Comparison of intra-articular versus intravenous application of tranexamic acid in total knee arthroplasty: a meta-analysis of randomized controlled trials

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Abstract

Introduction: There is much controversy about the optimal application of tranexamic acid (TXA) in total knee arthroplasty (TKA). The purpose of this meta-analysis was to compare the efficacy of the intra-articular and intravenous regimens of TXA in TKA.

Material and methods: A literature search of the PubMed, Embase and Cochrane Library databases was performed. Randomized controlled trials comparing the result of intra-articular and intravenous application of TXA during TKA were included. The focus was on the outcomes of blood loss, transfusion requirement and thromboembolic complications.

Results: Six studies were eligible for data extraction and meta-analysis. We found no statistically significant difference between intra-articular and intravenous administration of tranexamic acid in terms of total blood loss (WMD, 6.01; 95% CI: –96.78 to 108.79; p = 0.91), drain output (WMD = –20.26; 95% CI: –51.34 to 10.82; p = 0.20), hemoglobin drop (WMD = 0.33; 95% CI: 0.31 to 0.35; p < 0.01), or the incidences of transfusion (RR = 0.98; 95% CI: 0.26–1.70; p = 0.93) as well as deep vein thrombosis (RR = 0.49; 95% CI: 0.09–2.73; p = 0.42).

Conclusions: In comparison with intravenous application of TXA, intra-articular application had a comparable effect on reducing blood loss and the transfusion rate without increasing the complication rate.

Key words: tranexamic acid, intra-articular, intravenous, total knee arthroplasty, meta-analysis.

Introduction

With the aging of the population, the number of patients with osteoarthritis of the knee has increased dramatically. In patients with severe osteoarthritis, total knee arthroplasty (TKA) is widely used as an effective method to relieve pain, correct deformity, and restore function. However, because of the large exposed surface of cancellous bone, intraoperative and postoperative bleeding is one of the major complications following TKA [1, 2]. There is no doubt that a large amount of blood loss has a significant influence on morbidity and mortality, especially in old patients [3, 4]. Thus, seeking an effective method to reduce the loss of blood is necessary.

Tranexamic acid (TXA), as an antifibrinolytic agent, was introduced with the aim of reducing perioperative and postoperative bleeding. It
can block the lysine binding sites on plasminogen molecules, inhibit the formation of plasmin, and is believed to be able to help the body retain blood clots more effectively [5].

The intravenous application of TXA in orthopedic surgery has been well established in the literature. Many clinical studies and several meta-analyses have confirmed that this way could effectively reduce the rates of blood loss and transfusion in TKA without increasing the risk of complications [6–10]. In comparison with intravenous application, the intra-articular application of TXA has the advantages of being easy to administer, providing a maximum concentration of TXA at the bleeding site, and being associated with lower systemic absorption [11]. In recent years, intra-articular application of TXA has been put under the spotlight. However, based on current evidence, it is not clear whether intra-articular application of TXA is as effective as intravenous application measures.

Therefore, we conducted a systematic review and meta-analysis to compare intra-articular and intravenous administration of TXA in terms of blood loss, transfusion requirement and thromboembolic complications.

Material and methods

Literature search and inclusion criteria
PubMed, Embase and Cochrane Library databases were searched for randomized controlled trials (RCTs) that have been published from inception to March 2015. The following format of search terms was used: ('knee' or 'joint') and ('arthroplasty' or 'replacement') and 'tranexamic acid'. Search results were limited to human subjects, and no language restriction was imposed. We also manually checked the reference lists of RCTs in order to include other potentially eligible trials. The following inclusive selection criteria were applied: (a) study design: randomized controlled trials (RCT); (b) study population: adult patients receiving TKA; (c) intervention group: intra-articular application of TXA; (d) control group: intravenous application of TXA; and (e) outcome measure: total blood loss, drain output, hemoglobin drop, and incidents of transfusion, deep vein thrombosis (DVT) and pulmonary embolism (PE).

Data extraction and outcome measures
General characteristics and measured outcomes from each RCT were extracted independently by two authors. General characteristics included first author, publication year, country, number of patients (intervention/control group), and TXA dosage. Measured outcomes included total blood loss, drain output, hemoglobin drop, and the incidence of transfusion, DVT and PE. For continuous outcomes, if a group was divided into several subgroups, we combined numbers into a single sample size, and calculated means and standard deviations by the method introduced by the Cochrane Handbook [12]. When the same population was reported in several publications, we retained the most informative article or complete study to avoid duplication of information. Any disagreements were resolved by discussion and consensus.

Assessment of methodological quality
The methodological quality of these studies was evaluated without masking the trial names. Reviewers followed the instructions provided in the Cochrane Handbook for Systematic Reviews of Interventions [12]. A total of seven domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. If the information in a study was inadequate, we attempted to contact the authors in order to evaluate the study correctly.

Statistical analysis
Differences were expressed as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and weighted mean differences (WMDs) with 95% CIs for continuous outcomes. Heterogeneity was analyzed with both the $\chi^2$ test and the $I^2$ test. A p-value of $<0.10$ for the $\chi^2$ test was interpreted as evidence of statistical heterogeneity, and $I^2$ was used to estimate total variation across the studies. Studies with an $I^2$ statistic of 25–50% were considered to have low heterogeneity, those with an $I^2$ statistic of 50–75% had moderate heterogeneity, and those with an $I^2$ statistic of > 75% had high heterogeneity. The random effects model was used to pool RRs or WMDs in the case of significant heterogeneity ($p < 0.10$ or $I^2 > 50%$); otherwise, a fixed-effects model was used.

Because patient characteristics, TXA dosage, and other confounding factors were not consistent among studies, we further conducted sensitivity analysis to identify potential sources of heterogeneity.

The presence of publication bias was assessed by the Begg and Egger tests. A p-value $<0.05$ was regarded as statistically significant, except where otherwise specified. All statistical analyses were performed using Review Manager Version 5.1 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search results
After the initial database search, a total of 113 records were identified. However, on the basis of
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the titles and abstracts, 45 records were excluded because of duplicate studies and 54 were excluded for other reasons, such as reviews, non-randomized studies, or not relevant to our analysis. The remaining 14 were retrieved for full text review, but 8 of them were excluded because 5 did not report outcomes of interest, and 3 were cohort studies. Finally, 6 RCTs that met our inclusion criteria were included in the present meta-analysis [8, 13–17]. The selection process is shown briefly in Figure 1.

Study characteristics

The main characteristics of the 6 RCTs included in the meta-analysis are presented in Table I. All these studies were in English and published between 2012 and 2014. The populations of the RCTs ranged from 60 to 200 cases. There were a total of 676 patients involved. Among them, 305 were the intra-articular group and 371 were the intravenous group. All patients were diagnosed with osteoarthritis and underwent TKA. The dose of intra-articular application of TXA ranged from 1.5 g to 3 g and the intravenous application ranged from single-dose to triple-dose.

Assessment of risk of bias

The risk of bias is demonstrated graphically in Figure 2 and summarized in Figure 3. The randomization technique was mentioned in all 6 trials. However, only 2 trials described the process of random sequence generation [14, 16], and 2 trials stated the method of allocation concealment [8, 13]. Blinding of participants and personnel was used in 4 trials [8, 13–15], but none of the studies was blinded in the assessment of outcome. One trial was judged to be at low risk of attrition bias [13], and 5 were at low risk of reporting bias [13–17].

Outcome

Total blood loss

Two studies reported the data on total blood loss. The test for heterogeneity was not significant, and the studies have no statistical evidence

| Author       | Publication year | Country | Number of patients | TXA dosage | Intra-articular group | Intravenous group |
|--------------|------------------|---------|--------------------|------------|-----------------------|-------------------|
| Maniar [8]   | 2012             | India   | 40                 | 3 g TXA/100 ml NS | 10 mg/kg × (1–3) dose |
| Seo [16]     | 2013             | Korea   | 50                 | 1.5 g TXA/100 ml NS | 1.5 g TXA/100 ml NS |
| Soni [17]    | 2014             | India   | 30                 | 3 g TXA/100 ml NS | 10 mg/kg × 3 dose   |
| Sarzaeeem [15] | 2014         | Iran    | 100                | 3 g TXA/100 ml NS | 1.5 g TXA/100 ml NS |
| Patel [14]   | 2014             | USA     | 46                 | 2 g TXA/100 ml NS | 10 mg/kg × 1 dose   |
| Gomez-Barrena [13] | 2014    | Spain   | 39                 | 3 g TXA/100 ml NS | 15 mg/kg × 1 dose   |

TXA – tranexamic acid, NS – normal saline.
of heterogeneity (\(p\) for heterogeneity = 0.60; \(I^2 = 0\%\)). Using the fixed-effect model, there was no significant difference in total blood loss between the two groups (WMD = 6.01; 95% CI: –96.78 to 108.79; \(p\) = 0.91) (Figure 4).

### Drain output

Data on drain output were available for 5 trials. The test for heterogeneity was not significant, and the studies have no statistical evidence of heterogeneity (\(p\) for heterogeneity = 0.66; \(I^2 = 0\%\)). Using the fixed-effect model, the aggregated results suggested that there was no significant difference in drain output between the two groups (WMD = 20.26; 95% CI: –51.34 to 10.82; \(p\) = 0.20) (Figure 5). Excluding any single study did not materially alter the overall combined WMD, which ranged from –6.92 (95% CI: –48.31 to 34.47; \(p\) = 0.74) to –24.53 (95% CI: –56.32 to 7.27; \(p\) = 0.13).

### Hemoglobin drop

A reduction in hemoglobin after surgery was reported in 5 studies. There was high statistical heterogeneity among the studies (\(p\) for heterogeneity < 0.01; \(I^2 = 94\%\)). Pooling the data with a random-effect model revealed no statistically significant difference between the intra-articular group and the intravenous group (WMD = 0.33; 95% CI: –0.31 to 0.98; \(p\) = 0.31) (Figure 6). Excluding any single study did not materially alter the overall combined WMD, which ranged from 0.03 (95% CI: –0.24 to 0.30; \(p\) = 0.82) to 0.47 (95% CI: –0.29 to 1.22; \(p\) = 0.22), but excluding the trial conducted by Sarzaeem et al. [15] decreased the \(I^2\) from 94% to 53%.
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Transfusion requirement

All 6 studies provided data on the number of patients who needed a blood transfusion. In the intra-articular group, transfusions were found in 29 of 305 patients (9.5%), and in the intravenous group they were found in 43 of 371 patients (11.6%). The test for heterogeneity was not significant, and the studies have low statistical heterogeneity ($I^2 = 28\%$). Using the fixed-effect model, the rate of transfusion requirements was not significantly different between the intra-articular group and the intravenous group (RR = 0.98; 95% CI: 0.56–1.70; $p = 0.93$) (Figure 7). Excluding any single study did not materially alter the overall combined RR, which ranged from 0.75 (95% CI: 0.41–1.37; $p = 0.34$) to 1.55 (95% CI: 0.75–3.17; $p = 0.23$), but excluding the trial conducted by Sarzaeem et al. [15] decreased the $I^2$ from 28% to 0%.

DVT

All 6 studies provide data on the incidence of DVT after surgery. In the intra-articular group, DVT was found in 1 of 305 patients (0.3%), and in the intravenous group it was found in 3 of 371 patients (0.8%). There was low statistical heterogeneity among the studies ($p$ for heterogeneity = 0.16; $I^2 = 49\%$). Using the fixed-effect model, there was no significant difference in the incidence of DVT between the two groups (RR = 0.49; 95% CI: 0.09–2.73; $p = 0.42$) (Figure 8). Excluding any single study did not materially alter the overall combined RR, which ranged from 0.13 (95% CI: 0.01–2.67; $p = 0.19$) to 3.08 (95% CI: 0.12–77.91; $p = 0.50$).

PE

Data on PE were reported in 5 studies. There was no incident of PE in any study. Thus, no statistical analysis was performed.
Heterogeneity:

| Study or subgroup | Intra-articular | Intravenous | Weight (%) | Odds ratio M-H, fixed, 95% CI, year |
|-------------------|----------------|-------------|------------|-----------------------------------|
| Maniar 2012       | 0              | 40          | 0          | 160                               |
| Seo 2013          | 0              | 50          | 3          | 50                                |
| Patel 2014        | 0              | 46          | 0          | 42                                |
| Sarzaeem 2014     | 0              | 100         | 0          | 50                                |
| Gomez-Barrena 2014| 1              | 39          | 0          | 39                                |
| Soni 2014         | 0              | 30          | 0          | 30                                |
| Total (95% CI)    | 305            | 371         | 100.0      | 0.49 (0.09, 2.73)                  |
| Heterogeneity: χ² = 1.96, df = 1 (p = 0.16), I² = 49% |
| Test for overall effect: Z = 0.81 (p = 0.42) |

Figure 8. Forest plot showing the rate of deep vein thrombosis between the intra-articular group and the intravenous group.

Publication bias

Because of the limited number (< 10) of studies included in each analysis, we did not assess publication bias.

Discussion

Blood loss is a major concern both during and after TKA surgery [1, 2]. The TXA, as a synthetic antifibrinolytic agent, has been found to effectively reduce blood loss and the need for transfusion [5]. However, there is no consensus regarding the most effective regimen for TXA administration. Meta-analysis, as an efficient method to integrate valid information, can provide a basis for making a clinical decision [18–20]. In the current study, we included all available RCTs, and performed a meta-analysis. The pooled results revealed that there were no statistically significant differences in total blood loss, drain output, hemoglobin drop, incidence of transfusion, or DVT when comparing intra-articular and intravenous administration of TXA in TKA. This means that intra-articular application of TXA had a comparable effect on reducing blood loss and the transfusion rate without increasing the complication rate.

Intra-articular application of TXA has been investigated by many authors in recent years [11, 21–23]. As the drugs are applied predominantly to the joint cavity, the site of bleeding could achieve a higher therapeutic concentration. This could effectively limit blood loss with little or no systemic absorption or subsequent systemic side effects. Additionally, TXA is easy to administer in this way. In this study, compared with intravenous administration of TXA, intra-articular application is equally effective and safe to reduce blood transfusion after TKA, which means that this method could be widely used in clinical practice.

Though it has not been proven clinically, TXA could carry a high risk of thrombosis [24, 25]. Also, DVT is a common complication of TKA and can result in morbidity or even mortality when it progresses to PE [26]. Thus, surgeons should pay close attention to them. In comparison with intra-venous application of TXA, the intra-articular application was considered to feature less systemic absorption and a better local effect, so it may lead to a lower incidence of thrombosis. In this meta-analysis, DVTs were found in 1 of 305 patients (0.3%) in the intra-articular group and in 3 of 371 patients (0.8%) in the intravenous group. It seems that intravenous application of TXA is associated with a higher risk of DVTs; however, this difference is not statistically significant. This result could be due to the rare incidence of DVT or the relatively small sample size. Therefore, we cannot draw a definite conclusion yet, and corresponding findings require further confirmation. Also, the incidence of PE did not show a significant difference because no incident of PE was reported in any study. Further large-scale studies should also pay attention to this complication.

In the process of pooling some of the outcomes, substantial heterogeneity was observed among these studies, which was not surprising given the differences in characteristics of populations, doses of drug, and various methods of injecting TXA. Our sensitivity analyses suggested that the trial conducted by Sarzaeem et al. [15] probably contributed to the heterogeneity. This study differed from the others in some aspects. A major difference is the way of injecting TXA. Unlike other trials, TXA was injected through the drain in some patients instead of direct irrigation. This way had the advantage of topical application of TXA into the surgical field, and could result in significantly smaller amounts of post-operative blood loss, but it did not seem to be more effective than the other method to reduce the hemoglobin drop. However, this conclusion was derived from only one study. In the future, one may focus on this special method of administration of TXA. More well-performed RCTs could be performed to verify whether this method is better than the other way.

This meta-analysis has several potential limitations. First, we included only RCTs in an attempt to obtain reliable results. However, all these trials had methodological flaws, such as failure to blind the outcome assessor, or neglect of allocation con-
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Yaming Liu and Fantao Meng contributed equally to this work.

Conflict of interest

The authors declare no conflict of interest.

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