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Original article

The efficacy of fibrin sealant in knee surgery: A meta-analysis

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ABSTRACT

Background: Fibrin sealant is frequently used in knee surgery as an adjuvant method for reducing postoperative bleeding, however, there is no consensus regarding the efficacy of fibrin sealant.
Hypothesis: Fibrin sealant achieves better efficacy in terms of blood loss control, transfusion rate and units in knee surgery compared with controls.
Methods: A search of the Cochrane Collaboration (2013 Issue 09), Embase (1974–2013.09), PubMed (1966–2013.09) and Chinese databases (up to 2013.09) were conducted. The Cochrane Collaboration's tool was used to assess for bias and data were analyzed by RevMan 5.29 software.
Results: This study included nine RCTs and four prospective comparative trials with a total of 1299 patients. Compared to the control, fibrin sealant achieved a decrease in hemoglobin reduction [MD = 1.14, 95% CI (0.61–1.67)], transfusion rate [OR = 0.36, 95% CI (0.25–0.51)], transfusion units [MD = 0.47, 95% CI (0.24–0.71)], hospital stay [MD = 2.22, 95% CI (0.56–3.88)] and the incidence of complications [OR = 0.56, 95% CI (0.38–0.83)]. And it also reduced total blood loss, while there was no significant difference [MD = 155.83, 95% CI (–525.02–213.15)].
Conclusion: Patients undergoing knee surgery would benefit from high-dose fibrin sealant with reduced transfusion rate and unit, hospital stay and complications, while they might benefit little from it in total blood loss. However, the effects of a low-dose of fibrin in knee surgery remain inconclusive.
Level of evidence: Level III.

1. Introduction

Serious knee arthritis can lead to varying degrees of pain and/or functional disability, including decreased flexion and extension ability [1]. Total knee arthroplasty (TKA) and total knee replacement (TKR) are both common, successful surgeries that are widely used to treat patients with serious knee arthritis [2]. TKA and TKR are frequently followed by postoperative bleeding and often result in significant blood loss. The drain output from patients, measured using knee drains, ranges from 1200 mL to 1800 mL [2,3], though this can be even higher due to hidden blood loss [4,5]. A tourniquet is always used intra-operation, but a meta-analysis by Tai et al. showed that this could only save operation time [6], not reduce blood loss [7]. In addition, patients managed with a tourniquet can have higher risks of thromboembolic complications postoperation [8].

Fibrin sealant is comprised mostly of fibrinogen and human thrombin [9] and can initiate the last phase of physiological blood coagulation [10]. Although it has been used for decreasing postoperative blood loss in surgery for 20 years, the effects of fibrin sealant on knee surgery remain unclear. Some studies have indicated that additional fibrin sealant significantly reduces blood loss, thus, reducing the need for blood transfusion [2,11,12]. Other studies have shown that the difference in blood transfusion requirement between fibrin sealant groups and control groups were not statistically significant [13,14]. Furthermore, the cost of the additional fibrin sealant is three times greater than that of the required blood transfusion [2].

To date, there is no consensus in the medical community with regard to the efficacy of fibrin sealant in knee surgery and there is limited evidence from systematic reviews or meta-analyses. In this study, we evaluate the efficacy and safety of fibrin sealant in knee surgery through analysis of relevant randomized controlled trials (RCTs) and prospective comparative studies. The hypothesis of the present study was that fibrin sealant achieves better efficacy in knee surgery compared with controls. The use of fibrin sealant allows decreasing the total

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blood loss, the transfusion rate and the mean transfusion unit in TKR.

2. Materials and methods

2.1. Literature search

Online databases, such as the Cochrane Library (2013 Issue 09), Embase (1974–2013.09), PubMed (1966–2013.09) and the Science Citation Index Expanded were searched up to September 2013. In addition, our search included the following Chinese databases: the Chinese biomedicine literature database (CMB), the Chinese periodical full text database (CNKI) and the Wan fang database, and they were all searched up to September 2013. A range of search terms were used: "(knee surgery OR total knee arthroplasty OR TKA OR total knee replacement OR TKR) AND (fibrin sealant OR fibrin glue OR fibrin tissue adhesive)". Based on the primary search results, future supplementary searches included reading abstracts, studies, conference proceedings and citations.

2.2. Inclusion criteria

Only published RCTs and prospective comparative studies were included, regardless of blinding and allocation concealment. Reviews, case reports and experience-based communications were excluded from the study. Patients suffering from serious bilateral or unilateral knee joint disease who were willing to receive total knee arthroplasty or total knee replacement were eligible for inclusion in the study. Participants were divided into two groups: the treatment group was treated with fibrin sealant during surgery and the control group was not. Other interventions, including drugs and functional recovery training, were permitted only when comparable between the two groups.

The main outcome measures were total blood loss, transfusion rate, and transfusion units. Secondary outcome measures were Hb reduction, drain-out volume, hospital stay, and complications.

2.3. Data extraction and quality assessment

All studies obtained from the initial searches were independently assessed for eligibility by two researchers according to specific characteristics. Only studies evaluating the effectiveness of fibrin sealant in TKA or TKR were considered and analyzed. Next, two researchers independently extracted the data for the outcome measures. Three reviewers independently performed a methodological quality assessment on the studies according to the Cochrane Handbook [15], based on methods of randomization, allocation concealment, blinding, comparable baseline, follow-up, and free of selective reporting. Any disagreements about eligibility, methodological quality and data were resolved through discussion.

2.4. Statistical analysis

Statistical analysis was performed using RevMan 5.29. Heterogeneity was estimated using the Chi^2 test and was considered to be significant when $I^2 > 50\%$; in this case, a random-effects model was applied. When there was not significant heterogeneity, a fixed-effects model was applied. Effect size was expressed using a relative odds ratio (OR) for dichotomous data and mean differences (MD) for continuous data and all 95% confidence intervals (95% CI) were presented. Subgroup meta-analysis, including low-dose (≤ 5 mL) and high-dose (> 5 mL) [9] was conducted. Sensitivity analysis and publication bias were also performed.

3. Results

3.1. Flow diagram of trial selection

Nine RCTs [11–14,16,17,20–22] and four prospective comparative studies [2,13,18,23] assessing the use of fibrin sealant in patients who received knee surgery were retrieved from electronic databases. Of these, two studies reported data from one trial and both of them were included [13,23]. Another study contained three arms: two fibrin sealant arms (5 mL and 10 mL, respectively) and one control arm; we deemed this two independent trials [17]. The flow diagram (Fig. 1) illustrates the trial selection process from the results of the initial literature search to the final decision.

3.2. Characteristics and methodological quality of included studies

Table 1 shows specific characteristics including sample size, age, preoperative Hb level, and intervention. A total of 1299 patients were included in the study. The methodological quality of each study was assessed using the Cochrane handbook 5.0.1 and the results are shown in Table 2.

3.3. Effect size of interventions

3.3.1. Blood loss

Both drain-out blood loss and total blood loss were reported. A total of seven studies [11,14,16–18,20,22] reported data on drain-out blood loss and there was heterogeneity between them ($I^2 = 94\%$). The random-effects model revealed that fibrin sealant significantly reduced drain-out blood loss by a mean of 316.81 mL compared to the control group [95% CI (180.76–452.87); $P < 0.01$]. A subgroup analysis of four studies [2,16,19,20] reported total blood loss and random-effects model showed that fibrin sealant reduced the total blood loss by a mean of 155.93 mL, but it failed to reach statistical significance [95% CI (–525.02–213.15); $I^2 = 86\%$], as shown in Fig. 2.

To further explore the dose-effect, we also performed another subgroup analysis. A subgroup analysis of two studies [11,17] showed that a low-dose of fibrin sealant reduced drain-out put by a mean of 391.28 mL [95% CI (313.10–469.47); $P = 0.60$; $I^2 = 0\%$]. A subgroup analysis of four studies [14,17,18,22] revealed that a high-dose of fibrin sealant obtained a reduction in blood loss by a mean of 319.09 mL [95% CI (93.2–544.98); $P = 0.006$; $I^2 = 96\%$], as shown in Fig. 3.

3.3.2. Transfusion rate

Eight studies [2,11–14,17,19,20] were analyzed for transfusion rate. The fixed-effects model revealed that fibrin sealant reduced transfusion rate compared to control group [OR = 0.36; 95% CI (0.25–0.51); $I^2 = 0\%$]. A subgroup analysis of three studies [2,11,17] showed that a low-dose of fibrin sealant reduced transfusion rate [OR = 0.27; 95% CI (0.14–0.50); $I^2 = 0\%$]. Finally, a subgroup analysis of seven studies [2,12–14,17,19,20] showed that a high-dose of fibrin sealant reduced transfusion rate compared to the control group [OR = 0.40; 95% CI (0.27–0.62); $I^2 = 42\%$], as shown in Fig. 4.

3.3.3. Blood transfusion unit

Due to significant heterogeneity ($I^2 = 78\%$), the random-effects model was applied and this revealed that fibrin sealant reduced blood transfusion units by a mean of 0.47 U compared to the control group [95% CI (0.24–0.71); $P < 0.0001$]. A subgroup analysis of two studies [2,17] showed that a low-dose of fibrin sealant reduced blood transfusion units by a mean of 0.45 U [95% CI (0.17–0.73); $P = 0.73$; $I^2 = 0\%$]. A subgroup analysis of five studies [11,13,17–19] showed that high-doses of fibrin sealant reduced blood transfusion