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Review

Topical fibrin sealant versus intravenous tranexamic acid for reducing blood loss following total knee arthroplasty: A systematic review and meta-analysis

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HIGHLIGHTS

- The use of intravenous TXA significantly reduced blood transfusions and maintained higher hemoglobin levels in TKA.
- There are no statistical differences in total calculated blood loss and complications between the two groups.
- Our meta-analysis suggests that it would be prudent administer TXA via the intravenous route in preference to topical FS.

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ABSTRACT

Purpose: Efficacy and safety of topical application of a fibrin sealant (FS) compared with intravenous administration of tranexamic acid (TXA) for reducing blood loss after total knee arthroplasty (TKA) is controversial. We undertook a meta-analysis to compare the effects of topical application of FS or intravenous administration of TXA on blood loss after TKA.

Methods: PubMed, Medline, Embase, Web of Science and the Cochrane Library were searched to identify studies comparing FS with TXA for TKA patients. The mean difference (MD) of blood loss, hemoglobin value, and odds ratios (ORs) of transfusion requirements and adverse events in FS and TXA groups were pooled throughout the study. Relevant data were analyzed using RevMan v5.3.

Results: Five studies involving 359 patients were included (181 FS *vs.* 178 TXA). TXA use had a significantly lower prevalence of blood transfusion (OR = 3.14; 95% confidence interval (CI), 1.67 to 5.90, P = 0.0004) and higher hemoglobin level (MD = −1.23; 95% CI, −2.19 to −0.27, P = 0.01) than FS in the early postoperative period. No significant difference was seen in total blood loss between the two groups (MD = 198.06; 95% CI, −267.45 to 663.57; P = 0.40). There were no significant differences in adverse events, superficial infections, or deep-vein thrombosis among study groups.

Conclusions: Our meta-analysis suggests that intravenous administration of TXA for patients undergoing TKA may reduce blood-transfusion requirements and maintain higher hemoglobin levels compared with topical application of FS in the early postoperative period. There were no significant differences in total calculated blood loss and prevalence of complications between the two groups. However, owing to the variation of included studies, no firm conclusions can be drawn.

1. Introduction

Total knee arthroplasty (TKA) is a very successful surgical procedure used to treat end-stage knee osteoarthritis so that pain can be relieved and joint function restored. However, TKA can be associated with considerable (1000–1790 mL) blood loss in the perioperative period that usually results in allogeneic blood transfusion [1]. Various blood-preservation protocols have been

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created to prevent blood loss: acute normovolemic hemodilution; minimally invasive surgery; perioperative salvage and reinfusion of blood; administration of erythropoietin; hypotensive anesthesia; transfusion of pre-donated autologous blood [2–4]. Nevertheless, many patients require blood transfusion for intraoperative/postoperative blood loss. Blood transfusion can lead to adverse immunologic reactions, disease transmission, intravascular hemolysis, transfusion-related lung injury, renal impairment/failure, and increased costs [5,6]. Therefore, more effective and safer measures for reducing bleeding and blood-transfusion requirements during and after TKA are needed.

Pharmacologic interventions that have been shown to reduce perioperative blood loss and prevalence of blood transfusion in TKA include topical application of fibrin sealants (FSs) [7–9] and intravenous administration of tranexamic acid (IV-TXA) [10–12]. FSs (also known as "fibrin glues" and "fibrin tissue adhesives") consist mainly of fibrinogen and thrombin derived from human blood products, which form a stable fibrin clot by reproducing the final step of the coagulation cascade [13,14]. FSs have been shown to be efficacious and safe in reducing blood loss and transfusion requirements without increasing the risk of deep-vein thrombosis (DVT), pulmonary embolism (PE), superficial infection, fever, hematoma or other complications for patients undergoing TKA [7–9]. However, their main disadvantage is their cost: they are more expensive than TXA [15,16].

TXA is a synthetic derivative of the amino acid lysine that inhibits local degradation of plasma fibrin by blocking the lysine binding sites on plasminogen and exerts an anti-fibrinolytic effect [17]. TXA can also be administered *via* oral or intra-articular routes, but the most common route is intravenous [18]. Use of TXA in primary TKA is accepted widely. Multiple studies [10–12] have clearly demonstrated the efficacy of IV-TXA for reducing blood loss without an increased prevalence of postoperative complications or increased cost in patients undergoing TKA. However, little is known about its efficacy and safety compared with topical application of FS. Some studies have demonstrated that IV-TXA significantly reduces perioperative blood loss and blood-transfusion requirements in patients undergoing TKA compared with patients using topically applied FS [19,20]. Different conclusions have been reached by other scholars who have not found significant differences in blood loss between FS and TXA for TKA patients [15,16].

There is controversy over which of these two methods leads to a safer and more effective hemostatic effect after TKA. Many of these studies have been criticized for poor design, low statistical power, inconclusive results, and short duration of follow-up. Thus, we conducted a meta-analysis to ascertain if TXA given *via* the intravenous route is superior to topical application of FS in reducing postoperative blood loss and blood-transfusion requirements in primary TKA.

2. Materials and methods

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [21] reporting guidelines for the meta-analysis of intervention trials.

2.1. Search strategy

PubMed, Medline, Embase, Web of Science and the Cochrane Library were searched up to January 2016 for comparative studies involving FS and TXA for reducing blood loss in patients undergoing TKA. Search terms were: "fibrin sealant" OR "fibrin glues" OR "fibrin tissue adhesives" AND "total knee arthroplasty" OR "total knee replacement". The language of publications was limited to English. 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.

2.2. Inclusion criteria and study selection

We identified studies comparing FS with TXA in patients undergoing primary TKA. Evaluated outcomes were: blood loss; hemoglobin level; blood transfusion; length of hospital stay; cost; complications (including DVT/PE, superficial infection, fever, and hematoma). 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 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. Data on patient characteristics (age, sex and other baseline characteristics), intervention and outcomes were extracted in duplicate by the two authors using a standardized form. Data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval (CI)) were converted to mean ± SD according to the *Cochrane Handbook* [22]. If data were not reported numerically, we extracted them by manual measurements from published figures.

Methodological quality of randomized control trials (RCTs) was assessed using a modified version of the Jadad Scale [0 ("very poor") to 7 ("rigorous")] was used to assess the methodological strength of a clinical trial. The modified Jadad Scale (mJS) contained two-questions each on randomization and masking, and one question on the reporting of dropouts and withdrawals [23]. The Newcastle–Ottawa Quality Assessment Scale (NOQAS) was used for non-randomized control trials (nRCTs). The NOQAS is used to assess population selection, comparability of exposed and unexposed, and adequacy of outcome assessment (including ascertainment and attrition of outcome) [24]. Data extraction and quality assessment were undertaken independently by two of the authors. If there were disagreement, the third author discussed until consensus was reached.

2.4. Statistical analysis

All calculations were made using RevMan v5.3. Mean difference (MD) with a 95% CI was calculated for continuous data. Odds ratios (ORs) with 95% CI were calculated for dichotomous data. Heterogeneity among studies was estimated using the I^2 statistic; substantial heterogeneity was represented by $I^2 > 50\%$. A fixed-effects model was used if the heterogeneity test did not reveal significance ($I^2 < 50\%$; $P > 0.1$). Otherwise, we adopted the random-effects model. $P < 0.05$ was considered significant.

3. Results

3.1. Search results

The initial search yielded 78 citations, of which 68 were excluded owing to duplication. After screening the titles and abstracts and reading full text, five studies were excluded based on inclusion criteria. Finally, five studies [15,16,19,20,25] involving 359 patients were eligible for data extraction and meta-analysis (Fig. 1).