F/M)</th>
<th>Mean±SD Age, y</th>
<th>Mean±SD BMI, kg/m²</th>
<th>TXA Dosage</th>
<th>Tourniquet Pressure</th>
<th>Drain</th>
<th>Blood Transfusion Protocol</th>
<th>DVT Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al[26]</td>
<td>TXA</td>
<td>31 (25/6)</td>
<td>68.4±10.4</td>
<td>31.3±5.4</td>
<td>1500 mg/100 mL</td>
<td>350 mm Hg</td>
<td>No drain</td>
<td>Hb &lt;80 g/L Low-molecular-weight heparin for 10 d after surgery</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>35 (22/13)</td>
<td>67.0±19.9</td>
<td>32.7±5.5</td>
<td>100 mL</td>
<td></td>
<td></td>
<td>Hb &lt;100 g/L with symptoms of ischemia</td>
</tr>
<tr>
<td>Ishida et al[27]</td>
<td>TXA</td>
<td>50 (44/6)</td>
<td>73.3±5.0</td>
<td>26.7±3.1</td>
<td>2000 mg/20 mL</td>
<td>NS</td>
<td>Clamped for 30 min</td>
<td>Active ankle motion to move the legs and train patient to walk</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>50 (44/6)</td>
<td>73.5±6.1</td>
<td>27.4±3.9</td>
<td>20 mL</td>
<td>Removed at 48 h</td>
<td></td>
<td>Arteriovenous impulse system; 10,000 IU heparin sodium</td>
</tr>
<tr>
<td>Sa-Ngasoongsong et al[8]</td>
<td>TXA</td>
<td>24 (22/2)</td>
<td>69.0±8.2</td>
<td>27.0±3.4</td>
<td>250 mg/25 mL</td>
<td>Clamped for 2 h</td>
<td>Hct &lt;25% Hb &lt;8 g/dL; symptoms of ischemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>24 (18/6)</td>
<td>69.2±7.6</td>
<td>26.8±4.1</td>
<td>25 mL</td>
<td>Removed at 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roy et al[29]</td>
<td>TXA</td>
<td>25 (15/10)</td>
<td>66.5±7.2</td>
<td>27.1±2.8</td>
<td>500 mg/5 mL</td>
<td>Clamped for 1 h</td>
<td>Hct &lt;28%; drain collection &gt;500 mL in first 8-10 h along with Hb loss &gt;4 g/dL; subjective symptoms of anemia</td>
<td>Compression stocking and early mobilization; 5000 IU low-molecular-weight heparin once a day</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>25 (16/9)</td>
<td>66.6±8.0</td>
<td>26.9±2.0</td>
<td>5 mL</td>
<td>Removed at 48 h</td>
<td></td>
<td>Range of motion exercise and walker-aided ambulation</td>
</tr>
<tr>
<td>Seo et al[10]</td>
<td>TXA</td>
<td>50 (45/5)</td>
<td>67.5±6.6</td>
<td>27.8±3.5</td>
<td>1500 mg/100 mL</td>
<td>NS</td>
<td>Clamped for 30 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>50 (44/6)</td>
<td>67.8±6.1</td>
<td>27.9±3.3</td>
<td>100 mL</td>
<td>Removed at 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alshryda et al[27]</td>
<td>TXA</td>
<td>79 (49/30)</td>
<td>65.5±9.6</td>
<td>32.24±5.93</td>
<td>1000 mg/50 mL</td>
<td>Clamped for 30 min</td>
<td>Hb &lt;70 g/L; Hb &lt;100 g/L with symptoms of ischemia</td>
<td>Calf pump and body mass index &gt;30 kg/m²; low-molecular-weight heparin beginning on postoperative day 1 and continuing until discharge</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>78 (34/44)</td>
<td>67.1±10.2</td>
<td>31.05±5.03</td>
<td>50 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
same search terms, the authors manually searched for further relevant studies, such as those from the Annual Congress of the European Federation of National Association of Orthopaedic and Trauma, the Annual Congress of the British Orthopaedic Association, and the Google database. These databases were also searched for entries to identify articles that may have been missed in the earlier database search. The reference lists of the full-text papers that were found were examined to identify more studies. No restrictions were made on the language of publication. The search strategy is shown in Figure 1.

**Quality Assessment**

According to the Cochrane Handbook for Systematic Reviews of Interventions 5.0, the risk of bias of the included studies was assessed independently by 2 reviewers (Y.Z., Y.-M.L.). Disagreements were resolved by discussion. When no consensus could be achieved, a senior author (Z.-J.L.) made the final decision. To assess the methodologic quality of the selected studies, the authors applied the Cochrane Collaboration’s tool to assess the risk of bias, which includes the following key domains: adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias.

**Data Extraction**

For each eligible study, 2 reviewers (Y.Z., Y.-M.L.) independently extracted all relevant data. Any disagreement was resolved by discussion; when no consensus could be achieved, the senior author (Z.-J.L.) was the adjudicator who made the final decision. The following data were extracted: (1) demographic data on the participants; (2) information about the TKA procedure; and (3) total blood loss, indication for blood transfusion, number of patients who received allogeneic blood transfusion, and complications. In addition, other outcomes mentioned in individual studies were considered for inclusion. In the case of studies with incomplete or unclear data, attempts were made to contact the investigators for clarification.

**Data Analysis and Statistical Methods**

The meta-analysis was conducted using Review Manager software 5.1 for Windows (RevMan, Version 5.1; The Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark). The authors assessed statistical heterogeneity using the standard chi-square test, with significance set at $P<.1$, and quantified heterogeneity using the $I^2$ statistic. An $I^2$ value of 50% or more was considered to indicate substantial heterogeneity. For trials that showed heterogeneity, pooled data were meta-analyzed with a random-effects model. Otherwise, a fixed-effects model was used. For continuous outcomes, such as total blood loss, means and standard deviations were pooled to a mean difference (MD) and 95% confidence interval (CI). Risk ratios (RRs) and 95% CIs were calculated for dichotomous outcomes, such as requirement for transfusion and incidence of complications.

**RESULTS**

**Search Results**

Figure 1 shows the literature search procedure for selecting studies, according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. The authors identified 102 citations as potentially relevant studies. After screening the title and reading the abstract and the entire article, the authors identified 7 randomized controlled trials comparing the intra-articular application of tranexamic acid with a control group. Among these studies, Onodera et al used carbazochrome sodium sulfonate hydrate in the tranexamic acid group and Maniar et al compared the intra-articular application of tranexamic acid with a control group that was a similar cohort of 40 patients who underwent TKA performed by the same surgeon in January and February 2009, when tranexamic acid was not in use. After
excluding these 2 randomized controlled trials, only 7 placebo-controlled randomized trials comprising a total of 622 patients were eligible for data extraction and meta-analysis. The Table summarizes the key characteristics of the included studies. The individual sample sizes of the 7 studies ranged from 48 to 157 patients. Of the 622 patients (174 men, 448 women), 309 were in the tranexamic acid group and 313 were in the placebo (control) group. Drug dosages varied from 0.25 to 2.0 g per patient. Blood transfusion protocols also differed among the studies.

**Quality Assessment**

Figure 2 shows the methodologic quality of the included studies. This risk of bias tool incorporates the assessment of randomization (sequence generation and allocation concealment), blinding (participants, personnel, and outcome assessors), completeness of outcome data, selection of outcomes reported, and other sources of bias. The items were scored as “yes (+),” “no (-),” and “unsure (?),”

Figure 2: Assessment of the methodologic quality of the included studies. This risk of bias tool incorporates the assessment of randomization (sequence generation and allocation concealment), blinding (participants, personnel, and outcome assessors), completeness of outcome data, selection of outcomes reported, and other sources of bias. The items were scored as “yes (+),” “no (-),” and “unsure (?).”

**Effects of Intervention**

**Total Blood Loss**

Data on total blood loss were available in 4 trials with a total of 344 patients. The pooled results showed a positive effect of tranexamic acid in all treatment groups, with significant reduction in total blood loss (MD, -396.42 mL [95% CI, -629.64 to -163.20]; P=0.0009). However, there was significant heterogeneity in the finding (chi-square=27.16, d=3, I²=89%; P<0.0001) among studies (Figure 4). According to clinical experience, the most

Figure 4: Forest plot showing the effect of tranexamic acid on total blood loss. Abbreviations: CI, confidence interval; IV, intravenous; SD, standard deviation.

Figure 3: Risk of bias. The risk of bias in each item is presented as percentages across all included studies.

Figure 5: Forest plot showing the effect of tranexamic acid on drainage. Abbreviations: CI, confidence interval; IV, intravenous; SD, standard deviation.

Figure 6: Forest plot showing the effect of tranexamic acid on the reduction of hemoglobin. Abbreviations: CI, confidence interval; IV, intravenous; SD, standard deviation.
probable reason for heterogeneity was the use of different methods of measurement to determine total blood loss; therefore, the authors did not perform subgroup analysis to investigate the reason for the high heterogeneity.

**Drainage**

Data on drainage were available for 3 trials. The pooled results showed a positive effect of tranexamic acid in all treatment groups, with a significant reduction in drainage (MD = -286.89 mL [95% CI, -481.54 to -92.24]; P = 0.004). However, there was no evidence of statistically significant heterogeneity in this finding among the included studies (chi-square = 25.95, df = 3, I^2 = 71%; P < 0.00001) among the studies (Figure 5).

**Reduction in Hemoglobin**

The reduction in hemoglobin after surgery was provided in 4 studies. The pooled results indicated a positive effect of tranexamic acid in all treatment groups, with less decrease in hemoglobin (MD = -0.71 g/dL [95% CI, -1.12 to -0.30]; P = 0.0007). There was no evidence of statistically significant heterogeneity in this finding among the included studies (chi-square = 10.43, df = 5, I^2 = 77%; P = 0.02) (Figure 6).

**Requirement for Transfusion**

The number of patients who required transfusion after surgery was provided in all 7 studies. The pooled results indicated that 5.8% (18 of 309) of tranexamic acid-treated patients required transfusion compared with 27.2% (85 of 313) of placebo-treated patients. This difference was significant (RR = 0.22; 95% CI, 0.14-0.35; P < 0.00001). There was no evidence of statistically significant heterogeneity in this finding among the included studies (chi-square = 6.84, df = 3, I^2 = 12%; P = 0.34) (Figure 7).

**Complications**

No complications were documented in studies by Ishida et al., S. Ngasoongsong et al., and Roy et al. The pooled results indicated that there was no significant difference between the groups in the incidence of deep venous thrombosis (RR, 0.83; 95% CI, 0.35-1.98; P = 0.68) or pulmonary embolism (RR, 0.54; 95% CI, 0.10-2.85; P = 0.46).

**DISCUSSION**

A variety of methods have been used to reduce blood loss during TKA, including autologous blood transfusion, intra- and postoperative blood recovery, drug treatment, controlled hypotension, and a combination of several methods. Antifibrinolytic drugs, especially tranexamic acid, have been used in cardiac, orthopedic, and liver surgery to reduce blood loss without increasing related complications or the risk of deep venous thrombosis. Intravenous tranexamic acid administration has been found to effectively reduce blood loss and the need for transfusion. In recent years, intra-articular injection of tranexamic acid has been used in many studies, with better results. However, the small study size and the different tranexamic acid dosages used in these studies limited their statistical power. Therefore, the goal of the current study was to pool the current evidence for intra-articular injection of tranexamic acid in TKA and objectively evaluate the safety and efficacy of this treatment. Methodologic quality assessment identified some limitations of the current evidence. Only 9 randomized controlled trials satisfied the defined eligibility criteria, and the size of the comparative groups was small. The overall methodologic quality of the included studies was relatively high. Although all of the studies reported randomization, 4 studies did not describe the specific methods of binding. The lack of binding of surgeons and assessors to the injection solution could have introduced expectation bias and potential statistical type II errors for these clinical outcomes. Some degree of clinical heterogeneity was induced by the following factors. First, clinical heterogeneity may be introduced because of differences in the indications for transfusion, the surgical techniques at different centers, and the complexity of the surgical procedures. Second, total blood loss may be affected by surgical time and type of implant. Finally, characteristics of the patients in the individual studies, such as age, preexisting comorbidities, and economic reasons, may also be confounding factors that influence the stability of the pooled results. Accordingly, these defects in methodologic quality should be considered when interpreting the findings.

This meta-analysis showed that compared with placebo, intra-articular tranexamic acid injection significantly reduced total blood loss and the need for blood transfusion in TKA. Patients who undergo TKA often experience considerable blood loss and even coagulation disorders that may necessitate blood transfu...
Allogeneic blood transfusions are associated with risks, such as transmission of infectious diseases, allergic reactions, transfusion reactions, and acute lung injury. Furthermore, homologous blood transfusions are expensive. Although the indications for blood transfusions varied among the studies, the most important result of this review was that tranexamic acid reduced the rate of transfusions. More patients required transfusions in the placebo group than in the tranexamic acid-treated group, which was consistent with the results of the included studies and other studies.

Deep venous thrombosis is a common complication of TKA and can result in morbidity or even mortality when it progresses to pulmonary embolism. Prophylactic measures against deep venous thrombosis were adopted in all of the included randomized controlled trials and were as follows: continuous passive motion after removal of the drains, use of an arteriovenous impulse system, application of compression stockings, early mobilization, and treatment with heparin sodium or low-molecular-weight heparin until discharge. The results showed that there was no significant difference between groups in the incidence of complications, indicating that tranexamic acid did not increase the risk of severe complications. This finding was consistent with the results of other studies.

The current meta-analysis had several potential limitations. First, only 7 studies were included, and the sample sizes were small. The authors could not perform a valid statistical analysis for the safety assessment of the use of tranexamic acid in TKA. Statistical efficacy could be improved by including more studies with larger sample sizes in the future. Second, operative procedures and methods of calculating perioperative blood loss differed among the included studies. This difference could introduce bias in the amount of blood lost during surgery. Third, because of the limited scope of the included studies, subgroup analysis could not be performed for any source of heterogeneity, and this may influence the consistency of outcomes. Finally, the potential incompleteness of the reviewed evidence may have limited the validity of the pooled results. However, the current meta-analysis had several strengths, such as the inclusion of well-designed randomized controlled trials with quantitative analysis and comprehensive methodological quality.

**CONCLUSION**

Based on the current evidence, this meta-analysis showed that intrarticular application of tranexamic acid is a safe and efficacious treatment to reduce blood loss and the need for blood transfusion in TKA without increasing the incidence of complications. Further high-quality randomized controlled trials should be designed to examine the best therapeutic dosage and application time of tranexamic acid to reduce blood loss in TKA.

**REFERENCES**