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Review

Combined use of intravenous and topical versus intravenous tranexamic acid in primary total joint arthroplasty: A meta-analysis of randomized controlled trials

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HIGHLIGHTS

- This is the first meta-analysis to study the combined use of intravenous and topical tranexamic acid in primary total joint arthroplasty.
- Only RCTs were included in this study.
- Combined use of intravenous and topical tranexamic acid is safe and more effective in primary total joint arthroplasty.

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ABSTRACT

Objective: To compare the safety and efficacy of combined use of intravenous and topical tranexamic acid with that of intravenous tranexamic acid in primary total joint arthroplasty.
Methods: Literature was searched in PubMed, Cochrane Library, Embase, Medline, and China National Knowledge Infrastructure databases. Only randomized controlled trials were included in our study. Data were using fixed-effects or random-effects models with standard mean differences and risk ratios for continuous and dichotomous variables, respectively.
Results: Seven randomized controlled trials encompassing 683 patients were retrieved for this meta-analysis. Outcomes showed that when compared with intravenous tranexamic acid, combined use of intravenous and topical tranexamic acid could significantly reduce total blood loss by a mean of 138.70 mL [95% confidence interval (CI): −196.14 to −81.26, $p < 0.001$], transfusion rates (risk ratio 0.42, 95% CI: 0.2 to 0.85, $p < 0.001$). No significant difference in the occurrence of deep vein thrombosis, pulmonary embolism was found between the two groups.
Conclusions: This meta-analysis indicated that comparing with only intravenous tranexamic acid, combined use of intravenous and topical tranexamic acid can significantly reduce blood loss and transfusion rate in primary total joint arthroplasty without increasing the risk of thrombotic complications. Therefore, we suggest that tranexamic acid should be intravenously combined with topically administered in primary total joint arthroplasty.

1. Introduction

Total hip and knee arthroplasty are associated with excessive blood loss [1–4], which may increase the risk of allogeneic blood transfusion [5,6]. Allogeneic blood transfusion may result in potentially serious complications [7,8], such as immunologic reaction and virus infection.

Several interventions have utilised to reduce blood loss and postoperative transfusion rates, such as preoperative autologous donation, cell salvage, tourniquet, controlled hypotension, regional anesthesia, and the use of antifibrinolytics [9,10].

Compared with other antifibrinolytic drugs, tranexamic acid (TXA) is cheaper and safer. Some review and meta-analyses [11–16] have upheld the safety and efficacy of intravenous TXA in both total knee arthroplasty (TKA) and total hip arthroplasty (THA). However,

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the intravenous TXA administration would increase the incidence rate of thrombotic events, such as deep vein thrombosis and pulmonary embolism. Topical or intra-articular application of tranexamic acid can decrease systemic absorption, so as to lower the risk of adverse events. Recently, more and more researches have focused on the issue that when compared with only intravenous tranexamic acid (IV group), whether combination application of intravenous and topical tranexamic acid (combined group) has bigger value in primary total joint arthroplasty (TJA) [17–23].

Therefore, we conduct this meta-analysis to evaluate the efficiency and safety of combined use of intravenous and topical tranexamic acid undergoing primary TJA.

2. Materials and methods

2.1. Inclusion criteria

For the meta-analysis, randomized controlled trials (RCTs) that describe trials of TXA and primary TJA were obtained by searching PubMed, Cochrane Library, Medline, Embase, and China National Knowledge Infrastructure (CNKI) databases. The search strategy was created using a combination of terms consist of “tranexamic acid”, “total hip arthroplasty”, “total knee arthroplasty”, “total hip replacement”, “total knee replacement”, “total joint arthroplasty”, “total joint replacement”.

The inclusion criteria for the meta-analysis were reproduced below. First, operation type contained in the studies was unilateral primary TJA. Second, studies were RCTs that included two intervention groups, an IV group and a combined group. In the IV group, tranexamic acid was intravenously used, while in the combined group, tranexamic acid was intravenously and topically administered. Both groups reported at least one of the following outcomes: total blood loss, the ratio of patients who needed blood transfusion, and the percentage of patients with deep vein thrombosis or pulmonary embolism.

Quality of the studies were evaluated according to the evaluation tool (QAS) published in previous studies [14–16,24]. The methodological quality of each study was scored from 0 to 24, where higher scores represented better quality. Two reviewers assessed all eligible RCTs. Disagreements were settled through discussion.

2.2. Statistical analysis

Two reviewers independently extracted relevant data, which include author names, published years, sample sizes, protocol of TXA administration, and transfusion criteria, total blood loss, the ratio of patients who needed allogeneic blood transfusion, the incidence of deep vein thrombosis and pulmonary embolism. Data were analyzed with the Review Manager 5.3. Total blood loss was expressed with mean difference and 95% CI, blood transfusion rate and the incidence of deep vein thrombosis were based on relative risks and 95% confidence intervals. The I^2 value was used to evaluate the heterogeneity level among different studies. We used a fixed-effect model analysis to compare trials showing low heterogeneity ($P \geq 0{\cdot}10$; $I^2 \leq 50\%$). Otherwise, we employed the random-effects model, and the data would be pooled by subgroup analysis according to the different operation type (TKA or THA). Funnel plot for blood transfusion rate was generated to evaluate potential publication bias among studies.

3. Results

3.1. Characteristics of the appropriate studies

617 RCTs were previously found in the databases we searched, of which 112 were duplicates. With the review of all titles and abstracts, 10 RCTs complied with the inclusion criteria. After screening the full texts, 3 trials were excluded with reasons. Eventually 7 studies [17–23]matched the standard for analysis (Fig. 1), and detail information was demonstrated in Table 1.

3.2. Total blood loss

Six studies [17–21]with a total of 643 patients were entitled to this outcome. Combined group dramatically decreased total blood loss by a mean of 138.70 mL (95% CI: −196.14 to −81.26, $p < 0.001$). However, there was significant heterogeneity among the studies included ($I^2 = 65\%$) (Fig. 2), a random-effect model was accustomed. Subgroup analysis indicated that combined use of intravenous and topical TXA can markedly reduce blood loss both in primary TKA ($p = 0.002$) and THA ($p < 0.001$).

3.3. Blood transfusion rate

Six studies [17–21,23]including 643 patients reported this outcome. Combined group significantly reduced the number of patients who needed allogeneic blood transfusion (risk ratio 0.42, 95% CI: 0.2 to 0.85, $p = 0.02$). Little heterogeneity among studies was consulted (Q, $p = 0.36$, $I^2 = 9\%$, Fig. 3).The funnel plot (Fig. 4) showed that there was mild potential publication bias among studies.

3.4. Thromboembolic complications

Three studies [17,19,21]containing 424 patients recorded this outcome. There was no significant difference between combined and IV groups ($P = 1.00$) and no heterogeneity among studies ($P = 0.68$, $I^2 = 0$, Fig. 5).

4. Discussion

Tranexamic acid, an antifibrinolytic agent, contributes to reduce blood loss by binding to plasminogen and blocking the interaction of plasminogen with fibrin [25]. Many published randomized controlled trials have indicated that intravenous TXA reduces blood loss and the need for transfusion, without increasing the risk of thromboembolic complications [17–23,26–33]. However, one prospective cohort study reported intravenous TXA can increase the occurrence of vascular occlusive events, although this finding was confined to the calf veins [34]. Combined use of intravenous and topical TXA may be a better way to solve this problem.

This meta-analysis demonstrated that combined use of intravenous and topical TXA significantly reduced total blood loss. However, the extent of the benefit was indecisive, because significant heterogeneity among studies was recorded ($I^2 = 65\%$). High heterogeneity may derive from variations in clinical practice, such as different surgical techniques, different protocol of TXA, different operation time, different means of anesthesia, different time of tourniquet releasing and so on. Subgroup analysis showed that combined use of intravenous and topical TXA has a similar effect on reducing total blood loss both in THA and TKA.

There were several advantages of our meta-analysis. Firstly, to the best of our knowledge, this is the first meta-analysis to evaluate the safety and efficiency of combined use of intravenous and topical versus intravenous tranexamic acid in primary TJA. Secondly, to ensure the quality of the meta-analysis, we only incorporated RCTs. The quality assessment score of the most studies included was high (16–24). Thirdly, RCTs in any language were searched to minimize publication bias. Meanwhile, subgroup analysis and random-effects model were employed to minimize heterogeneity among studies.