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## Review

# Effect of fibrin sealant on blood loss following total knee arthroplasty: A systematic review and meta-analysis

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## ABSTRACT

**Objective:** A systematic review of randomized controlled trials was conducted to examine the efficacy of fibrin sealants for the reduction of postoperative blood loss and allogeneic red blood cell transfusion in total knee arthroplasty (TKA).

**Methods:** Studies published through May 2013 were identified from PubMed, Embase, the Cochrane library, ScienceDirect, and other databases. Two independent reviewers assessed the quality of methodology using the Grade of Recommendations Assessment, Development and Evaluation approach and extracted data from literature. The mean difference (MD) of blood loss, hemoglobin loss, and risk ratios (RR) of transfusion rate and adverse events in the fibrin-treated and placebo groups were pooled throughout the study. The relevant data were analyzed using Stata 11.0 software.

**Results:** Eight studies were included in the review, with a total sample size of 558 patients. The drainage blood loss [MD = −354.02 mL, 95% confidence interval (CI) (−500.87 to −207.18);  $P < 0.05$ ], reduction in calculated total blood loss [MD = −402.12, 95% CI (−599.16 to −205.08);  $P < 0.05$ ], hemoglobin loss [MD = −0.86 g/dL, 95% CI (−1.10 g/dL to −0.61 g/dL);  $P < 0.05$ ], and transfusion rate [RR = 0.62, 95% CI (0.45–0.86);  $P < 0.05$ ] were all significantly reduced following treatment with fibrin sealants. There were no significant differences in the incidence of adverse events [RR = 0.69, 95% CI (0.32–1.59);  $P > 0.05$ ] among the study groups.

**Conclusions:** The results of the present meta-analysis suggest that fibrin sealants for patients undergoing TKA may reduce blood loss and maintain higher hemoglobin levels, particularly when fibrin sealants are used at higher dosage. Furthermore, fibrin sealants do not increase the risk of postoperative deep vein thrombosis, superficial infection, pulmonary embolism, and hematoma. Further evaluation is required to confirm our findings before fibrin sealants can be used in patients undergoing TKA.

**Level of evidence:** II.

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Total knee arthroplasty (TKA) is an effective orthopedic treatment that has been commonly practiced since its introduction in the late 1960s. TKA is associated with significant perioperative blood loss, ranging from 500 to 1500 mL, necessitating the transfusion of 1–2 units of allogeneic blood in 10%–38% of patients.<sup>1–4</sup> Decreasing this postoperative blood loss could potentially reduce patient morbidity, length of hospitalization, and costs involved by eliminating the need for transfusion, which is associated with adverse immunological reactions, disease transmission, intravascular hemolysis, transfusion-induced coagulopathy, renal

impairment or failure, and increased mortality.<sup>5,6</sup> Various blood preservation techniques following TKA that can reduce the exposure to allogeneic blood have been described. These include controlled autologous blood transfusion; hypotension; epidural anesthesia; compression bandage; cryotherapy; and the administration of various intravenous (IV), intra-articular, and oral medications.<sup>7–10</sup> However, safer and more effective interventions are required to reduce the incidence of blood transfusions during and immediately after TKA.

The use of dry plasma<sup>11</sup> and fibrin patches<sup>12</sup> at the injury site to reduce blood loss dates back to the beginning of the twentieth century. These treatment modalities are the predecessors of the modern concept of treatment with fibrin sealants, also known as fibrin glues and fibrin tissue adhesives. The use of fibrin sealants formed by plasma fibrinogen mixed with thrombin was first

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reported during World War II.<sup>13</sup> Fibrin sealants used as topical agents<sup>14</sup> consist of plasma fibrinogen mixed with thrombin to form a fibrin clot adhesive, which mimic the last step of the coagulation cascade: thrombin activates fibrinogen to polymerize to form an unstable clot, which is then stabilized by activated factor XIII in the fibrinogen concentrate by catalyzing the cross-linkage between the fibrin molecules. Factor XIIIa also cross-links between natural plasmin inhibitors that prevent fibrinolysis, because of which some sealants contain additional fibrinolytic inhibitors such as bovine aprotinin or tranexamic acid (TXA). The fibrin may also function in blood loss prevention by sealing and plugging the bone marrow sinusoids; furthermore, it may prevent extravasation from the cut edges of tissues by suppressing enhanced fibrinolysis.<sup>15</sup>

Yasukawa and Takizawa reported that the fibrin sealant and TXA of the intra-articular as ‘cocktail’ given were hemostatic agents; therefore, the reduction in blood loss could not solely be attributed to the fibrin glue.<sup>16</sup> Another study reported that human fibrin sealant Quixil<sup>®</sup> used in patients undergoing total knee replacement (TKR) probably reduced the blood loss and transfusion rate without increasing the incidence of adverse events.<sup>17</sup> Many studies have reviewed fibrin sealants, and fibrin tissue adhesive is used in all fields of surgery such as prostatectomy,<sup>18</sup> partial pulmonary excision,<sup>19</sup> carotid endarterectomy<sup>20</sup> and hepatectomy with liver mobilization. However, due to the absence of clear evidence concerning the safety and efficacy of fibrin sealants, most commercial fibrin sealants have not been approved by the Food and Drug Administration in the United States. Indeed, blood-bank products and bovine thrombin concentrates, which have considerably less

safety than commercial products, are used extensively in the United States.<sup>15</sup>

This article aimed to report a meta-analysis of the published randomized controlled trials investigating the effectiveness of fibrin sealants used in patients undergoing TKA and to establish whether it is an efficient product to reduce blood loss, transfusion rate, and related complications.

**1. Material and methods**

*1.1. Study design*

A meta-analysis and systematic review was conducted according to the guidelines predefined by the Cochrane Collaboration (2008).<sup>21</sup> All the data were reported according to the Quality of Reporting for meta-analyses provided by the Handbook for Systematic Reviews of Interventions version 5.0.<sup>22</sup>

*1.2. Search strategy*

Relevant studies published from their establishment to May 22, 2013, were extracted from the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, and the ISI Wed of Knowledge databases by using the medical subject heading (MeSH) terms “fibrin sealant” OR “total knee arthroplasty” to maximize the search specificity and sensitivity. As presented in Fig. 1, only published, unpublished and ongoing trials on human subjects that attempted to gather information on fibrin sealants or TKA were

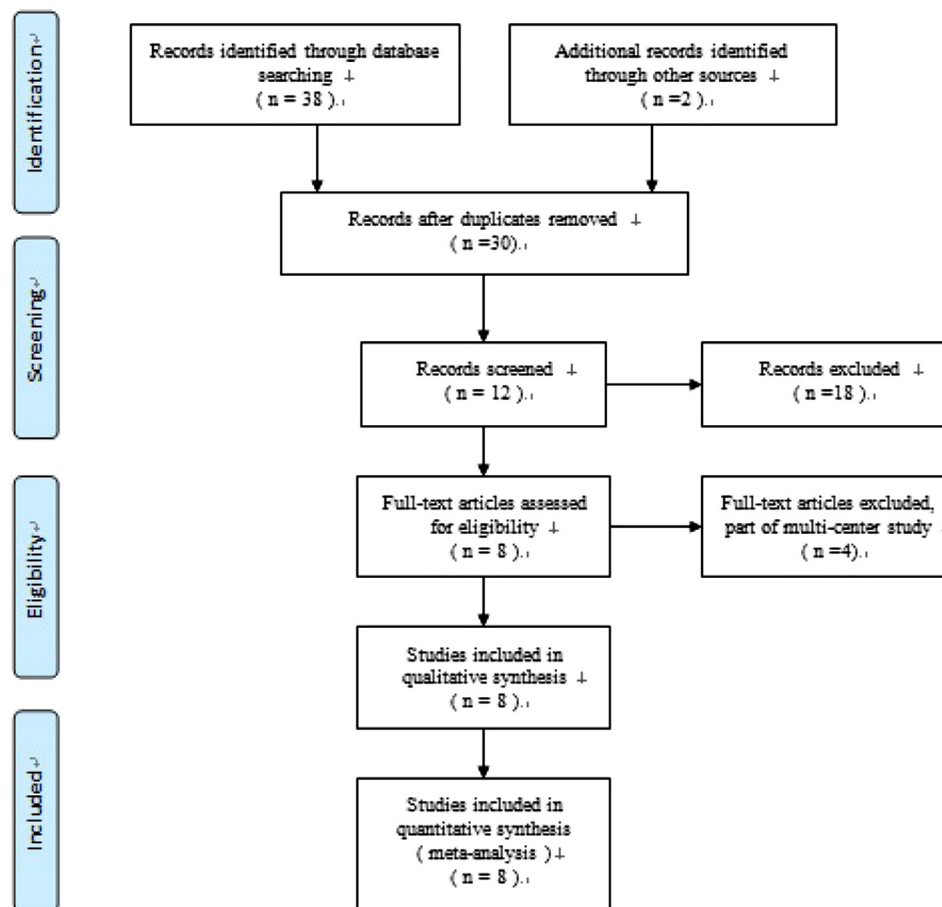


Fig. 1. Flowchart of the study selection.

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