Review Article
Multiple doses versus single dose of intravenous tranexamic following total joint arthroplasty: a meta-analysis of randomized controlled trials

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Abstract: Background: The use of intravenous tranexamic acid (TXA) in total joint arthroplasty (TJA) has been proven effective and safe. However, the optimal dose remains controversial. The principal objective of this meta-analysis was to compare the efficacy and safety of multiple doses with a single dose of intravenous TXA in patients following total knee and hip arthroplasty (TKA and THA). Methods: Electronic databases were searched, including PubMed, Web of Science, EMBASE, Cochrane Library, the Chinese Biomedical Literature database, Wanfang database, and CNKI database, from 1966 to October 2017. Randomized control trials (RCTs) of patients undergoing TJA that compared multiple doses with a single dose of intravenous TXA were retrieved. Primary outcomes included hidden blood loss (HBL) and transfusion rates, along with incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE). Secondary outcomes included total blood loss (TBL), postoperative drainage volume (day 1 and day 2 after surgery), and length of hospital stay (LOH). All data were analyzed using RevMan 5.3 software. Result: At total of 17 RCTs, involving 1,767 patients, were included. The current meta-analysis showed that TBL, HBL, transfusion rates, and postoperative drainage volume were significantly lower in patients receiving multiple doses of intravenous TXA, compared to a single dose. LOH also seemed to be shorter in the multiple-dose group. No statistical differences were found in incidence of DVT or PE. Conclusion: This meta-analysis demonstrates that multiple doses may be superior to a single dose of intravenous TXA for patients undergoing TJA.

Keywords: Tranexamic acid, total joint arthroplasty, allogeneic transfusions, blood loss, meta-analysis

Introduction

Total knee arthroplasty and hip arthroplasty (TKA and THA) have been quite successful surgeries for many end-stage knee and hip diseases, in terms of pain relief and functional recovery [1-3]. The demand for primary total knee arthroplasties has been projected to grow by 673% to 3.48 million procedures, in the United States alone, by 2030 [4]. However, TKA and THA have been associated with substantial perioperative blood loss and transfusion, carrying significant risks of immunological reactions and transmission of disease, along with increased morbidity and costs [5, 6]. To solve these problems, TXA has been extensively used in the perioperative period of THA and TKA [7].

TXA is a synthetic amino acid derivative that inhibits the conversion of plasminogen to plasmin through the reversible blockade of lysine binding sites on the plasminogen molecule, resulting in the inhibition of fibrinolysis [8-10]. Intravenous, topical, oral, and combined application routes are available to administer TXA [11-13]. However, the most common route is the intravenous form. Numerous studies have demonstrated that intravenous TXA administration for TJA is effective and safe [6, 14, 15]. In addition, Blanié et al. [16] showed that fibrinolysis peaked 6 hours after the end of surgery and maintained for about 18 hours (h) after TJA. The biological half-life of TXA in joint fluid is about 3 hours [9]. Consequently, it is necessary to use multiple doses of TXA during the perioperative period of TJA to gain better results. However, theoretical concerns do exist because of a nonnegligible risk of thromboembolic complications, due to its antifibrinolytic activity.
To the best of our knowledge, no meta-analyses have been reported comparing efficacy and safety between multiple doses of intravenous TXA and a single dose in TJA. Therefore, this meta-analysis was conducted answer the question whether multiple doses of intravenous TXA are more effective regarding total blood loss (TBL), hidden blood loss (HBL), transfusion rates, drainage volume, and length of hospital stay (LOH), without sacrificing the safety profile.

**Material and methods**

**Search strategy**

Electronic databases were searched, including PubMed, Web of Science, EMBASE, the Cochrane Library, Chinese Biomedical Literature database, Wanfang database, and the CNKI database, from 1966 to October 2017. Key words used in search methods included “total knee replacement OR arthroplasty”, “total hip replacement OR arthroplasty”, “total joint replacement OR arthroplasty”, and “tranexamic acid”. References of included literature were also checked for potentially relevant studies. There were no language restrictions. Both English and non-English studies were included in this meta-analysis. Since this was a meta-analysis, no Ethics Committee or Institutional Review Board approval was necessary.

**Inclusion criteria and study selection**

All RCTs were retrieved that compared multiple doses of intravenous TXA with a single dose in patients, following THA or TKA, reporting data of target outcomes. Studies were excluded if (1) Quality was too low; or (2) Outcome data was insufficient, even after contacting the authors by e-mail. After exclusion of duplicates, one reviewer screened titles and abstracts to discard studies that were clearly ineligible, such as non-RCTs, case reports, conference abstract, letters, comments, and reviews. Reviewers then obtained the full text of remaining references. Full texts were reviewed to assess whether the studies should be included based on predefined selection criteria. Disagreements regarding which studies to include were resolved by discussion with a senior investigator.

**Outcome measurements and data extraction**

Primary outcomes included HBL, transfusion rates, and incidence of DVT and PE. Secondary outcomes included TBL, postoperative drainage volume (day 1 and day 2 after surgery), and LOH. Data regarding patient characteristics, such as age, gender, body mass index, and other baseline characteristics, were extracted. Authors were contacted via E-mail to obtain data if the article provided incomplete data.

**Quality assessment of included studies**

Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) was used for assessing the risk of bias of included studies. This was carried out by 2 authors, independently. Content for assessment included random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Based on information provided from included studies, each item was recorded with “Yes (low risk of bias)”, “No (high risk of bias)”, or “Unclear (lack of information or unknown risk of bias)”. Moreover, all studies were reviewed by two independent investigators using Jadad scores. Studies with a Jadad score of 1 were considered poor, scores of 2 were considered adequate, and a score of 3 or higher was considered as high quality. All disagreements were resolved by consultation with the senior investigator.

**Statistical analysis**

This meta-analysis was performed using RevMan 5.3 (The Cochrane Collaboration, Oxford, UK) with a significance threshold of p ≤ 0.05. Heterogeneity was assessed using Chi-square test and I² statistic. If I² < 50% or P > 0.1, a fixed-effects model was used, otherwise a random-effects model was used. For continuous outcomes, this study calculated the mean difference (MD) with 95% confidence interval (CI). Risk ratios (RR) with 95% CI were calculated for discontinuous data. Subgroup analysis was used to compare different doses of intravenous TXA with a single dose. If any article had two groups of, data of two doses and three doses at the same time, the date of single dose patients was used twice, compared with the other two groups, respectively.
Results

Search results and study characteristics

In the initial research, a total of 696 articles were identified, with 437 articles reviewed due to duplication. When records were reviewed, most articles were excluded after the title and abstracts were scanned. Two articles were excluded because the data was incomplete and have no response to the first author's E-mail was received.

No gray literature was included. Finally, 17 RCTs [17-33], published between 2012 and 2017, were included in the present meta-analysis. Figure 1 shows the steps of study selection. These studies included total 1,767 patients, consisting of 216 patients in the three-dose group, 778 patients in the two-dose group, and 773 patients in the single-dose group. Eight RCTs were published in English while the others were in Chinese. A total of 9 RCTs were about TKA while 8 RCTs were about THA. Sample sizes of included trials ranged from 40 to 167 and mean age of participants ranged from 53 to 72 years. All but one study [30] performed unilateral arthroplasty. All patients in included studies received chemical thrombo-prophylaxis, some of them also received physical therapy. Statistically similar baseline characteristics were observed between the groups. Baseline characteristics of the included studies are shown in Table 1.

Quality assessment

Methodological quality assessment is summarized in Figure 11. Each risk of bias item is presented as the percentage across all included studies, indicating the proportion of different levels of risk of bias for each item (Figure 12). RCTs in English were relatively well designed, compared to Chinese RCTs. Randomization was performed in all 22 trials. Details of the method were mentioned in all except 5 trials [23, 25, 26, 29, 31]. Allocation concealment was shown in 6 RCTs and details of blinding were clearly reported in 6 studies. Additionally, 9 studies [17-22, 24, 28, 33] had a Jadad score of three or higher, while 7 studies [23, 25-27, 30-32] were two, and 1 study [29] was only one. A funnel plot (Figure 2) shows trials scattered around the pooled RR, approximately, indicating low relatively risk of publication bias.

Outcomes for meta-analysis

Total blood loss: A total of 11 RCTs provided data of TBL after TJA. Subgroup analysis and pooled results, respectively, indicated that TBL of multiple doses of intravenous TXA was significantly lower than a single dose (MD=-143.98, 95% CI: -150.52 to -76.61, P < 0.00001, Figure 3).
### Table 1. Characteristics of included trials showing general patient information

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Country</th>
<th>Surgical methods</th>
<th>TXA intervention</th>
<th>Number male/female</th>
<th>Mean age (years)</th>
<th>BMI (kg/m²)</th>
<th>Pre-operation HB (g/L)</th>
<th>Anesthesia methods</th>
<th>Prosthesis type</th>
<th>Thromboprophylaxis</th>
<th>Transfusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun/2017 [17]</td>
<td>China</td>
<td>Primary unilateral TKA</td>
<td>1:5:30 mg/kg pre-op, 2:0:15 mg/kg pre-op + post-op, 3:15 mg/kg pre-op + post-op, 3 h, 6 h respectively</td>
<td>S:45 13/32 D:45 17/28 T:45 10/35</td>
<td>S:67.2±8.1 D:67.3±7.2 T:68.1±7.9</td>
<td>S:25.8±5.6 D:26.2±3.9 T:26.1±4.9</td>
<td>S:126.7±10.1 D:127.4±10.9 T:125.7±13.7</td>
<td>Spinal anesthesia</td>
<td>Cemented</td>
<td>LMWH + rivaroxaban</td>
<td>Hb &lt; 8.0 g/dL + symptoms</td>
</tr>
<tr>
<td>Zufferey/2017 [18]</td>
<td>France</td>
<td>Primary unilateral THA</td>
<td>1:5:1 g pre-op, 2:0:1 g pre-op + 1 g continuous infusion for 8 h</td>
<td>S:83 44/39 D:84 37/28 T:86 33/23</td>
<td>S:67.3±9.1 D:68.3±8.0 T:67.6±7.0</td>
<td>S:29.4±5.5 D:28.6±4.2 T:27.7±4.8</td>
<td>S:142±15 D:142±15</td>
<td>General or spinal anesthesia</td>
<td>---</td>
<td>Apixaban</td>
<td>7 g/dL + symptoms</td>
</tr>
<tr>
<td>Maniar/2012 [19]</td>
<td>India</td>
<td>Primary unilateral TKA</td>
<td>1:5:10 mg/kg, 2:0:10 mg/kg, 3 h after the first dose, 3:0:10 mg/kg pre-op + intra-op respectively, 4:10 mg/kg pre-op + intra-op + 3 h after the second dose</td>
<td>S:41 10/30 D:41 11/29 T:41 12/29</td>
<td>S:53 (57,78) D:57 (59,73) T:55 (58,77)</td>
<td>S:67.2±9.1 D:67.3±8.0 T:67.6±7.0</td>
<td>S:126.7±10.1 D:127.4±10.9 T:125.7±13.7</td>
<td>General or spinal anesthesia</td>
<td>---</td>
<td>Apixaban</td>
<td>7 g/dL + symptoms</td>
</tr>
<tr>
<td>Xie/2017 [20]</td>
<td>China</td>
<td>Primary unilateral THA</td>
<td>1:5:20 mg/kg pre-op, 2:0:20 mg/kg pre-op + 1 g, 3 h after the first dose, 3:0:20 mg/kg pre-op + 1 g, 3 h, 4 h after the first dose respectively</td>
<td>S:50 22/28 D:50 18/32 T:50 20/30</td>
<td>S:57.2±13.05 D:54.7±12.57 T:54.3±11.80</td>
<td>S:24.6±3.62 D:24.7±3.73 T:24.3±3.22</td>
<td>S:133.3±15.04 D:133.8±14.42 T:133.3±14.67</td>
<td>General anesthesia</td>
<td>Cemented</td>
<td>Rivaroxaban + physical therapy</td>
<td>Hb &lt; 7 g/dL + symptoms</td>
</tr>
<tr>
<td>Lin/2012 [21]</td>
<td>Taiwan (China)</td>
<td>Primary unilateral TKA</td>
<td>1:5:10 mg/kg intra-op, 2:0:20 mg/kg pre-op, intra-op respectively</td>
<td>S:52 9/43 D:49 7/41 T:50 16/37</td>
<td>S:70.6±8.0 D:69.8±7.59 T:69.6±7.51</td>
<td>S:28.0±3.84 D:28.1±3.92 T:27.8±3.82</td>
<td>S:134±11.8 D:133±12.2</td>
<td>General anesthesia</td>
<td>Cemented</td>
<td>Enoxaparin</td>
<td>8 g/dL + symptoms</td>
</tr>
<tr>
<td>Barrach-Ina/2016 [22]</td>
<td>Spain</td>
<td>Primary unilateral TKA</td>
<td>1:5:15 mg/kg pre-op, 2:0:10 mg/kg pre-op, 3 h after the start of surgery</td>
<td>S:35 19/16 D:36 16/20</td>
<td>S:69.2±10.2 D:62.5±13.0 T:64.9±10.3</td>
<td>S:22.5±3.5 D:22.8±2.4 T:22.6±3.2</td>
<td>S:143±15 D:145±14</td>
<td>Subarachnoid spinal block</td>
<td>Cementless</td>
<td>Enoxaparin</td>
<td>8.5 g/dL + symptoms</td>
</tr>
<tr>
<td>Imai/2012 [23]</td>
<td>Japan</td>
<td>Primary THA</td>
<td>1:5:1 g intra-op, 2:5:2 g pre-op, 3:10:1 g intra-op, 6 h after the first dose, 4:0:2 g intra-op, 6 h after the first dose respectively</td>
<td>S:124 4/20 D:25 4/21 T:126 4/20</td>
<td>S:64.4 (49-74) D:63.3 (47-80) T:62.2 (50-85)</td>
<td>S:21.3 (19.7-29.7) D:22.2 (19.8-26.3) T:21.9 (16.6-29.2)</td>
<td>S:132.7±15.7 D:129.0±9.1 T:128.3±12.6</td>
<td>General anesthesia</td>
<td>Cemented</td>
<td>Enoxaparin + physical therapy</td>
<td>--</td>
</tr>
<tr>
<td>Xie/2016 [24]</td>
<td>China</td>
<td>Primary unilateral TKA</td>
<td>1:5:20 mg/kg pre-op, 2:0:20 mg/kg pre-op, 10 mg/kg 3 h later, 3:10:20 mg/kg pre-op, 10 mg/kg 3 h, 6 h later</td>
<td>S:50 17/33 D:50 14/36 T:51 10/41</td>
<td>S:66.2±9.1 D:65.3±6.8 T:63.5±7.6</td>
<td>S:24.8±3.2 D:25.3±3.2 T:25.0±3.9</td>
<td>S:132.7±15.7 D:129.0±9.1 T:128.3±12.6</td>
<td>General anesthesia or spinal anesthesia</td>
<td>Cemented</td>
<td>Enoxaparin + rivaroxaban + physical therapy</td>
<td>Hb &lt; 7 g/dL + symptoms</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Intervention</th>
<th>Dose</th>
<th>Timing</th>
<th>Pain Scores</th>
<th>Anesthesia</th>
<th>Anticoagulant Therapy</th>
<th>Other</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang/2017 [25]</td>
<td>China</td>
<td>TKA</td>
<td>1S: 15 mg/kg intra-op, 2D: 15 mg/kg post-op</td>
<td>S:30 10/20, D:30 12/18</td>
<td>S:71±5, D:72±5</td>
<td>Intra-spinal anesthesia</td>
<td>Cemented</td>
<td>Rivaroxaban</td>
<td>Hb &lt; 8 g/dL</td>
</tr>
<tr>
<td>Wang/2015 [26]</td>
<td>China</td>
<td>THA</td>
<td>1S: 10 mg/kg intra-op, 2D: 10 mg/kg post-op</td>
<td>S:49 11/38, D:53 14/39</td>
<td>S:54.6±10.2, D:57.6±10.74</td>
<td>General anesthesia</td>
<td>Anticoagulant therapy</td>
<td>--</td>
<td>Hb &lt; 7 g/dL + symptoms</td>
</tr>
<tr>
<td>Chen/2017 [27]</td>
<td>China</td>
<td>THA</td>
<td>1S: 15 mg/kg intra-op, 2D: 15 mg/kg post-op, 10 mg/kg pre-op, 3 h</td>
<td>S:50 0/50, D:50 11/39</td>
<td>S:64.7±9.7, D:62.6±8.5</td>
<td>General anesthesia and femoral nerve block</td>
<td>Cementless</td>
<td>Enoxaparin + rivaroxaban + physical therapy</td>
<td>Hb &lt; 7 g/dL + symptoms</td>
</tr>
<tr>
<td>Hu/2014 [28]</td>
<td>China</td>
<td>THA</td>
<td>1S: 10 mg/kg before close incision, 2D: 10 mg/kg before close incision, post-op 3 h respectively</td>
<td>S:50 8/42, D:50 11/39</td>
<td>S:64.7±9.7, D:62.6±8.5</td>
<td>General anesthesia</td>
<td>Cemented</td>
<td>LMWH + physical therapy</td>
<td>HB &lt; 9 g/dL or drainage volume ≥ 600 mL</td>
</tr>
<tr>
<td>Zhao/2017 [30]</td>
<td>China</td>
<td>Bilateral TKA</td>
<td>1S: 15 mg/kg pre-op, 2D: 15 mg/kg pre-op before close incision</td>
<td>S:35 19/16, D:35 18/17</td>
<td>S:56±2.5, D:57±2.6</td>
<td>Combined spinal-epidural anesthesia</td>
<td>Cemented</td>
<td>Anticoagulant therapy</td>
<td>--</td>
</tr>
<tr>
<td>Li/2017 [31]</td>
<td>China</td>
<td>THA</td>
<td>1S: 10 mg/kg pre-op, 2D: 15 mg/kg pre-op before close incision, 3 T: 15 mg/kg pre-op, 3 h later respectively</td>
<td>S:1:30 23/7, S:2:30 22/8, T:30 21/9</td>
<td>S:62.2±6.6, S:62.7±6.5, T:61.8±13.0</td>
<td>--</td>
<td>--</td>
<td>Cementless</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Zhang/2014 [32]</td>
<td>China</td>
<td>THA</td>
<td>1S: 1 g intra-op, 2D: 1 g intra-op, 3D: 1 g intra-op, 4D: 1 g intra-op, 7 h respectively</td>
<td>S: 1:25 13/12, S:2:25 12/13, D:2:25 11/14</td>
<td>S:63.9±6.1, S:63.7±4.9, D:63.4±5.1</td>
<td>--</td>
<td>--</td>
<td>Enoxaparin</td>
<td></td>
</tr>
<tr>
<td>Xu/2016 [33]</td>
<td>China</td>
<td>TKA</td>
<td>1S: 15 mg/kg intra-op, 2D: 15 mg/kg intra-op, post-op 3 h respectively, 3D: 15 mg/kg intra-op, post-op 3 h, 6 h respectively</td>
<td>S:25 8/13, D:25 8/13, D:25 8/13</td>
<td>S:63.4±6.8, D:62.0±6.0, D:61.8±5.8</td>
<td>Combined spinal-epidural anesthesia</td>
<td>Cemented</td>
<td>Rivaroxaban + physical therapy</td>
<td>Hb &lt; 8 g/dL + symptoms</td>
</tr>
</tbody>
</table>

Pre-op: pre-operation; post-op: post-operation; intra-op: intraoperative; S: single-dose group; D: double-dose group; T: triple-dose group. LMWH: low-molecular-weight heparin. --: no information in the study. (1): shown as the mean (25th, 75th percentiles). (2): most of patients received general while a few received spinal anesthesia, some of them also received femoral nerve or fascia iliaca block at the same time. (3): shown as the peripheral blood volume. (4): are presented as mean (range).
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Hidden blood loss: A total of 7 RCTs provided data of HBL after TJA. Subgroup analysis and pooled results both revealed that HBL of multiple doses of intravenous TXA was significantly lower than a single dose (MD=-98.30, 95% CI: -155.97 to -40.63, P=0.0008, Figure 4).

Transfusion rates: Transfusion rates after TJA were reported in 14 RCTs. Pooled results indicated that transfusion rates of multiple doses of intravenous TXA were significantly lower than a single dose (RR=0.56, 95% CI: 0.41 to 0.75, P=0.0001, Figure 5).

Drainage volume at day 1 after TJA: A total of in 6 RCTs reported the drainage volume at day 1 after TJA. Subgroup analysis and pooled results both showed that drainage volume at day 1 after TJA of multiple doses of intravenous TXA was significantly lower than a single dose (MD=-88.78, 95% CI: -127.75 to -49.82, P < 0.00001, Figure 6).

Drainage volume at day 2 after TJA: Drainage volume at day 2 after TJA was provided in 5 RCTs. Subgroup analysis and pooled results indicated that drainage volume at day 2 after TJA of multiple doses of intravenous was significantly lower than a single dose (MD=-128.44, 95% CI: -180.46 to -76.42, P < 0.00001, Figure 7).

Length of hospital stay: LOH after TJA was reported in 5 RCTs. Pooled results revealed that LOH of multiple doses of intravenous TXA was shorter than a single dose. (MD=-0.58, 95% CI: -1.17 to -0.05, P=0.05, Figure 8).

Deep vein thrombosis: DVT after TJA was provided in 17 RCTs. Both the subgroup analysis and pooled results showed no significant differences between multiple doses of intravenous TXA and a single dose (RR=-0.90, 95% CI: 0.47 to 1.76, P=0.77, Figure 9).

Pulmonary embolism: A total of 13 RCTs reported PE after TJA. Pooled results indicated no significant differences between multiple doses of intravenous TXA and a single dose (RR=1.42, 95% CI: 0.28 to 7.04, P=0.67; Figure 10).

Discussion

To the best of our knowledge, this is the first meta-analysis comparing the efficacy and safety of multiple doses with a single dose of intravenous TXA in patients following TKA or THA. Results of our meta-analysis, based on the available evidence, demonstrated that multiple doses of intravenous TXA was associated with significantly lower TBL, HBL, transfusion rates, and postoperative drainage volume, without increasing incidence of DVT and PE, compared to a single dose, in patients following TKA and THA. Moreover, it may also be associated with shorter LOH.

TXA has been used in TKA and THA for a long time, with positive clinical results. When TXA is applied intravenously, it is widely distributed throughout the extracellular and intracellular compartments and diffused into the joint fluid and synovial membranes, reaching the same concentration in the joint fluid as in the serum [9, 34]. The biological half-life of TXA in joint fluid is about 3 hours [9]. In addition, Blanié et al. [16] showed that fibrinolysis peaked 6 hours after the end of surgery and maintained for about 18 hours after TJA. Maniar et al. [19] also revealed that a single dose of TXA did not give effective results, while two doses of TXA was the least amount necessary for effective results in TKA. Consequently, this meta-analysis was...
conducted to compare the efficacy and safety of multiple doses with a single dose of intravenous TXA in patients following TKA and THA.

Substantial articles have demonstrated that the application of TXA is associated with satisfactory outcomes for patients in TKA and THA [6, 35-37]. The present meta-analysis suggests that multiple doses of TXA can lead to smaller TBL (MD=−143.98, 95% CI: −150.52 to −76.61, \( P < 0.00001 \)) and lower HBL (MD=−98.30, 95% CI: −155.97 to −40.63, \( P = 0.0008 \)), compared to a single dose, with results more obvious in the three-dose group. Blood loss and transfusions remain a concern despite advances in blood conservation [38], the TBL consists of HBL, and visible blood loss that includes the volume of postoperative drainage and intraoperative loss in TJA [20, 39]. HBL is often ignored while intraoperative blood loss and volume of postopera-
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Figure 5. Comparison between multiple-dose group and single-dose group in transfusion rates.

Figure 6. Comparison between multiple-dose group and single-dose group in drainage volume at day 1 after TJA.

tive drainage is measured and recorded [40]. However, HBL that extravasates into the tissues can induce limb swelling and prolong postoperative recovery [41]. Chen et al. showed

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that TXA significantly reduces HBL and can be used as a standard drug to prevent or reduce HBL in TKA [42], consistent with the present findings.

The present meta-analysis found that drainage volumes of the multiple-dose group were smaller than the single-dose group at day 1 (MD = -88.78, 95% CI: -127.75 to -49.82, P < 0.00001) and day 2 (MD = -128.44, 95% CI: -180.46 to -76.42, P < 0.00001) after TJA. However, there was important clinical heterogeneity that may have influenced present results. Intra-articular drains were used in 9 studies, removed at different times. Two studies also reported that the intra-articular drains were clamped for 30 minutes [20] and 2 hours individually [19] after the procedure. The clamping of drain tubes could reduce postoperative blood loss. Clamping the drainage tube prevents immediate blood loss and promotes blood clot formation in a time-dependent manner [43, 44].

LOH is a major predictor of total cost of hospital care for total joint arthroplasty. LOH is extensively concerned with the development of the idea of enhanced recovery after surgery (ERAS)
The present study showed that multiple doses, especially three doses, of TXA may reduce LOH in TJA. Moreover, Lei et al. [47] showed that a 5-dose TXA regimen can further reduce LOH, compared to 4-dose and 3-dose regimes in TKA. However, only five studies in the meta-analysis reported LOH, thus pooled results may be controversial (MD=-0.58, 95% CI: -1.17 to -0.05, P=0.05). Future studies are necessary to confirm outcomes.

Patients undergoing TKA and THA are at risk of perioperative blood loss. Many will need allogeneic transfusions without using antifibrinolytics [11, 35, 48], likely resulting in adverse effects and potentially even life-threatening effects associated with anemia and allogeneic blood, such as immunologic reactions, infection, hemolysis, and additional financial burden. Liu et al. [48] reported that application of TXA intravenously could reduce transfusion rates. All but one included study [29] mentioned transfusion rates, showing no differences between multiple doses of intravenous TXA and the single group. Pooled results showed that transfusion rates were significantly lower in patients of multiple doses of intravenous TXA. The reason that incidence of transfusion rates was low may be related to insufficient sample sizes in most studies. In addition, differences in transfusion criteria could influence transfusion rates. Liu et al. [29] reported that high transfusion rates may be caused by conservative transfusion criteria (HB < 9 g/dL or drainage volume ≥ 600 mL).

There would be a high risk of thrombotic complications that could cause severe consequences when utilizing TXA for the antifibrinolytic effects, due to its mechanism action in TKA and THA [35]. The most common thrombotic events were DVT and PE. It is important to determine whether multiple doses of intravenous TXA application increase incidence of

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Figure 9. Comparison between multiple-dose group and single-dose group in deep vein thrombosis.
thrombotic events (DVT and PE). Many previous studies have indicated that application of TXA intravenously was not associated with an increase of thrombotic events in TKA and THA [6, 49]. No differences in incidence of DVT (RRR=0.90, 95% CI: 0.47 to 1.76, P=0.77) and PE (RRR=1.42, 95% CI: 0.28 to 7.04, P=0.67) between multiple doses and single dose of intravenous TXA were found after TJA in this meta-analysis. All included studies took measures, consisting of chemical and physical therapies, to prevent thrombotic complications in early stages after the operation. This may have contributed to low incidence of DVT and PE. However, the follow-up periods of some included studies were short [25, 26] or unclear [30], which would underestimate incidence of thrombotic complications. Well-designed, larger, and longer follow-up RCTs are required to make sure multiple doses of intravenous TXA is safe, without increasing incidence of DVT and PE.

There were several limitations to this meta-analysis. 1) The methods of random sequence generation and allocation concealment had a risk of bias. 2) The risk of bias in blinding of participants and personnel was unclear. 3) The risk of bias in incomplete outcome data was low. 4) The risk of bias in selective reporting was high. These limitations may have affected the results of the meta-analysis.

Figure 10. Comparison between multiple-dose group and single-dose group in pulmonary embolism.

Figure 11. Risk of bias.
Abstract, introduction, material and methods, results, discussion and conclusion

generation, allocation concealment, and blinding were unclear or not described in some included studies, which may have influenced results; 2) Short-term follow-ups may have caused the underestimation of complications, including DVT and PE; 3) If a study had two groups data of two doses and three doses of TXA at the same time, the dose of single dose group was used twice, compared to the other two groups, respectively.

Moreover, there was important clinical heterogeneity. 1) The meta-analysis consisted of 9 studies of TKA and 8 studies of THA. Differences between the two operation methods may have influenced results; 2) Patients with femoral neck fractures were included in the study [26]. Differences in surgical time, technique, approaches, prosthesis type, and thromboprophylaxis may have affected results to some extent; 3) Different anesthesia methods may affect blood loss and transfusion requirements; 4) This meta-analysis compared differences in times of doses, but did not take administration dosage and intervals into account. Therefore, future research should also focus on optimal dose and intervals with TXA in TKA and THA.

Conclusion

Multiple doses of TXA in TKA or THA are associated with significantly lower TBL, HBL, transfusion rates, and postoperative drainage volume, without increasing incidence of DVT and PE. Moreover, it may also be associated with shorter LOH. However, larger, well-designed, and high-quality RCTs, with long-term follow-ups, are still required to confirm the present results.

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