Efficacy of topical vs intravenous tranexamic acid in reducing blood loss and promoting wound healing in bone surgery: A systematic review and meta-analysis

Jian-Wen Xu, Hong Qiang, Ting-Li Li, Yi Wang, Xiao-Xiao Wei, Fei Li

META-ANALYSIS

BACKGROUND
Tranexamic acid (TXA) has been used as an anti-fibrinolytic drug for over half a century and has received much attention in recent decades.

AIM
To evaluate the efficacy of topical vs intravenous TXA in reducing blood loss and promoting wound healing in bone surgery.

METHODS
From the electronic resources, PubMed, Cochrane Library, Embase, ISI, and Scopus were used to perform a literature search over the last 10 years between 2010 and 2020. EndNote™ X8 was used for managing the electronic resource. Searches were performed with mesh terms. The data were retracted blindly by two independent reviewers. Random effects were used to deal with potential heterogeneity and I² showed heterogeneity. Chi-square (I²) tests were used to quantify the extent of heterogeneity (P < 0.01 was considered statistically significant). The efficacy of topical TXA in reducing blood loss and promoting wound healing in bone surgery was compared with intravenous TXA and placebo.

RESULTS
According to the research design, 1360 potentially important research abstracts and titles were discovered in our electronic searches, and 18 papers remained in...
agreement with our inclusion criteria. It was found that TXA reduced 277.51 mL of blood loss compared to placebo, and there was no significant difference between topical TXA and IV TXA in reducing blood loss in bone surgery. Our analyses also showed that TXA significantly reduced blood transfusion compared to placebo and there was no significant difference between topical TXA and IV TXA.

**CONCLUSION**

The use of both topical and intravenous TXA are equally effective in reducing blood loss in bone surgery, which might be beneficial for wound healing after surgery.

**Key Words:** Tranexamic acid; Blood loss; Wound healing; Bone surgery; Meta-analysis

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Core Tip: Although tranexamic acid (TXA) is regularly used by surgeons, a comprehensive guideline on safe topical doses and methods for TXA administration has remained controversial. This study showed that both topical and intravenous TXA are equally effective in reducing blood loss in bone surgery, which is thus beneficial for wound healing after surgery.

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**INTRODUCTION**

Wound healing is a natural biological process, in which all four stages, including homeostasis (stop bleeding), inflammation, proliferation, and maturation, must occur within a time frame for successful wound healing[1,2]. The use of tranexamic acid (TXA) as an anti-fibrinolytic drug has been available for over half a century and has received much attention in recent decades[3]. By binding to plasminogen, TXA prevents the conversion of plasminogen to plasmin, thus preventing fibrinolysis[4]. The use of TXA reduces blood loss and blood transfusion in major orthopedic surgery, and the safety is also well recognized[5-8]. Previous studies have not confirmed any increased risk of thromboembolism after the use of TXA in various surgeries[9-11]. Topical use of TXA is increasingly popular today, but surgeons do not have a comprehensive guideline on safe topical doses and methods of administration, as topical use is still off-label[12]. There have been two meta-analysis studies discussing efficacy of topical vs intravenous TXA in total hip arthroplasty and total knee arthroplasty, respectively[13,14]. However, the efficacy of topical vs intravenous TXA in reducing blood loss and promoting wound healing in bone surgery remains to be systemically reviewed.

Therefore, the aim of this systematic review and meta-analysis was to evaluate the efficacy of topical vs intravenous TXA in reducing blood loss and promoting wound healing in bone surgery.

**MATERIALS AND METHODS**

**Search strategy techniques**

From the electronic resources, PubMed, Cochrane Library, Embase, ISI, and Scopus were used to perform a literature search over the last 10 years between 2010 and 2020. EndNote™ X8 was used for managing the electronic resources. Searches were performed with mesh terms: (“Tranexamic Acid/administration and dosage”[Mesh]
OR "Tranexamic Acid/adverse effects"[Mesh] OR "Tranexamic Acid/blood"[Mesh] OR "Tranexamic Acid/standards"[Mesh] OR "Tranexamic Acid/toxicity"[Mesh]) AND ("Wound Healing/blood"[Mesh] OR "Wound Healing/blood supply"[Mesh] OR "Wound Healing/ complications"[Mesh] OR "Wound Healing/drug effects"[Mesh] OR "Wound Healing/innervation"[Mesh] OR "Wound Healing/pharmacology"[Mesh] OR "Wound Healing/surgery"[Mesh] OR “Wound Healing/therapy”[Mesh])) OR (“Blood Loss, Surgical”[Mesh] OR “Hemorrhage”[Mesh] OR “Postoperative Hemorrhage”[Mesh] ) OR “Homeostasis”[Mesh] ) OR “Bleeding Time”[Mesh] ) OR “Inflammation”[Mesh] ) OR “Cell Proliferation”[Mesh].

The present systematic review and meta-analysis protocol was prepared by PRISMA checklist[15], and Population/Patient, Exposure/Intervention, Comparison, and Outcome strategy (Table 1).

Selection criteria

Inclusion criteria: Randomized controlled trials, controlled clinical trials, and prospective and retrospective cohort studies; human; topical TXA or intravenously administered TXA; adults; bone surgery trials; and in English.

Exclusion criteria: In vitro studies, case studies, case reports, and reviews; animal studies; oral TXA; and studies without a control group.

Data extraction and method of analysis: The data were extracted from the related studies including years, study design, number of patients, mean/range of age, interventions group, control group, and clinical endpoints. The quality of studies included was assessed using the Cochrane Collaboration’s tool [16]. The scale score for low risk was 1 and that for high and unclear risk was 0. Scale scores ranged from 0 to 6. A higher score indicated higher quality.

Two reviewers blindly and independently extracted the data. Odds ratio (OR) with 95% confidence interval (CI), fixed effects model and Mantel-Haenszel method and mean difference with 95%CI, random effect model and restricted maximum likelihood method were calculated. Random effects were used to deal with potential heterogeneity and $I^2$ showed heterogeneity. Chi-square ($P$) tests were performed to quantify the extent of heterogeneity ($P$ value < 0.01 was considered statistically significant). $I^2$ values > 50% indicated moderate-to-high heterogeneity. Software Stata/MP v.16 (fastest version of Stata) was used for statistical analysis.

RESULTS

According to the research design, 1360 potentially important research abstracts and titles were discovered in our electronic searches. In the first phase of the study selection, 1312 studies were left after removing copies. Then 1247 in vitro studies, case studies, case reports, and reviews or those that did not meet the eligibility criteria were excluded. Therefore, we fully assessed the complete full-text papers of the remaining 65 studies in the second stage, and 47 publications were excluded due to the lack of the defined inclusion criteria. Finally, 18 papers remained in agreement with our inclusion criteria required (Figure 1).

Characteristics

Eighteen studies (randomized controlled trials) were included. The total sample size was 1994. All of the studies evaluated the efficacy of TXA in bone surgical patients. In detail, nine studies evaluated the efficacy of TXA in total knee arthroplasty, two evaluated the efficacy of TXA in trochanteric fracture surgery, one evaluated the efficacy of TXA in intertrochanteric fractures, two evaluated the efficacy of TXA in total shoulder arthroplasty, two evaluated the efficacy of TXA in total hip replacement and one evaluated the efficacy of TXA in orthognathic surgery (Table 2)[17-34].

Transfusion rate

The effects of TXA and placebo were compared in 10 studies about bone surgery. The OR was -1.56 (95%CI: -1.96 to -1.17; $P = 0.00$), and moderate heterogeneity was found ($P = 35.63%$). Our results showed that TXA significantly reduced blood transfusion compared to placebo (Figure 2).

The effects of topical TXA and IV TXA were compared in five studies about bone surgery. The OR was 0.20 (95%CI: -0.50 to 0.89; $P = 0.58$), and there was mild hetero-
Table 1: Population/Patient, Exposure/Intervention, Comparison, and Outcome strategy

| PICO or PECO strategy | Description |
|-----------------------|-------------|
| P                     | Population/Patient: Adult patients |
| E                     | Exposure/Intervention: Tranexamic acid |
| C                     | Comparison: Placebo or standard care |
| O                     | Outcome: Blood loss |

PECO: Population/Patient, Exposure, Comparison, and Outcome; PICO: Population/Patient, Intervention, Comparison, and Outcome.

Table 2: Studies selected for systematic review and meta-analysis

| Ref. | Study design | Sample size | Procedure | Intervention group and control group |
|------|--------------|-------------|-----------|--------------------------------------|
| 1    | Lei et al[17], 2020 | RCT | 132 | Total knee arthroplasty | IV TXA, placebo |
| 2    | Luo et al[18], 2019 | RCT | 90 | Trochanteric fracture surgery | IV TXA, placebo |
| 3    | Chen et al[19], 2019 | RCT | 166 | Trochanteric fracture surgery | IV TXA, placebo |
| 4    | Zhang et al[20], 2019 | RCT | 50 | Total knee arthroplasty | Topical TXA, IV TXA |
| 5    | Zhou et al[21], 2019 | RCT | 100 | Intertrochanteric fractures | Topical TXA (1 g), placebo |
| 6    | Cvetanovich et al[22], 2018 | RCT | 110 | Total shoulder arthroplasty | TXA, placebo |
| 7    | Huang et al[23], 2017 | RCT | 150 | Total knee arthroplasty | Topical TXA (1 g), IV TXA, placebo |
| 8    | Vara et al[24], 2017 | RCT | 102 | Total shoulder arthroplasty | Topical TXA, placebo |
| 9    | Goyal et al[25], 2017 | RCT | 168 | Total knee arthroplasty | TXA, IV TXA |
| 10   | Chen et al[26], 2016 | RCT | 100 | Total knee arthroplasty | Topical TXA, IV TXA |
| 11   | Drosos et al[27], 2016 | RCT | 90 | Total knee arthroplasty | Topical TXA: 1 g, placebo, IV TXA |
| 12   | Keyhan et al[28], 2016 | RCT | 120 | Total knee arthroplasty | Topical TXA: 3 g, placebo, IV TXA (500 g) |
| 13   | North et al[29], 2016 | RCT | 139 | Total hip replacement | Topical TXA: 2 g, IV TXA (2 g) |
| 14   | Aguilera et al[30], 2015 | RCT | 150 | Total knee arthroplasty | Topical TXA: 1 g, IV TXA (2 g), placebo |
| 15   | Eftekharian et al[31], 2015 | RCT | 56 | Orthognathic surgery | Topical TXA: 1 g, placebo |
| 16   | Gillespie et al[32], 2015 | RCT | 111 | Total shoulder arthroplasty | Topical TXA: 2 g, placebo |
| 17   | Taheriazam et al[33], 2015 | RCT | 80 | Total hip replacement | Topical TXA, IV TXA |
| 18   | Yang et al[34], 2015 | RCT | 80 | Total knee arthroplasty | Topical TXA, placebo |

RCT: Randomized Controlled Trial; TXA: Tranexamic acid.

Our results showed there was no significant difference between topical TXA and IV TXA in reducing blood transfusion in bone surgery (Figure 3).

**Blood loss**

The blood loss after topical TXA vs IV TXA was compared among six studies about bone surgery, and the mean difference was 74.06 mL (mean difference [MD]: 74.06, 95%CI: -8.17 to 156.39; \( P = 0.08 \)), with high heterogeneity found (\( I^2 = 88.98 \% \)). Our results showed there was no significant difference between topical TXA and IV TXA in reducing blood loss in bone surgery (Figure 4).

The blood loss after TXA vs placebo administration was compared among 12 studies about bone surgery, and the mean difference was -277.51 mL (MD: -277.51, 95%CI: -410.47 to -144.5; \( P = 0.00 \)), with high heterogeneity (\( I^2 = 97.94 \% \)). The results showed that TXA reduced 277.51 mL of blood loss compared to placebo (Figure 5).
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Figure 1 Study attrition. Eighteen papers were finally included in the meta-analysis.

DISCUSSION

The present meta-analysis showed that TXA reduced 277.51 mL of blood loss compared to placebo in bone surgery, and there was no significant difference between topical TXA and IV TXA in reducing blood loss. Moreover, TXA significantly reduced blood transfusion compared to placebo in bone surgery and there was no significant difference between topical TXA and IV TXA. In a systematic review and meta-analysis study with a sample size of 10488 patients, regardless of the type of TXA administration, it was shown that 30% of patients only needed an injection. These results were consistent with our study. If a theoretical comparison is made between the topical TXA and IV TXA, the topical TXA would result in a 90% reduction in plasma concentrations. Also, a study with regression analysis showed no significant relationship between topical TXA and reduced dose-dependent risk of transmission, and topical TXA also has the advantage of lower doses and medical costs. Moreover, previous studies have shown that there is no significant advantage of systemic TXA in various surgical and non-surgical procedures compared to topical TXA. Taken together, these findings indicate that topical TXA is recommended to reduce blood loss and transfusion at least in bone surgery.

Much blood loss is common in bone surgery, which is a major source of mortality, and blood transfusions are often required during the perioperative period. However, blood transfusions may lead to increased length of hospital stay, a raised risk of infection, and an increased medical cost. TXA prevents the conversion of plasminogen to plasmin, thus preventing fibrinolysis and blood loss. Thus, it is clinically significant to use TXA to reduce blood loss and transfusion in bone surgery, which might be beneficial for wound healing.

However, our study also had some limitations. First, the optimal dose and timing of the topical TXA were not evaluated in our study due to lack of clinical guideline for TXA and inconsistency in dose and timing of TXA across studies, which remain to be evaluated in the further research. Second, significant heterogeneity was detected in blood loss and our findings remain to be further verified by more well-designed studies.

CONCLUSION

We found that the use of both topical and intravenous TXA are effective in reducing blood loss and might be beneficial for wound healing in bone surgery. Given the consideration of smaller dose and less medical cost, topical TXA is recommended for bone surgery. However, more studies are needed to further verify our findings in the future.
## Risk of bias assessment

| Ref. | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome Assessment | Incomplete outcome data | Selective reporting | Total score |
|------|---------------------------|------------------------|---------------------------------------|-------------------------------|------------------------|---------------------|-------------|
| Lei et al[17], 2020 | + | + | + | + | + | + | 6 |
| Luo et al[18], 2019 | + | + | + | + | + | + | 6 |
| Chen et al[19], 2019 | ? | + | + | + | + | + | 5 |
| Zhang et al[20], 2019 | + | + | + | + | + | + | 6 |
| Zhou et al[21], 2019 | + | ? | ? | + | + | + | 4 |
| Ovetanovich et al[22], 2018 | + | + | ? | + | + | + | 5 |
| Huang et al[23], 2017 | + | + | + | + | + | + | 5 |
| Vara et al[24], 2017 | + | + | + | + | + | + | 5 |
| Goyal et al[25], 2017 | + | ? | ? | + | + | + | 4 |
| Chen et al[26], 2016 | + | + | + | + | + | + | 5 |
| Drosos et al[27], 2016 | + | + | + | + | + | + | 4 |
| Keyhan et al[28], 2016 | + | + | + | + | + | + | 5 |
| North et al[29], 2016 | + | + | + | ? | + | + | 4 |
| Aguilera et al[30], 2015 | + | + | + | + | + | + | 5 |
| Eftekharian et al[31], 2015 | + | + | ? | + | + | + | 4 |
| Gillespie et al[32], 2015 | + | + | + | + | + | + | 4 |
| Taheriazam et al[33], 2015 | + | + | ? | + | + | + | 5 |
| Yang et al[34], 2015 | + | + | ? | + | + | + | 4 |

(+) Low; (?) Unclear; (-) High.

**Figure 2 Risk of bias assessment.** (+): Low; (?) Unclear; (-): High.
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Figure 3 Forest plot showed odds ratio (95% confidence interval) for risk of blood transfusion between tranexamic acid and placebo in bone surgery. CI: Confidence interval.

Figure 4 Forest plot showed odds ratio for risk of blood transfusion between topical tranexamic acid and IV tranexamic acid in bone surgery. CI: Confidence interval; TXA: Tranexamic acid.

Figure 5 Forest plot showed mean difference (95% confidence interval) of blood loss between topical tranexamic acid and IV tranexamic acid in bone surgery. CI: Confidence interval; SD: Standard deviation; TXA: Tranexamic acid.
Tranexamic acid (TXA) as an anti-fibrinolytic drug has been available for over half a century and Topical use of TXA is more and more popular today.

Although TXA is regularly used in surgeons, a comprehensive guideline on safe topical doses and methods for TXA administration has remained controversial.

This study evaluated the efficacy of topical vs intravenous TXA in reducing blood loss and promoting wound healing in bone surgery.

From the electronic resources, PubMed, Cochrane Library, Embase, ISI, and Scopus were used to perform a literature search over the last 10 years between 2010 and 2020. EndNote™ X8 was used for managing the electronic resource. Searches were performed with mesh terms. The data were retracted blindly by two independent reviewers. Random effects were used to deal with potential heterogeneity and I² showed heterogeneity. Chi-square (I²) tests were used to quantify the extent of heterogeneity (P < 0.01 was considered statistically significant). The efficacy of topical TXA in reducing blood loss and promoting wound healing in bone surgery was compared with intravenous TXA and placebo.

According to the research design, 1360 potentially important research abstracts and titles were discovered in our electronic searches, and eighteen papers remained in agreement with our inclusion criteria required. It was found that TXA reduced 277.51 mL of blood loss compared to placebo, and there was no significant difference between topical TXA and IV TXA in reducing blood loss in bone surgery. Our analysis also showed that TXA significantly reduced blood transfusion compared to placebo and there was no significant difference between topical TXA and IV TXA.

This meta-analysis showed that both topical and intravenous TXA are effective in reducing blood loss and might be beneficial for wound healing in bone surgery. Given the consideration of smaller dose and less medical cost, topical TXA is recommended.
for bone surgery.

**Research perspectives**

Both topical and intravenous TXA are effective in reducing blood loss and might be beneficial for wound healing in bone surgery.

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