Effect of Topical Tranexamic Acid in Reducing Bleeding and Transfusions in TKA

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educational objectives

As a result of reading this article, physicians should be able to:

1. Recognize the efficacy and safety of topical tranexamic acid (TXA) for reducing bleeding and transfusions in total knee arthroplasty (TKA).
2. Describe the main methods of application of topical TXA in TKA.
3. Identify the potential advantages of topical TXA compared with intravenous TXA.
4. Recognize the possible differences between high-concentration and low-concentration topical TXA in reducing bleeding and transfusions in TKA.

ABSTRACT

Topical tranexamic acid (TXA) has been identified to be effective in total knee arthroplasty (TKA), but the effect of topical application is still unclear. Therefore, the authors conducted a meta-analysis to assess the effect of topical TXA in TKA. Twelve trials with a total of 1179 knees were included. The results revealed that the application of topical TXA in TKA significantly reduced total blood loss by a mean of 280.65 mL and reduced transfusions without increasing the risks of deep venous thrombosis and pulmonary embolism. Topical TXA also reduced postoperative drain output by a mean of 194.59 mL and lowered postoperative hemoglobin drop by a mean of 0.66 g/dL. In addi-
Total knee arthroplasty (TKA) is routinely used to treat end-stage osteoarthritis and other joint diseases, such as rheumatoid arthritis. The final result of TKA is satisfactory in most patients. However, TKA is associated with significant blood loss,1,2 often requiring allogenic blood transfusions. A transfusion rate of 11% to 21% has been reported in TKA.3 However, transfusion may carry potential risks, such as immunological reactions, infection, intravascular hemolysis, renal failure, and even death, and it should be avoided if possible.4,5

Numerous methods of controlling bleeding have been used to avoid transfusion, including autologous blood transfusion, intraoperative blood saving, hypotensive anesthesia, erythropoietin, and the use of antifibrinolytic agents.6,7 Tranexamic acid (TXA), a kind of synthetic antifibrinolytic, can inhibit both fibrinolysis and the activation of plasminogen by plasminogen activator; therefore, it is able to delay fibrinolysis and stop bleeding.8

Tranexamic acid has been used successfully in dental extraction, tonsillectomy, prostate surgery, heavy menstrual bleeding, and cardiac surgery and in patients with hemophilia.7 Benoni et al9 first reported the efficacy of TXA in TKA in 1994, and numerous studies have explored the efficacy and safety of intravenous (IV) TXA in reducing blood loss and transfusions.10-19 Almost all of these studies reached the positive conclusion that IV TXA may reduce bleeding and transfusion rate without increasing the risk of deep venous thrombosis (DVT) in TKA.

Compared with IV TXA, topical TXA has the advantages of being easy to administer, providing a maximum concentration of TXA at the bleeding site, and being associated with little or no systemic TXA absorption.20 Wong et al21 reported that topical application of TXA directly into the surgical wound reduced postoperative bleeding by 300 to 400 mL, resulting in 16% to 17% higher postoperative hemoglobin levels compared with placebo. Alshryda et al22 reported that topical TXA was effective in reducing the need for blood transfusion after TKA without adverse effects. However, some studies had the shortcomings of poor design, small sample size, low power, and inconclusive results, so the results may have prejudiced the use of these potentially valuable agents. In addition, although 2 related systematic reviews assessed the effect of topical TXA in TKA and reached the same positive conclusion,22,23 the quantity of literature included in the reviews was insufficient, so their conclusions may be biased. Therefore, the current authors performed a systematic review and meta-analysis to investigate the efficacy and safety of topical TXA for reducing bleeding and transfusions in TKA.

## Materials and Methods

### Search Strategy

Two reviewers (C.Y., P.K.) independently completed a systematic review and meta-analysis to investigate the efficacy and safety of topical TXA for reducing bleeding and transfusions in TKA.

### Quality Assessment of the Included Literature

The Jadad score24 was used to assess the methodological strength of the included literature, and the authors considered a Jadad score of more than 3 points to indicate high quality. Two authors (C.Y., P.K.) completed the assessments independently, and there were no differing views. The Jadad scale criteria are listed in Table 1.

### Statistical Analysis

The included studies were analyzed with RevMan 5.2 statistical software (The Cochrane Collaboration, London, United Kingdom). Continuous data (total blood loss, total drain output, and postoperative hemoglobin drop) were recorded as weighted mean differences.
and 95% confidence intervals (CIs). Dichotomous data (transfusion rate and DVT and PE events) were recorded as proportions, and the effect of intervention was recorded as a risk ratio. All results were assessed for statistical heterogeneity with the chi-square test and $I^2$ test. A fixed-effects model was used when the $P$ value was .1 or greater and the $I^2$ value was 50% or less (considered no $I^2=0\% \text{ to } 25\%$ or low $I^2=25.1\% \text{ to } 50\%$ statistical heterogeneity). A random-effects model was used when the $P$ value was less than .1 and the $I^2$ value was greater than 50% (considered moderate $I^2=50.1\% \text{ to } 75\%$) or high $I^2=75.1\% \text{ to } 100\%$ statistical heterogeneity).

Subgroup Analysis

The authors also evaluated the influence of different topical application doses and concentrations. For different doses, 2 subgroups were created: the low-dose topical TXA group included studies in which the total dose of topical TXA did not achieve 2 g, and the high-dose topical TXA group included studies in which the total dose of topical TXA was not less than 2 g. Similarly, for different concentrations, 2 subgroups were created: the low-concentration topical TXA group included studies in which the concentration of topical TXA was less than 20 mg/mL, and the high-concentration topical TXA group included studies in which the concentration of topical TXA was 20 mg/mL or more.

Subgroup analyses of different dose groups and concentration groups were performed for all the primary outcomes except PE.

RESULTS

Online Search

A total of 613 studies were identified after a search of Ovid, PubMed, EMBASE, the Cochrane Library, and CNKI and of the references of the retrieved articles. Duplicate studies were removed, leaving 47 studies. After reading the abstracts, 31 studies were excluded for being retrospective, for examining oral or IV TXA application, or for other reasons. The remaining 16 studies were assessed by reading the full texts, and 4 were excluded for poor design or too-small sample sizes. Finally, 12 studies involving 1179 knees met the inclusion criteria and were included in the

Table 1

| Jadad Scale |
|---------------------|---------------------|
| **Item Assessed** | **Description** | **Score** |
| Randomization | A detailed and appropriate description for randomization | 2 |
| | General comments without a detailed description | 1 |
| | The description is inappropriate | 0 |
| Blinding | A detailed and appropriate description for blinding | 2 |
| | General comments without a detailed description | 1 |
| | The description is inappropriate | 0 |
| Withdrawals | A detailed and appropriate description for withdrawals and drop-outs | 1 |
| and drop-outs | No description or the description is inappropriate | 0 |

Figure 1: Flowchart of study selection.
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients (TXA/Control)</th>
<th>Dose/Concentration of TXA</th>
<th>Intervention</th>
<th>Drainage</th>
<th>Blood Transfusion Protocol</th>
<th>DVT Prophylaxis</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alshryda et al</td>
<td>157 (79/78)</td>
<td>1.0 g TXA/50 mL NS</td>
<td>Sprayed into the wound at end of operation</td>
<td>Drain clamped for 30 min</td>
<td>Hb &lt;7 g/dL; Hb &lt;8 g/dL and tolerated anemia poorly; 7 g/dL &lt; Hb &lt; 10 g/dL + clinical symptoms</td>
<td>Mechanical and mechanical + LMWH when BMI &lt; 30 kg/m²</td>
<td>5</td>
</tr>
<tr>
<td>Wong et al</td>
<td>99 (33 [3 g/31 [1.5 g/35]</td>
<td>1.5 g TXA/100 mL NS</td>
<td>Local application at end of operation</td>
<td>No drains</td>
<td>Hb &lt; 8.0 g/dL; Hb &lt; 10.0 g/dL + clinical symptoms</td>
<td>LMWH</td>
<td>5</td>
</tr>
<tr>
<td>Sa-ngasoongsong et al</td>
<td>135 [45 [500 mg/45 [250 mg/45]</td>
<td>250 mg TXA/25 mL NS</td>
<td>Injected into the knee joint after fascia closure</td>
<td>Clamping for 2 h</td>
<td>Hct &lt; 25%; Hb &lt; 8.0 g/dL</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Martin et al</td>
<td>50 (25/25)</td>
<td>2 g TXA/100 mL NS</td>
<td>Intra-articular injection before joint closure</td>
<td>No drains</td>
<td>Symptomatic hypotension + Hb &lt; 7 g/dL</td>
<td>Mechanical + warfarin (in hospital) and aspirin (out of hospital)</td>
<td>4</td>
</tr>
<tr>
<td>König et al</td>
<td>159 (130/29)</td>
<td>3 g TXA/100 mL NS</td>
<td>Intra-articular injection before fascia closure</td>
<td>Clamping for 1 h</td>
<td>Hb &lt; 8.0 g/dL + clinical symptoms</td>
<td>NR</td>
<td>2</td>
</tr>
<tr>
<td>Georgiadis et al</td>
<td>101 (50/51)</td>
<td>2 g TXA/75 mL NS</td>
<td>Applied to the wound during cement hardening for 5 min</td>
<td>NR</td>
<td>Hb &lt; 8.0 g/dL + clinical symptoms; Hb &lt; 7.0 g/dL</td>
<td>LMWH</td>
<td>5</td>
</tr>
<tr>
<td>Roy et al</td>
<td>50 (25/25)</td>
<td>0.5 g TXA/5 mL NS</td>
<td>Intra-articular application at end of operation</td>
<td>Clamping for 1 h</td>
<td>Hct &lt; 28%; drain &lt; 500 mL in first 8 - 10 h; Hb drop &lt; 4 g/dL + clinical symptoms</td>
<td>Mechanical + LMWH</td>
<td>4</td>
</tr>
<tr>
<td>Ishida et al</td>
<td>100 (50/50)</td>
<td>2 g TXA/20 mL NS</td>
<td>Intra-articular application at end of operation</td>
<td>Clamping for 30 min</td>
<td>NR</td>
<td>Heparin</td>
<td>3</td>
</tr>
<tr>
<td>Rajesh et al</td>
<td>80 (40/40)</td>
<td>3 g TXA/100 mL NS</td>
<td>Local application before tourniquet release</td>
<td>Clamping for 2 h</td>
<td>Hb &lt; 8.5 g/dL; Hb &lt; 10.0 g/dL + cardiac disorder; 8.5 &lt; Hb &lt; 10.0 g/dL + clinical symptoms</td>
<td>LMWH</td>
<td>3</td>
</tr>
<tr>
<td>Onodera et al</td>
<td>100 (50/50)</td>
<td>1 g TXA/50 mL NS</td>
<td>Intra-articular application</td>
<td>Clamping for 60 min</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Sa-ngasoongsong et al</td>
<td>48 (24/24)</td>
<td>250 mg TXA/25 mL NS</td>
<td>Intra-articular injection after fascia closure</td>
<td>Drain clamp for 2 h</td>
<td>Hct &lt; 25%; Hb &lt; 8.0 g/dL</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Seo et al</td>
<td>101 (50/50)</td>
<td>1.5 g TXA/100 mL NS</td>
<td>Directly into the joint cavity while suturing</td>
<td>NR</td>
<td>Hb &lt; 8.0 g/dL + clinical symptoms; Hb &lt; 7.0 g/dL</td>
<td>NR</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; DVT, deep venous thrombosis; Hb, hemoglobin; HCT, hematocrit; LMWH, low-molecular-weight heparin; NR, not reported; NS, normal saline; TXA, tranexamic acid.
meta-analysis. The details of study identification and inclusion and exclusion criteria are listed in Figure 1.

Description of Included Studies
All included studies were published in English; no Chinese studies met the inclusion criteria. Most of the studies included small samples, but the studies had high Jadad scores. Of the 12 included studies, 3 received a Jadad score of 5,20,21,28 4 received a Jadad score of 4,25,26,29,33 and 4 received a Jadad score of 3,30-32,34; these 11 studies were considered high quality. One study received a Jadad score of 2 points27, however, its sample size was larger than those in the other studies, so it was included in the meta-analysis.

The most common diagnosis was osteoarthritis. Different doses and modes of TXA were used in different studies. The highest dose for topical application of TXA was 3 g, which was reported in 3 studies21,27,31; the lowest dose was 0.25 g, which was reported in 2 studies.25,33 The concentrations of topical TXA ranged from a low of 10 mg/mL25,33 to a high of 100 mg/mL.29,30 Temporary postoperative clamping ranging from 30 minutes to 2 hours was reported in 8 studies20,25,27,29-33; Wong et al21 and Martin et al26 did not report the use of drainage. Ten studies20,21,25-29,31,33,34 described the blood transfusion protocol. In addition, 7 studies20,21,25,28-31 gave detailed descriptions of the methods of prophylaxis against DVT; low-molecular-weight heparin (LMWH) or LMWH combined with mechanical prophylaxis were the most common methods, used in all studies except those of Ishida et al30 and Martin et al.26 The included studies are described in Table 2.

Effect of Intervention
Primary Outcomes. Total Blood Loss.
Eight studies examining 880 patients, including 513 patients in the TXA group and 367 patients in the control group, reported total blood loss. The use of topical TXA significantly reduced total blood loss by a mean of 280.65 mL (95% CI, -376.43 to -184.88; P<.00001). However, there was significant heterogeneity among the studies (I²=90%), so a random-effects model was used (Figure 2).

Transfusion Rate. Transfusion rate was reported in 11 studies examining 1129 knees (652 in the TXA group and 477 in the control group). The current meta-analysis indicated a significantly lower risk of transfusion requirements in the TXA group compared with the control group (risk ratio=0.26; 95% CI, 0.19 to 0.37; P<.0001; F=34%; fixed-effects model) (Figure 3).
Deep Venous Thrombosis and Pulmonary Embolism Events. All 12 included studies examining 1179 knees reported DVT and PE events, including 677 knees in the TXA group and 502 knees in the control group. The meta-analysis showed that the risk of DVT was not significantly different among study groups (risk ratio=0.87; 95% CI, 0.41 to 1.86; P=0.73; I²=0%; fixed-effects model), nor was the risk of PE (risk ratio=0.66; 95% CI, 0.09 to 4.80; P=0.68; I²=0%; fixed-effects model) (Figures 4-5).

Secondary Outcomes. Total Drain Output. Total drain output was reported in 5 studies examining 470 knees in the TXA group and 212 in the control group. Total drain output in the TXA group was significantly less than that in the control group. Topical TXA effectively decreased drainage by a mean of 194.59 mL (95% CI, -315.86 to -73.32; P<.002). However, there was significant heterogeneity among the included studies (I²=63%), so a random-effects model was used (Figure 6).

Postoperative Hemoglobin Drop. Postoperative hemoglobin drop was reported in 7 studies with 693 knees (419 in the TXA group and 274 in the control group). The use of TXA significantly reduced postoperative hemoglobin drop by a mean of 0.66 g/dL (95% CI, -0.81 to -0.52; P<0.0001; I²=41%) (Figure 7).

Subgroup Analysis Outcomes. Different Dosage Groups. Using a forest plot of subgroup analysis for different doses, both high-dose and low-dose topical TXA significantly reduced total blood loss and transfusions without increasing the risk of DVT. However, the differences in total blood loss and transfusion between study groups were not significant (total blood loss: mean reduction of 294.43 mL in high-dose group vs 277.41 mL in low-dose group; transfusion rate: risk ratio=0.25 in high-dose group vs 0.26 in low-dose group) (Figure 8).

Different Concentration Groups. Subgroup analysis of different concentrations presented a different result. Both high-concentration and low-concentration topical TXA significantly reduced total blood loss and transfusions without increasing the risk of DVT. However, there were significant differences in total blood loss and transfusions between different concentration groups (total blood loss: mean reduction of 335.79 mL in high-concentration group vs 213.47 mL in low-concentration group; transfusion rate: risk ratio=0.23 in high-concentration group vs 0.37 in low-concentration group) (Figure 9).

DISCUSSION

The result of this meta-analysis showed that the topical application of TXA can effectively reduce total blood loss and transfusion rate without increasing the risk of DVT and PE in TKA. In addition, topical TXA can reduce total
drain output and postoperative hemoglobin drop. The topical application of TXA in TKA is safe and effective.

The reductions in total blood loss and transfusions and the safety of topical TXA, namely not increasing the risk of DVT and PE events, were its most important effects; therefore, the authors chose total blood loss, transfusion rate, and DVT and PE events as the primary outcomes.

A total of 12 studies examining 1179 knees were analyzed in this meta-analysis. The results revealed that the application of topical TXA significantly reduced total blood loss by a mean of 280.65 mL (95% CI, -376.43 to -184.88; P<.00001) and significantly decreased the transfusion rate (risk ratio=0.27; 95% CI, 0.19 to 0.38; P<.00001) in TKA. The risks of DVT (risk ratio=0.87; 95% CI, 0.41 to 1.86; P=.73) and PE (risk ratio=0.66; 95% CI, 0.09 to 4.80; P=.68) among the study groups were not statistically significant. In addition, topical TXA reduced postoperative drain output by a mean of 194.59 mL (95% CI, -315.86 to -73.32; P<.002) and postoperative hemoglobin drop by a mean of 0.66 g/dL (95% CI, -0.81 to -0.52; P<.00001).

Systematic reviews by Panteli et al.22 and Chen et al.23 showed different effects of high-dose and low-dose topical TXA. However, the number of studies they included was not high enough; therefore, to verify this conclusion, the current authors also performed subgroup analysis. In addition, previous studies reported that a topical TXA solution of 10 to 20 mg/mL was the lowest appropriate concentration for antifibrinolytic action,23,35,36 and the effect of different concentrations of topical TXA for reducing bleeding and transfusions may be not the same, so the current authors also performed subgroup analysis on different concentrations. The results of subgroup analysis showed that bleeding and transfusion rates were related to the concentration of topical TXA rather than to the total dosage of topical TXA.

**Figure 8:** Forest plot of subgroup analysis of different dosage groups for total blood loss. Abbreviations: CI, confidence intervals; df, degrees of freedom; IV, inverse variance; Random, random-effects model; TXA, tranexamic acid (A). Forest plot of subgroup analysis of different dosage groups for transfusion rate. Abbreviations: CI, confidence intervals; df, degrees of freedom; Fixed, fixed-effects model; IV, inverse variance; TXA, tranexamic acid (B). Forest plot of subgroup analysis of different dosage groups for deep venous thrombosis (DVT). Abbreviations: CI, confidence intervals; df, degrees of freedom; Fixed, fixed-effects model; IV, inverse variance; TXA, tranexamic acid (C).
The heterogeneity of total blood loss was very high, so the authors used a random-effects model to analyze these data, which may result in bias. The authors thought that several things may have resulted in the high heterogeneity, such as different drug dosages, different methods of anticoagulation, and different calculation methods. They felt that the most important reason for the high heterogeneity was that the calculation methods for total blood loss differed in different studies. Onodera et al.32 and Seo et al.34 did not report the calculation method used for total blood loss. Alshryda et al.20 used the Gross formula37 to calculate total blood loss. König et al.,27 Georgiadis et al.,28 and Rajesh et al.31 used the formulas of Nadler et al.38 and Good et al.10 to evaluate total blood loss; Sa-ngasoongsong et al.33 reported that they used a specific formula39,40 but did not give a detailed description. These different methods may carry bias and increase heterogeneity. For postoperative drain output, the heterogeneity was very high (I² = 90%), and this may be caused by the different timing of drain clamping, drug dosages, and perioperative management protocols. The authors used a random-effects model to assess this, which may carry bias.

This meta-analysis has several strengths. First, compared with a related systematic review22 and a previously published meta-analysis,23 the current meta-analysis included more studies reported in the past year, so the results and conclusions may be more reliable. Second, the quality assessment scores for almost all of the included studies were high, which contributed to the strength of their conclusions. Third, through the subgroup analysis, the authors found that a high concentration of topical TXA can reduce bleeding and transfusions more effectively than a low concentration. However, high-dose TXA may not be more effective than low-dose TXA, a result that has not been previously reported.
The main limitation of this meta-analysis was the high heterogeneity of total blood loss. The authors analyzed these data with a random-effects model, which may increase bias for the result. However, the authors did not feel that it would significantly influence the conclusion.

CONCLUSION

Through this meta-analysis, the authors proved that (1) topical TXA can effectively reduce bleeding and transfusions in TKA without increasing the risk of DVT and PE and can also reduce post-operative drain output and hemoglobin drop; (2) both high-dose (≥2 g) and low-dose (<2 g) topical TXA can significantly reduce bleeding and transfusions, but a high dose may not be more effective in reducing bleeding and transfusions than a low dose; (3) high-concentration (≥20 mg/mL) topical TXA may be better at reducing bleeding and transfusions than low-concentration (<20 mg/mL) topical TXA.

REFERENCES


