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Review

Oral tranexamic acid can reduce blood loss after total knee and hip arthroplasty: A meta-analysis

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HIGHLIGHTS

- We conducted a meta-analysis to compare the efficacy of oral tranexamic acid plus after TKA and THA.
- Only randomized controlled trials were included.
- Oral TXA has comparable hemostasis effects with IV TXA and may reduce the costs for patients prepared for TJA.

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ABSTRACT

Objective: The aim of the present study was to compare the efficacy and safety of oral tranexamic acid (TXA) with controls or intravenous TXA in patients undergoing total joint arthroplasty (TJA) in a systematic review and meta-analysis.

Methods: We systematically searched randomized controlled trials (RCTs) from PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Google databases. Any studies comparing oral TXA versus a control group or intravenous TXA for patients prepared for TJA were included. The outcomes included the need for transfusion, hemoglobin drops, length of hospital stay and drain volume. We calculated the risk ratio (RR) with a 95% confidence interval (CI) for the need of transfusion and the weighted mean difference (WMD) with a 95% CI for hemoglobin drop, length of hospital stay and drain blood loss. Stata 12.0 was used for the meta-analysis.

Results: Five clinical trials (5 RCTs) involving 333 patients were finally included in this meta-analysis. When compared with the control group, oral TXA was associated with less need for transfusion, fewer hemoglobin drops, less drain volume and a shorter length of hospital stay ($P < 0.05$). When compared with IV TXA, oral TXA was associated with more hemoglobin drops ($P < 0.05$). However, there was no significant difference between the need for transfusion, drain volume and the length of hospital stay between oral TXA and IV TXA.

Conclusion: Oral TXA has comparable hemostatic effects with IV TXA and may reduce the costs for patients prepared for TJA. However, considering the limited quality and number of the included studies, more high-quality and multi-center RCTs are still needed to recommend oral TXA for routine administration.

1. Introduction

Total joint arthroplasty (TJA), including total knee arthroplasty (TKA) and total hip arthroplasty (THA), has been identified as the most effective surgery for end-stage knee or hip diseases [1]. The demand for TJAs is increasing as the population ages; by 2030 in the US alone, demand for primary TKA is projected to grow by 673% to 3.48 million, and demand for THA is projected to grow by 174%–572,000 procedures [2]. Some studies have shown that blood loss of 1450–1790 mL occurs without special intervention and that transfusions are needed for 10%–38% of patients undergoing TKA [3–7]. Transfusion was associated with a substantial risk of bacterial/viral infections, allergic reactions, transfusion-related acute lung injury and even mortality [8,9].

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There are several protocols to reduce postoperative blood loss and avoid homologous blood transfusion including topical or intravenous tranexamic acid (TXA), topical fibrin sealant and the use of tourniquets [10–12]. Among the above methods, TXA is the most potent drug for the control of blood loss. TXA, as a synthetic fibrinolytic inhibitor, can competitively inhibit plasmin, plasminogen, and fibrin from combining and directly inhibits plasmin activity. Previous studies indicated that intravenous TXA was effective in reducing perioperative blood loss without increasing thrombotic complications after TJA [13]. However, drug allergy with anaphylactic shock has been reported with intravenous TXA [14]. The topical form carries a theoretical risk of periprosthetic infection due to needle contamination and may even aggravate sepsis [15]. Currently, the ideal route of TXA administration remains controversial. Oral TXA was effective in primary TJA to reduce perioperative total blood loss and blood transfusions [16]. However, the relatively small number of participants has made the results of these studies inconclusive.

Based on the current clinical studies with oral TXA, we aimed to pool the results from published RCTs to identify the efficacy of oral TXA in TJA. The purpose of this meta-analysis was to study whether oral TXA was associated with the following: (1) less need for transfusion, (2) fewer hemoglobin drops, (3) less drain blood loss, (4) shorter lengths of hospital stay and fewer complications compared to the control group and IV TXA.

2. Material and methods

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [17] and was written in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist [18].

2.1. Search strategies

PubMed, Embase, Web of Science, the Cochrane Library and the Chinese Wanfang database were searched up to March 2017 for comparative studies involving oral TXA for reducing blood loss in patients undergoing TJA. The search strategies in the PubMed database were as follows: ((((((((((THR) OR "Arthroplasty, Replacement, Hip"[Mesh]) OR THA) OR total hip replacement) OR total hip arthroplasty) OR "Arthroplasty, Replacement, Knee"[Mesh]) OR TKR) OR TKA) OR total knee arthroplasty) OR total knee replacement)) AND tranexamic acid). The title and abstract of the 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. This meta-analysis was extracting relevant data from published tables or figures, and thus no ethic review approval was needed.

2.2. Inclusion criteria and exclusion criteria

Inclusion criteria: Participants were patients undergoing primary TJA, including primary TKA and THA. Intervention was oral TXA for blood loss control in TJA. Comparisons were IV TXA or a control group (placebo or nothing). The outcomes were the need for transfusion, hemoglobin drops, drain blood loss, length of hospital stay, and postoperative complications. Only 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.

2.3. Data extraction and quality assessment

Two authors (GL L and YM L) independently scanned all the 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 (transfusion criteria, age, sex and other baseline characteristics), interventions and outcomes were extracted in duplicate by the two authors (GL L and YM L) using a standardized form in a pre-designed Microsoft Excel worksheet. The data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval [CI]) were converted to the mean ± standard deviation (SD) according to the Cochrane Handbook [17]. If data were not reported numerically, we extracted them by manual measurements from published figures.

Two authors (GL L and YM L) 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 sources of bias [17]. Each aspect was measured as "low bias", "unclear bias" and "high bias" according to the Cochrane Handbook [17]. The quality of the studies were quantified by the Jadad five-point score [19]. Kappa values were used to measure the degree of agreement between the 2 reviewers and were rated as follows: fair, 0.40 to 0.59; good, 0.60 to 0.74; and excellent, 0.75 or more [20].

2.4. Statistical analysis

For each included study, the weighted mean differences (WMD) at the 95% confidence interval (CI) were calculated for continuous outcomes (hemoglobin drops, drain blood loss and the length of hospital stay), while risk ratios (RR) at 95% CI were calculated for dichotomous outcome (need for transfusion). When there was no statistical evidence of heterogeneity (I^2<50%, P>0.1), a fixed-effects model was adopted; otherwise, a random-effects model was adopted. All analyses were performed using Stata 12.0 software (Stata Corp., College Station, TX), and a *p*-value less than 0.05 was considered statistically significant. Because the number of included RCTs was less than ten studies, publication bias was not detected [21].

3. Results

3.1. Search results and study characteristics

The literature search and selection process are shown in Fig. 1. The initial search yielded 212 articles, and 155 papers were read when excluding the duplicates. In the next stage, 148 papers were excluded according to the inclusion criteria. Finally, we included 5 clinical studies with 333 patients for the meta-analysis [16,22–25]. The detailed baseline characteristics of the included studies are presented in Table 1. All the articles were published in English between the years 2004 and 2017. The sample size ranged from 20 to 43 (total = 333), and the mean age ranged from 63 to 70 years. The follow-up ranged from 6 weeks to 3 months. 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. The timing of the administration of TXA ranged from 1 h to 8 h before surgery.

3.2. Risk of bias of the included studies

The risk of bias summary and risk of bias graph for RCTs are shown in Figs. 2 and 3, respectively. All the RCTs described the random sequence generation, allocation concealment and blinding