Original Article

The efficacy and safety of oral tranexamic acid for reducing blood loss after total joint arthroplasty: a meta-analysis

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Abstract: Objective: This meta-analysis aimed to illustrate the efficacy and safety of oral tranexamic acid (TXA) for reducing blood loss after total joint arthroplasty (TJA). Methods: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Google database were searched for comparative studies comparing oral TXA versus control group or intravenous TXA for patients prepared for TJA. The outcomes including need for transfusion, hemoglobin drop, length of hospital stay and drain volume. We calculated risk ratio (RR) with a 95% confidence interval (CI) for need for transfusion, and the weighted mean difference (WMD) with a 95% CI for hemoglobin drop, length of hospital stay and drain volume. A random-effects model was used for all comparisons and Stata 12.0 was used for meta-analysis. Results: Six clinical trials (4 RCTs and 2 non-RCTs) involving 3258 patients were finally included for this meta-analysis. When compared with control group, oral TXA was associated with less need for transfusion, hemoglobin drop, drain volume and length of hospital stay (P<0.05). When compared with IV TXA, oral TXA was associated with more hemoglobin drop (P<0.05). However, there was no significant difference between the need for transfusion, drain volume and the length of hospital stay between oral TXA with IV TXA. Conclusion: Oral TXA has comparable hemostasis effects with IV TXA, and may reduce the costs for patients prepared for TJA. However, the limited quality and number of the included studies, more high quality and multi center RCTs are still need to recommend for routine administration.

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

Introduction

Total joint arthroplasty (TJA) including total knee arthroplasty (TKA) and total hip arthroplasty (THA), has been identified as the most effective surgeries for knee or knee diseases [1]. Indeed, the number of primary TJA procedures is expected to reach 3.48 million in 2030 in the United States, soaring eightfold from 2005 [2]. TJA can be associated with considerable blood loss, and transfusion carries a substantial risk of immunologic reaction and transmission of disease [3, 4]. Methods to reduce postoperative blood loss and avoid homologous blood transfusion include tranexamic acid (TXA), fibrin sealant and tourniquet [5-7]. Surgical trauma and administration with tourniquet will stimulate fibrinolysis after TJA. TXA poses antifibrinolytic effects by reversible complex with plasminogen. Previous meta-analysis has been identified that intravenous TXA can decrease the perioperative blood loss without increase the thrombotic complications [8]. However, drug allergy with anaphylactic shock has been reported and concern has arisen concerning the safety of intravenous TXA [9]. Topical form carries the theoretical risk of peri-prosthetic infection due to needle contamination and may even aggravate sepsis [10]. Oral TXA has been shown to be equally or even more effective in primary TJA to reduce blood loss, hemoglobin drop, and blood transfusion [11]. However, the relatively small number of participants have made their conclusions inconclusive.

Based on the current clinical studies with oral TXA, we tried to pool the results in a meta-anal-
Oral TXA for TJA

Analysis. The purpose of this meta-analysis was to study whether oral TXA was associated with less (1) need for transfusion, (2) hemoglobin drop, (3) drain volume, (4) length of hospital stay and complications than control group and IV TXA.

Material and methods

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines for the meta-analysis of intervention trials [12].

Search strategies

PubMed, Embase, Web of Science and the Cochrane Library were searched up to December 2016 for comparative studies involving oral TXA for reducing blood loss in patients undergoing TJA. The search terms were as follows: “tranexamic acid”, “total knee arthroplasty”, “knee arthroplasty”, “knee replacement”, “oral”, “joint arthroplasty”, “joint replacement”, “total hip arthroplasty”, “hip arthroplasty”, and “hip replacement”. The language of publications was not limited. The title and abstract of studies identified in the search were reviewed to exclude clearly irrelevant studies. Reference lists of all eligible studies and relevant reviews were searched manually for additional trials.

Inclusion criteria and study selection

Inclusion criteria: Participants: patients undergoing primary TJA; Intervention: oral TXA; Comparison: IV TXA or control group; Outcomes: need for transfusion, hemoglobin drop, drain volume, length of hospital stay, and postoperative complications. Study: RCTs and non-RCTs were included. Articles that reported at least one outcome were included and those without the outcome measures of interest were excluded. Letters, comments, editorials and practice guidelines were excluded.

Data extraction and quality assessment

Two authors (Jian Zhang and Jian Liu) independently reviewed all titles and abstracts of studies identified by searches according to the eligibility criteria described above. Full texts of articles that met the inclusion criteria were reviewed thoroughly. Disagreements were resolved by discussion to reach consensus. The data on patient characteristics (age, sex and other baseline characteristics), interventions and outcomes were extracted by the two authors using a standardized form pre-designed Excel. The data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval (CI)) were converted to mean ± standard deviation (SD) according to the Cochrane Handbook [13]. If data were not reported numerically, we extracted them by manual measurements from published figures.

Two authors (Weidong He and Min Wang) independently assessed the risk of bias of the included studies, based on the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other
Table 1. The general characteristic of the included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Control Group</th>
<th>Surgery</th>
<th>Intervention Group</th>
<th>Outcomes Follow-up</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alipour 2013</td>
<td>Iran</td>
<td>No TXA</td>
<td>TKA</td>
<td>27 1 2 h preoperatively, 6 hours and 18 hours postoperatively</td>
<td>1, 3, 4, 6, 7</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Bradshaw 2012</td>
<td>USA</td>
<td>No TXA</td>
<td>TKA</td>
<td>26 1.5 8 h preoperatively, 3 dose 2 hours after surgery, and a 4 dose 6 h postoperatively</td>
<td>1, 3, 4, 6, 7</td>
<td>3 months</td>
</tr>
<tr>
<td>Fillingham 2016</td>
<td>USA</td>
<td>IV TXA (1 g)</td>
<td>TKA</td>
<td>34 1.95 2 h preoperatively</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td>NS</td>
</tr>
<tr>
<td>Irwin 2013</td>
<td>USA</td>
<td>No TXA</td>
<td>TKA</td>
<td>302 25 mg/kg 12 h preoperatively</td>
<td>1, 2, 3, 4, 6, 7</td>
<td>2 months</td>
</tr>
<tr>
<td>Lee 2017</td>
<td>China</td>
<td>No TXA</td>
<td>THA</td>
<td>54 1 2 h preoperatively, 6 hours and 12 hours postoperatively</td>
<td>1, 2, 3, 4, 6, 7</td>
<td>3 days</td>
</tr>
<tr>
<td>Zohar 2004</td>
<td>India</td>
<td>Arm1=No TXA</td>
<td>TKA</td>
<td>20 1 1 h preoperatively</td>
<td>1, 5</td>
<td>3 months</td>
</tr>
</tbody>
</table>

TXA, tranexamic acid; TKA, total knee arthroplasty; THA, total hip arthroplasty; RCT, randomized controlled trials; RCS, retrospective controlled trials; NS, not stated; 1, need for transfusion; 2, total blood loss; 3, hemoglobin drop; 4, drain loss; 5, length of hospital stay; 6, the occurrence of deep venous thrombosis; 7, the occurrence of infection.

Results

Search results and study characteristics

The literature search and selection process were shown in Figure 1. The initial search yielded 213 articles, and 132 papers were read when excluded the duplicates. Next stage, 126 papers were excluded according to the inclusion criteria. Finally, we included 6 clinical studies with 3258 patients for meta-analysis [11, 16-20]. Among the included studies, 4 of were RCTs [11, 16-18] and 2 of were non-RCTs [19, 20]. The detailed baseline characteristics of the included studies were presented in Table 1. There were 6 studies included in our meta-analysis. All of the articles were published in English, between the year of 2004 and 2017. The sample size ranged from 20 to 2638 (total =3258) and mean age ranged from 63 to 70. The follow up ranged from 3 day to 3 month. The dose of oral TXA ranged from 1 g to 1.95 g. And the dose of IV TXA ranged from 900 mg to 1 g.

Risk of bias among the included studies

The summary risk of bias for RCTs can be seen in Figure 2. All of RCTs describe the random sequence generation, allocation concealment and blind to participant and personnel [11, 16-18]. Only one study has high risk of bias for blind to outcome assessor [11]. And one study did not reported the sample size calculations prior to interventions and assessed as unclear bias [11]. The summary risk of bias of non-RCTs can be seen in Table 2. The MINORS score of the study of Irwin et al. [19], and Lee et al. [20] was 18 and 24 respectively. The overall kappa value regarding the evaluation of risk of bias of included RCTs was 0.903, indicating an excellent degree of agreement between the 2 authors.

Results of meta-analysis

Need for transfusion: Four studies including 3338 patients tested the effect of oral TXA ver-
Oral TXA for TJA

sus IV TXA on the need for transfusion. There was no significant difference between oral TXA with IV TXA in the need for transfusion (RR=0.77, 95% CI 0.44 to 1.33, P=0.340; I²=8.5%) (Figure 3). Compared with control group, oral TXA was associated with less need for transfusion, however, the difference was not statistically significant (RR=0.52, 95% CI 0.17 to 1.57, P=0.243; I²=66.3%, Figure 3).

Hemoglobin drop: Two studies including 3218 patients tested the effect of oral TXA versus IV TXA on the need for transfusion. Compared with IV TXA, oral TXA was associated with more hemoglobin drop (WMD=0.19, 95% CI 0.06 to 0.33, P=0.005; I²=0.0%) (Figure 4). Compared with control group, oral TXA was associated with less hemoglobin drop (WMD=1.01, 95% CI -1.48 to -0.53, P=0.000; I²=27.0%, Figure 4).

Drain volume: One studies including 278 patients tested the effect of oral TXA versus IV TXA on the drain volume. Compared with IV TXA, no significant difference between oral TXA versus IV TXA in drain volume (WMD=0.19, 95% CI 0.06 to 0.33, P=0.815; I²=0.0%) (Figure 5). Compared with control group, oral TXA was associated with less drain volume (WMD=-116.9, 95% CI -220.7 to -13.1, P=0.012; I²=77.7%, Figure 5).

Length of hospital stay: Three studies including 299 patients tested the effect of oral TXA versus IV TXA on the length of hospital stay. Compared with IV TXA, no significant difference between oral TXA versus IV TXA in the length of hospital stay (WMD=0.00, 95% CI -0.41 to 0.41, P=1.000; I²=0.0%) (Figure 6). Compared with control group, oral TXA was associated with less length of hospital stay (WMD=-1.08, 95% CI -1.57 to -0.60, P=0.000; I²=0.0%, Figure 6).

Complications

Complications were reported in 2 RCTs, in which all patients received oral TXA or TXA group. The complications were related to DVT or infection. Fillingham et al. [18] reported 1 patient in control group underwent DVT and Bradshaw et al. [17] reported 1 patients in control group underwent infection.

Discussion

This is the first systematic review and meta-analysis that comparing oral TXA versus IV TXA and control group for reducing blood loss after TJA. The pooled results showed that oral TXA is effective and safe for reducing blood loss in TJA. However, there was no significant difference between oral TXA versus IV TXA in TJA. The level of evidence, which was undermined by heterogeneity and/or study design limitations, was low, indicating that the degree of benefit must be studied although the benefit is conclusive. The heterogeneity main comes fr-
om the joint surgeries type and different dose of TXA. The subgroup analysis was not performed since the limited included number of studies.

A major highlight of current analysis is the comprehensive and systematic search with strict statistical calculations. IV TXA can decrease blood loss without increasing the occurrence of DVT a has accumulated a large body of evidence [8, 21]. However, limited research has been done on the orthopedic applications of the less expensive oral form of the TXA. Current meta-analysis indicated that oral TXA has comparable effect with IV TXA and was superior than control group in reducing blood loss after TJA. The most efficacious timing and dose protocol for intravenous TXA and oral TXA has not yet been clearly determined. For The more common IV TXA dose appears to be around 10 mg/kg, and this has been shown to be both effective and to maintain the minimum therapeutic level for approximately 3 hours [22]. Oral TXA dose ranging from 1 g to 1.95 g and the time interval always from 1 to 2 h before operation. The TXA bioavailability was to be around 34% and elimination in blood occurred mostly within 8 hours. Based on serum and pharmacokinetic studies, a 2-gram dose of oral TXA takes approximately 2 hours to achieve therapeutic

Table 2. The Minors quality score of the non-RCTs

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irwin 2013</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Lee 2017</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>24</td>
</tr>
</tbody>
</table>

Numbers 1-12 in heading signified: 1, a clearly stated aim; 2, inclusion of consecutive patients; 3, prospective collection of data; 4, endpoints appropriate to the aim of the study; 5, unbiased assessment of the study endpoint; 6, follow-up period appropriate to the aim of the study; 7, loss to follow-up less than 5%; 8, prospective calculation of the study size; 9, an adequate control group; 10, contemporary groups; 11, baseline equivalence of groups; and 12, adequate statistical analyses.

Figure 3. Forest plots of the included studies comparing need for transfusion between the two groups.
Oral TXA for TJA

Figure 4. Forest plots of the included studies comparing hemoglobin drop between the two groups.

serum concentrations [23]. Inadequate dosing to reach the therapeutic threshold would account for Zohar et al. [11] showing a trend toward higher rates of transfusion for oral TXA compared to IV TXA groups and the lack of statistical significance in hematocrit on postoperative day 4 compared to placebo. Because oral and IV TXA are both systemically delivered drugs, oral TXA should be avoided in patients with contraindications to IV TXA such as renal impairment.

Although intravenous form has been shown to be safe and effective, there is a real risk anaphylactic shock [9]. So far, the allergic reactions, gastrointestinal disturbance, skin reactions and impaired color vision were reported for the oral form with milder and slower onset [24, 25]. Present meta-analysis indicated that oral TXA has no effect on the postoperative complications. The occurrence of infection and DVT was too small and thus meta-analysis was not proper to performed. Because oral TXA is cheaper than IV TXA, a transition to oral TXA would deliver even greater cost savings to the health care system. Fillingham et al. [18] reported that the oral TXA dosage cost $14 compared with $47-$108 depending on the availability of the generic IV formulation. Oral TXA seems to be a better choice than intravenous form, while provided similar drug efficacies with easily accessible and less costing than IV TXA.

Our meta-analysis also has several potential limitations: (1) patients treatment with different dose of TXA and different time to oral TXA preoperatively; (2) there was marked heterogeneity among the need for transfusion and hemoglobin drop between oral TXA with control group, reflecting the inconsistent benefit patients acquired from oral TXA, although these analyses were performed using a random effects model; (3) the follow-up in the included studies was limited after surgery. Thus, some adverse events may be underestimated. The occurrence of deep venous thrombosis and infection is too little to draw a final conclusion.

Conclusions

In conclusion, the present meta-analysis demonstrated Oral TXA has comparable hemostasis effects with IV TXA, and may reduce the costs for patients prepared for TJA. However, the limited quality and number of the included
Oral TXA for TJA

Figure 5. Forest plots of the included studies comparing the drain loss between the two groups.

Figure 6. Forest plots of the included studies comparing the length of hospital stay between the two groups.

studies, more high quality and multi center RCTs are still need to recommend for routine administration.

Disclosure of conflict of interest
None.
Oral TXA for TJA

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References


