

Original Article

Comparison of efficacy and safety of fibrin glue versus tranexamic acid for reducing blood loss in primary total knee arthroplasty: a systematic review and meta-analysis

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Abstract: Objective: A systematic review of randomized controlled trials (RCTs) and non-RCTs was performed to evaluate the efficacy and safety of reducing blood loss using fibrin glue and tranexamic acid in patients who underwent total knee arthroplasty (TKA). Method: Relevant randomized controlled trial (RCTs) and non-RCT literature dealing with fibrin glue and tranexamic acid in TKA for reducing total blood loss was collected and searched from Medline, Embase, Pubmed, and the Cochrane Library for publication dates up to September 2015. After testing for publication bias and heterogeneity across studies, data were aggregated for random-effects modeling when necessary. Results: Three RCTs and two non-RCTs were eligible for data extraction and thus were included for meta-analysis. Compared with fibrin sealant, intravenous tranexamic acid may be more effective in reducing the need for transfusion (RR 2.62, 95% CI 1.64 to 4.18, $P < 0.0001$). There was no significant difference in the total blood loss (MD=273.30, 95% CI -129.70.70 to 672.30, $P < 0.00001$), hemoglobin values (SMD -0.74, 95% CI -1.08 to -0.40, $P < 0.00001$), thromboembolic events (RR 4.00, 95% CI 0.46 to 35.15), fever (RR 0.63, 95% CI 0.21 to 1.85), hematoma (RR 1.03, 95% CI 0.28 to 3.70) or infection (RR 0.46, 95% CI 0.11 to 2.03) when comparing the fibrin glue group and the tranexamic acid group. Conclusions: The current meta-analysis indicated that tranexamic acid could be more effective in reducing the number of patients who need transfusions and can comparatively improve hemoglobin values. The fibrin glue and tranexamic acid groups had no distinction with respect to the incidence of thrombolism events. Furthermore, tranexamic acid is more economical than fibrin glue.

Keywords: Fibrin glue, tranexamic acid, total knee arthroplasty, meta-analysis

Introduction

Total knee arthroplasty (TKA) is an effective and common operation that has helped many osteoarthritis patients to relieve pain and recover normal quality of life. However, patients who undergo TKA may experience in blood loss ranging from 1450 ml to 1790 ml [1-3]. The blood loss and subsequent blood transfusion can result in many complications, such as the HIV infections, other infectious disease, fluid overload and graft-versus-host disease [4-7]. Many methods have been used to reduce the risk of transfusion-related complications. Pharmacokinetic measures that include topically used fibrin glue (FG) and the intravenous administration of tranexamic acid (TXA) has

been identified to reduce blood loss and, thus, lower the transfusion rate [8-11].

Fibrin glue is biological adhesive that consists of anthropogenic fibrinogen, retronectin, coagulation factor III and thrombin all dissolved in calcium chloride and aprotinin. The main mechanism of FG to achieve hemostasis is to mimic the stage at which fibrinogen is converted into fibrin threads [12]. A meta-analysis has demonstrated that the use of fibrin glue is effective and safe as a hemostatic therapy for patients with TKA [13]. Tranexamic acid is a synthetic antifibrinolytic drug that can powerfully bind to the lysine binding site of plasminogen as its chemical structure is similar to lysine, but the binding capacity is more powerful than lysine.

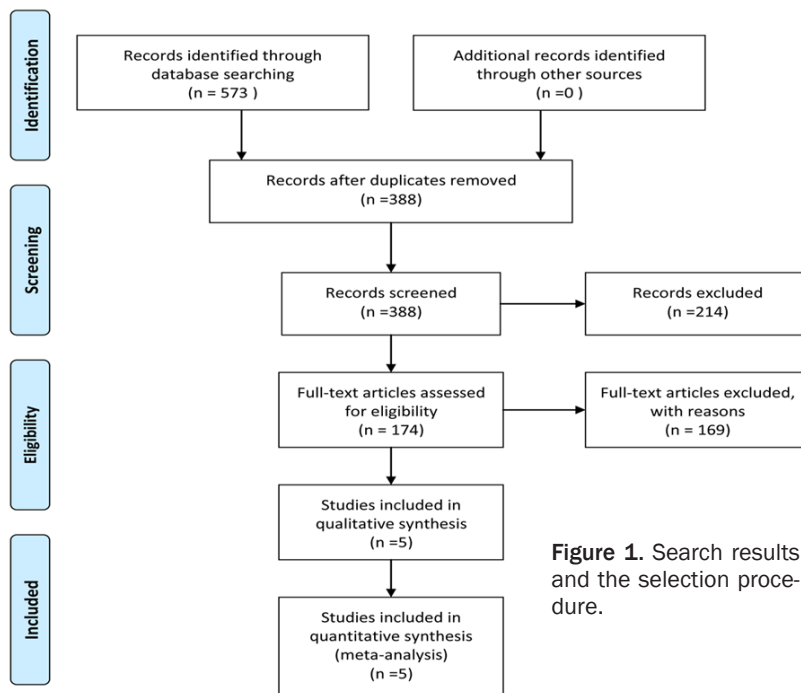


Figure 1. Search results and the selection procedure.

databases up to September 2015. In addition, Google was used to look for additional literature. Furthermore, the reference lists of all the full-text studies were reviewed to identify any initially omitted studies, and there was no restriction on the language of the publication. The search strategy is presented in **Figure 1**. The key phrases used in the searches strategy were the following: “fibrin glue”, “fibrin sealant”, “tranexamic acid”, “total knee arthroplasty”, “TKA”, “TKR” and “total knee replacement”. Meanwhile the medical subject heading (mesh) terms of these

Fbrinolysis is delayed through this method. Wu Q has identified that the intravenous or intra-articular use of TXA is effective and safe for reducing blood loss in TKA [13].

Both fibrin glue and tranexamic acid can decrease the blood loss and transfusion rate yet not increase the risk of thrombolism. However, there is no consensus about which is comparatively the most effective and safest way to address the blood loss after TKA. Additionally, the number studies comparing fibrin glue to tranexamic acid is limited. Therefore, we carried out a meta-analysis to improve the evidence to understand whether there were any differences between fibrin glue and tranexamic acid in terms of 1) total blood loss after TKA, 2) the postoperative hemoglobin (Hb) value and transfusion requirement, and 3) thromboembolic complications, including deep venous thrombosis (DVT) and pulmonary embolism (PE).

Materials and methods

Search strategy

The electronic databases including Medline, Embase, PubMed, CENTRAL (Cochrane Controlled Trials Register) and the Web of Science were searched for relevant studies published from the time of the establishment of these

studies were used to maximize the specificity and sensitivity of the search. These key words and the mesh terms were combined with the Boolean operators AND or OR.

Eligibility criteria and study quality

Study selection was performed according to the following inclusive criteria: (1) published RCTs and non-RCTs about patients undergoing primary total knee arthroplasty (2) intervention including fibrin glue and tranexamic acid (3) reported outcomes including postoperative total blood loss, the value of the postoperative hemoglobin, need for transfusions, and incidence with respect to DVT and PE. All the studies must have been clinical study, and trials using cadavers or artificial models or with patients with bleeding disorders were excluded. Two reviewers independently scanned the quality of the eligible studies, and discrepancies were resolved by a senior reviewer. The Cochrane Handbook for Systematic Reviews of Interventions was used to evaluate the methodological quality and risk bias for RCTs, which include (1) the randomization method; (2) the allocation concealment; (3) the blinding of participant, personnel and assessor; and (4) the complete outcome data. The methodological quality of non-RCTs were evaluated by the MINORS score [14].

Table 1. Characteristics of the five trials selected showing general patient information

Authors	Patients (n)		Age (Y)		Male patients		Country	Diagnosis	Unilateral TKA (no. patients)	Study	Quality score
	F	T	F	T	F	T					
Xu Q 2014	23	20	68	71	2	5	China	OA, RA	all	CCT	15
McConnell 2010	21	22	NS	NS	7	10	United Kingdom	NS	all	RCT	3
Mollory. DO 2007	50	50	NS	NS	NS	NS	Northern Ireland	NS	NS	RCT	5
Aguilera. X 2013	85	41	73	72	14	8	Spain	NS	NS	RCT	4
Sabatini L 2014	45	45	74	72	16	12	Italy	OA	NS	CCT	13

Abbreviations: F: fibrin glue; T: tranexamic acid; OA: osteoarthritis; RA: rheumatoid arthritis; RCT: randomized controlled trial; CCT: case-control trial; NS: not state.

Data extraction

The following data were extracted and recorded in a sheet: (1) demographic data about the patients in the literature, the author's name, the publication date, the patient sample size, the location of the study, the number of male patients, the preoperative diagnose and the number of patients who underwent unilateral TKA; (2) general surgical information including the surgical approach, doses of anesthesia, transfusion criteria and whether anticoagulation therapy was used; and (3) the total blood loss, the value of hemoglobin (Hb), the number of patients receiving blood transfusions, and thromboembolic complications including DVT and PE.

Outcome measures and statistical analysis

Total blood loss were expressed as mean differences (MD) with their respective 95% confidence intervals (CIs) and postoperative hemoglobin value were expressed as standard mean differences (SMD) with their respective 95% CIs. Dichotomous outcomes (the need for transfusion, DVT and PE rates) were expressed as relative risk (RR) with their 95% CIs. Statistical significance was set at $P < 0.05$ to summarize findings across the trials. The software RevMan 5.30 (The Cochrane Collaboration, Oxford, United Kingdom) was used for the meta-analysis. Statistical heterogeneity was tested using the chi-squared test and I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > 0.1$), a fixed effects model was adopted; otherwise, a random effect model was chosen. Publication bias was tested using funnel plots. Subgroup analysis was performed if the $I^2 > 50\%$. The sensitive analysis were performed by the software of Stata, version 12.0 (Stata Corp., College Station, TX) and describe how robust the pooled estimator is to removal of individual studies.

Results

Search result

In the initial search, we identified 573 potentially relevant studies. Of these, we included five clinical trials with 679 patients (739 knees) in the meta-analysis [9, 15-18]. Classification of the remaining studies resulted in a total of three RCTs and two CCTs. One report included two different types of fibrin glue (BSTC and Tissucol) that were compared with a group of tranexamic acid [15]. These groups were analyzed separately, which ultimately resulted in six component studies for the meta-analysis.

Of the included studies, all articles were in English and one was published in 2007. The others were published from 2012 to 2014. The characteristics of the studies that were included are shown in **Tables 1** and **2**. All participants in the five studies were adults that had prepared for TKA, and only two trials referred to the preoperative diagnosis. The age of the patients in the studies ranged from 68 to 74 years, and the male patients ranged from two to twelve. All of the studies came from different countries. The dose of fibrin glue ranged from 4.8 mL to 10 mL, and the doses of tranexamic acid was either 2 g or 10 mg/kg. Other than one trial that used uncemented prostheses, all included surgeries were conducted using cemented prostheses. All of the studies detailed the operative approach and the use of a tourniquet. Three trials referenced the transfusion criteria [15, 17, 18].

Results of the meta-analysis

Need for transfusion: A total of five component studies (449 patients) provided data on the patients who required a transfusion. Pooling data revealed a statistically significant difference in the patients with respect to transfu-

Fibrin glue versus tranexamic acid for blood loss during TKA

Table 2. Characteristics of the five trials selected showing general surgical information

Authors	Doses		Surgical protocol	Tourniquet	Transfusion criteria	Thromboprophylaxis	Type of prostheses
	F	T					
Xu Q 2014	5 mL Spray	2 g IV	Medial parapatell approach	yes	Hb<80 g/L	LMWH (14 days)	Cemented
McConnell 2010	10 mL Spray	10 mg/kg IV	Medial parapatell approach	yes	NS	150 mg aspirin	Cemented
Mollory DO 2007	10 mL Spray	500 mg IV	Midline incision approach	yes	NS	150 mg aspirin	Uncemented
Aguilera. X 2013	4.8 mL -	2 g IV	Ateromedial approach	yes	Hb<8 g/dL <8.5 g/DI, with smptoms, 8.5-9.0 g/dL *	LMWH (30 days)	Cemented
Sabatini L 2014	NS Intraarticular drainage	10 mg, max1 g IV	Medial parapatell approach	yes	Hb<8 g/dL	NS	Cemented

Abbreviations: LMWH: low molecular weight heparin; IV: intravenous infusion; *with heart disease, older than seventy years. NS: not state.

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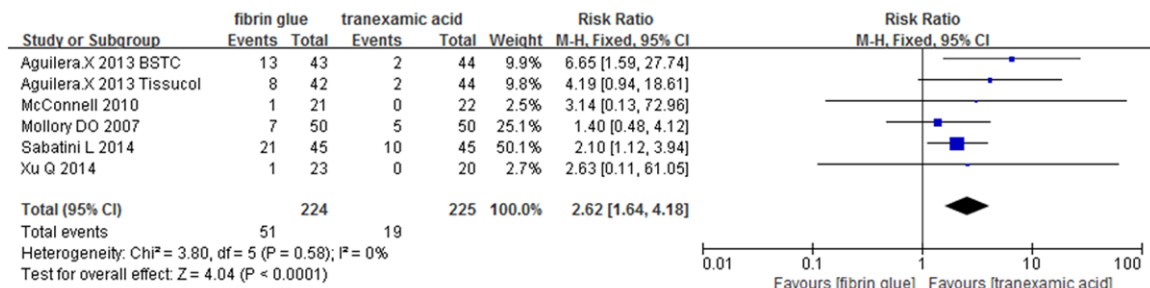


Figure 2. The meta-analysis of five trials included showed that there was statistical significance between fibrin glue and tranexamic acid in terms of the need for transfusion (RR 2.62, 95% CI 1.64 to 4.18, $P < 0.0001$). BSTC: Blood Bank of Catalonia.

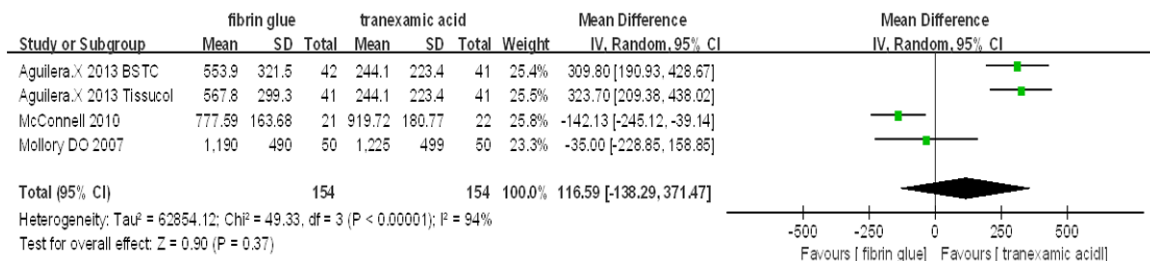


Figure 3. The meta-analysis of three trials included showed that there was no statistical significance between fibrin glue and tranexamic acid in terms of the blood loss (MD=116.59, 95% CI -138.29 to 371.47, $P = 0.37$). BSTC: Blood Bank of Catalonia.

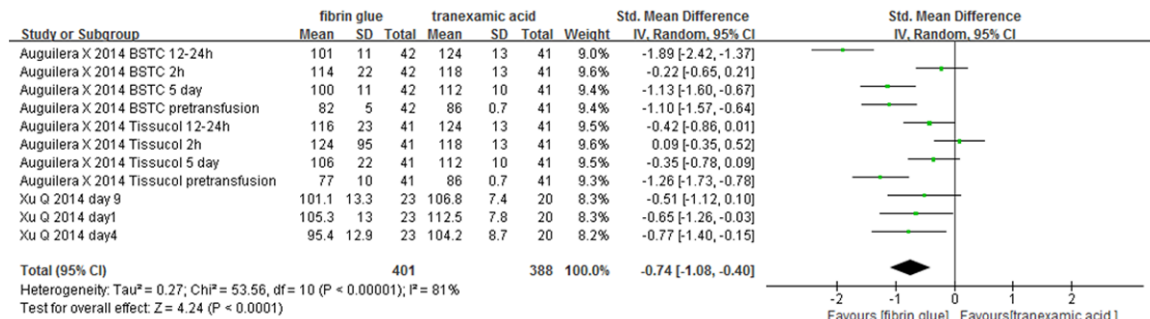


Figure 4. The meta-analysis of two trials included showed that there was statistical significance between fibrin glue and tranexamic acid in terms of the value of hemoglobin (SMD-0.74, 95% CI -1.08 to -0.40, $P < 0.00001$). BSTC: Blood Bank of Catalonia.

sions when comparing the fibrin glue and the tranexamic acid groups (RR 2.62, 95% CI 1.64 to 4.18, $P < 0.0001$, **Figure 2**).

Total blood loss: A total of three component studies (308 patients) provided data on total blood loss. There was no statistically significant difference between the groups with respect to the total blood loss (MD=116.59, 95% CI -138.29 to 371.47, $P = 0.37$, **Figure 3**). Nevertheless, these results should be inter-

preted with caution due to the presence of statistically significant heterogeneity ($P < 0.00001$, $I^2 = 93\%$, **Figure 3**).

The value of postoperative hemoglobin: A total of two component studies (252 patients) provided data on the postoperative value of hemoglobin. There was no statistical heterogeneity between studies ($P = 0.39$, $I^2 = 5\%$). The meta-analysis of the postoperative hemoglobin value demonstrated a statistically significant differ-

Fibrin glue versus tranexamic acid for blood loss during TKA

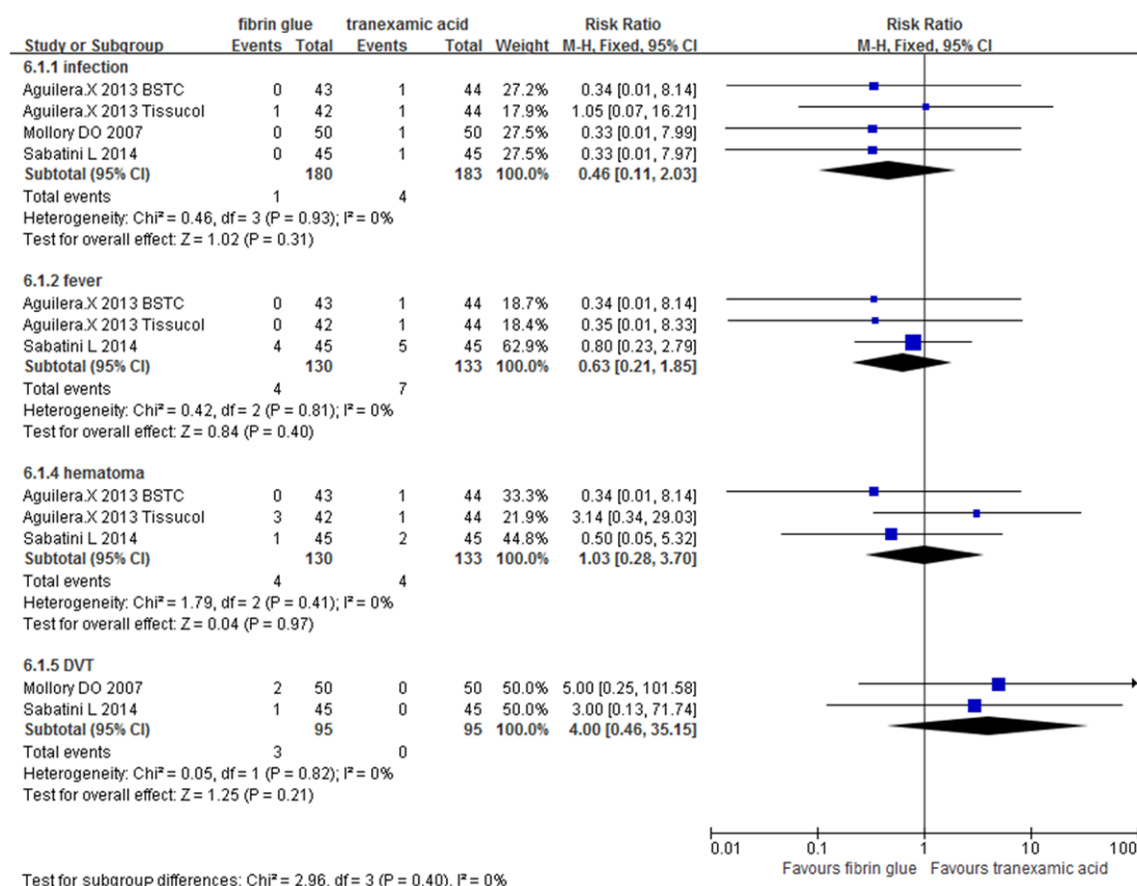


Figure 5. The meta-analysis of two trials included showed that there was no statistical significance between fibrin glue and tranexamic acid in terms of the occurrence of thromboembolic events (RR 4.00, 95% CI 0.46 to 35.15), fever (RR 0.63, 95% CI 0.21 to 1.85), hematoma (RR 1.03, 95% CI 0.28 to 3.70) and infection (RR 0.46, 95% CI 0.11 to 2.03).

ence in the fibrin glue group compared with the tranexamic acid group (SMD -0.74, 95% CI -1.08 to -0.40, $P < 0.00001$, **Figure 4**).

Complications: Complications about the topical administration FG and intravenous administration TXA are shown in **Figure 5**. The meta-analysis of two trials included showed that there was no statistical significance between fibrin glue and tranexamic acid in terms of the occurrence of thromboembolic events (RR 4.00, 95% CI 0.46 to 35.15), fever (RR 0.63, 95% CI 0.21 to 1.85), hematoma (RR 1.03, 95% CI 0.28 to 3.70) and infection (RR 0.46, 95% CI 0.11 to 2.03).

Sensitivity analysis: Sensitivity analysis showed that two studies [15, 16] have excessive influence on the total blood loss, the detailed information can be seen in **Figure 6**.

Discussion

The current study revealed that tranexamic acid can decrease the number of patients who need a transfusion and increase the level of hemoglobin compared with fibrin glue. Moreover, no significance was found in terms of total blood loss and the risk of thromboembolic events between the two groups.

Three RCTs and two CCTs were in accordance with the inclusive criteria that we established in the meta-analysis, and one study was published in 2007 with the remainder being published in 2010. All the studies show comparable baseline data. Three RCTs used randomization and concealment methods, whereas double-blind methods were only found in two papers. All five studies were included outcomes that measured the hemostatic effect. Only one study did not provide the intention of their study

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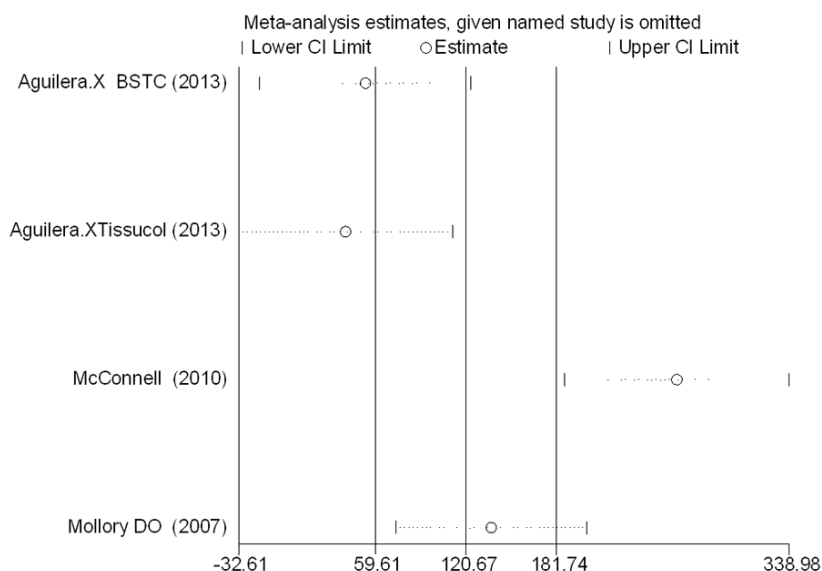


Figure 6. Analysis of influence of individual study on the total blood loss. Open circle, the pooled MD, given named study is omitted. Horizontal lines represent the 95% CIs.

whereas two study outcomes showed significant heterogeneity, so a subgroup analysis was conducted to determine the resource and attempt to eliminate it (Table 3).

Perioperative blood loss is one of the most common complications in TKA with 10% to 38% of patients requiring allogeneic blood transfusions [2, 19]. Fibrin glue has been used to decrease blood loss during surgery for one hundred years. In recent years, orthopedic surgeons have focused on fibrin glue and tranexamic acid to decrease blood loss in TKA. Li ZJ and Wang H [13, 20] have demonstrated that fibrin glue can decrease the blood loss in TKA. Tranexamic acid has also been identified to reduce the blood loss in TKA [21]. The present meta-analysis indicates that there is no significance difference between fibrin glue and tranexamic acid in total blood loss ($P=0.18$). Because this meta-analysis has heterogeneity, we attempted to use a subgroup analysis to analysis the source of the heterogeneity by considering that the type of prosthesis, the doses of the drugs and the surgical protocol may influence the outcomes.

Two trials refer to the postoperative Hb value [15, 17]. This measure can better represent the blood loss and the transfusion criteria. The current analysis indicated that fibrin glue can better decrease the blood loss and increase the

postoperative Hb value of patients undergoing total knee arthroplasty. This outcome was in agreement with the number of patients who required a transfusion. Compared with the fibrin glue group, the tranexamic acid could significantly reduce the rate of the patients requiring transfusion (8.4% vs. 22.7%). Both outcomes had a significant difference between the two groups ($P<0.0001$).

DVT is a fateful complication for all patients and its incidence will increase during perioperation. Therefore, when antico-

agulant drugs are suggested, the main question that must be considered is the safety of these drugs. This meta-analysis indicated that both of these drugs have no significant difference on the safety with respect to embolism events. However, these studies have referred to other complications, such as wound infection, infection and heart failure [15, 17, 18]. Therefore, a further, long-term study will be required to study the safety of these two drugs.

In addition to all of the advantages and complications of fibrin glue and tranexamic acid, one factor that affects the application is the cost of these two drugs. One study has reported that the cost of the pharmaceutical intervention involved in the topical fibrin group was £380 per patient whereas in the tranexamic acid group it was £4 less [22]. McConnell [9] reported that the cost per patient was £3.10 for tranexamic acid and £390 for fibrin spray. Another study has reported that the use of fibrin sealant in total hip arthroplasty was 13,313€ more than the control group [23]. Two independent studies conducted in France in 2012 evaluated the cost of utilizing fibrin sealant and TXA: the cost of fibrin glue was 26 times more expensive than that of TXA [24]. Therefore, the relatively high cost and lower efficacy of fibrin glue may hinder fibrin glue's wide application.

Table 3. Subgroup analysis of total blood loss

Outcome or subgroup	Studies	Effect estimate				
		χ^2	I^2 (%)	MD	95% CI	P value
Cemented prosthesis	2	46.58	96	162.75	[-149.01, 474.5]	0.31
10 mL fibrin glue	2	0.91	0	-118.55	[-209.50, -27.60]	0.01
Non-computer navigated TKA	2	10.76	81	216.39	[32.00, 400.79]	0.02

Abbreviations: TKA: total knee arthroplasty.

There were several potential limitations of this meta-analysis. (1) Only five reports were used, and the sample sizes in each trial were not large enough, which could affect the results. (2) Two non-RCTs were used in this meta-analysis, which lowers the evidence level. (3) The duration of follow-up in some studies was unclear; long-term follow-up periods are needed. (5) The publication bias that exists in all meta-analyses will also influence the results.

Conclusions

This report presents the first systematic review to evaluate the safety and efficiency of fibrin glue versus tranexamic acid with respect to reducing blood loss in TKA. High-quality RCTs and well-designed trials are still needed to detect the therapeutic dose or to detect other adverse effects in the future.

Disclosure of conflict of interest

None.

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