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Review Article

Topical fibrin sealant versus intravenous tranexamic acid in reducing blood loss during total joint arthroplasty: a systematic review and meta-analysis

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Abstract: Objective: Intravenous (IV) tranexamic acid (TXA) and topical fibrin sealant (FS) are two common agents that are used to decrease perioperative blood loss during total joint arthroplasty (TJA). However, which method is more effective is still a matter of debate. Thus, a systematic review and meta-analysis was performed to evaluate the efficacy and safety of IV-TXA and topical FS in reducing blood loss in patients who underwent TJA. Method: Relevant literature regarding the use of topical FS and IV-TXA in patients prepared for TJA was searched and collected from Embase, PubMed, the Cochrane Library and the Google database from inception to February 2017. Randomized controlled trials (RCTs) and non-RCTs were included without language restriction. Outcomes included the need for transfusion, total blood loss, hemoglobin drop and the occurrence of deep vein thrombosis (DVT). The random-effects model was utilized due to the different doses of TXA and FS that were administered. The Stata 12.0 software was used for the meta-analysis. Results: Five RCTs and two non-RCTs involving 646 patients (FS=346; and TXA=300) were eligible for data extraction and were thus included in the meta-analysis. Compared with FS, IV-TXA decreased the need for transfusion by 12.4% (relative risk (RR) 2.62, 95% confidence interval (CI) 1.64 to 4.18, $P<0.0001$). There were no significant differences in the total blood loss (weight mean difference (WMD)=273.30, 95% CI -129.70.70 to 672.30, $P<0.00001$); hemoglobin values (WMD -0.77, 95% CI -1.40 to -0.15); and incidence 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) between the topical FS group and the IV-TXA group. Conclusion: The present meta-analysis indicated that IV-TXA could be more effective in reducing the number of patients who need transfusions and could improve hemoglobin values. Thromboembolic events occurred with similar frequency in the topical FS and IV-TXA groups. Additionally, IV-TXA is more economical than topical FS.

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

Introduction

Total knee arthroplasty (TKA) and total hip arthroplasty (THA), also known as total joint arthroplasty (TJA), are two common surgeries for patients with degenerative arthritis and traumatic conditions such as displaced femoral neck fractures. The amount of blood loss during TKA has been reported to vary from 900 mL to 2,000 mL, whereas for THA, it ranges from 700 mL to 1,700 mL [1-3]. Perioperative blood loss and subsequent blood transfusion can result in additional economic costs and transfusion-related complications [4]. Many protocols have been developed to reduce perioperative and postoperative blood loss [5-7]. Pharmacokinetic measures, including topical fibrin sealant (FS) and intravenous tranexamic acid (TXA), have been developed to reduce blood loss and may lower the transfusion rate [7, 8].

FSs include anthropogenic fibrinogen and thrombin as well as calcium chloride and aprotinin. FSs achieve hemostasis effects by mimicking the final steps that convert fibrinogen into fibrin threads [9]. TXA is a synthetic antifibrinolytic drug that can strongly bind to the lysine binding site of plasminogen, as its chemical structure is similar to lysine, but its binding

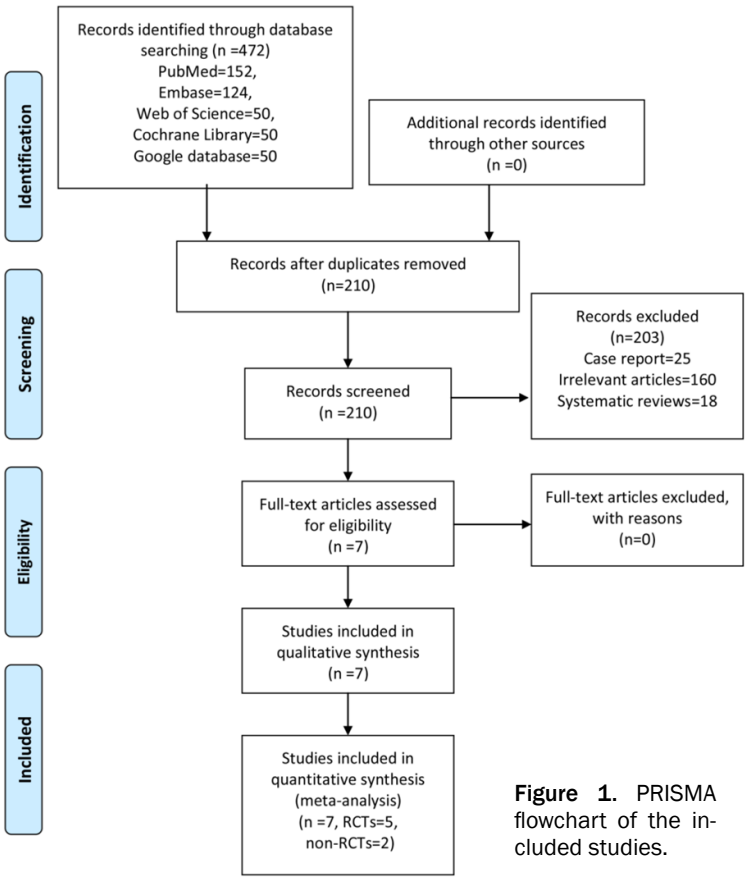

Figure 1. PRISMA flowchart of the included studies.

capacity is stronger than lysine [10]. Both topical FS and IV-TXA can decrease blood loss and transfusion rates without increasing the risk of thromboembolism. Although a previous meta-analysis was performed, the meta-analysis included a limited number of studies, and the results were inconclusive [11, 12]. Until now, there has been no consensus on which is the more effective and safer method to address blood loss during TJA. Thus, we carried out a meta-analysis to better understand whether there were any differences between FS and TXA in terms of (1) the need for transfusion; (2) total blood loss; (3) hemoglobin drop; and (4) the length of hospital stay and the occurrence of complications.

Materials and methods

Search strategy

Electronic databases, including PubMed, Embase, Web of Science, the Cochrane Library, and the Google database, were searched for relevant studies published from the time of the establishment of these databases up to February 2017. Furthermore, the references of all the full-text literatures were reviewed to identify any initially omitted studies, and there was no restriction on the language of the publication. The keywords used in the search include the following: “fibrin glue”, “fibrin sealant”, “tranexamic acid”, “total knee arthroplasty”, “total knee replacement”, “total hip arthroplasty”, and “total hip replacement”. Meanwhile, their corresponding medical subject heading (Mesh) terms were used to maximize the specificity and sensitivity of the search. These keywords and Mesh terms were combined with the Boolean operators AND or OR.

Eligibility criteria and study quality

Study selection was performed according to the following inclusion criteria: (1) Patients who were prepared for primary TKA or THA; (2) Intervention was IV-TXA for blood loss; (3) Comparison intervention was topical FS for blood loss; (4) Reported outcomes included the need for transfusion, total blood loss, hemoglobin drop, the length of hospital stay and the occurrence of complications; and (4) RCTs as well as non-RCTs.

Two reviewers independently determined the quality of the eligible studies, and the 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, which included (1) randomization sequence generation; (2) allocation concealment; (3) blinding of participant and personnel; (4) blinding of the outcome assessor; (5) incomplete outcome data; (6) selective reporting and (7) other bias. The Methodological index for non-randomized studies (MINORS) was used to assess the quality of non-RCTs [13].

Table 1. The general characteristic of the included studies

Study (Year)	Country	Cases (FS/TXA)	Mean Age (FS/TXA)	Male patients (FS/TXA)	Doses of TXA	Volume of FS	Transfusion criteria	Type of prosthesis	DVT prophylaxis	Study	Joint arthroplasty
Xu Q 2014	China	23/20	68/71	2/5	2 g IV	5 ml	Hb<80 g/L	Cemented	LMWH (14 days)	CCT	TKA
McConnell 2010	USA	21/22	NS	7/10	10 mg/kg IV	10 ml	NS	Cemented	Enoxaparin 4000 U	RCT	TKA
Mollory DO 2007	Germany	50/50	NS	NS	500 mg IV	10 ml	NS	Uncemented	Warfarin NS	RCT	TKA
Aguilera X 2013	USA	85/41	73/72	14/8	2 g IV	Arm1=4.8 ml (BSTC) Arm2=4.8 ml (Tissucol)	Hb<80 g/L	Cemented	Aspirin 150 mg	RCT	TKA
Sabatini L 2014	USA	45/45	74/72	16/12	10 mg IV	NS	Hb<80 g/L	Cemented	NO	CCT	TKA
Mahmood A 2017	Germany	100/100	64/66	40/51	1 g IV	4 ml	Hb<80 g/L	Cemented	Dalteparin 40 mg	RCT	THA
McConnell 2011	Germany	22/22	NS	5/7	10 mg/kg IV	10 ml	NS	Cemented	Aspirin 150 mg (35 days)	RCT	THA

LMWH, low-molecular-weight heparin; NS, not stated, TKA, total knee arthroplasty; THA, total hip arthroplasty; Y, yes.

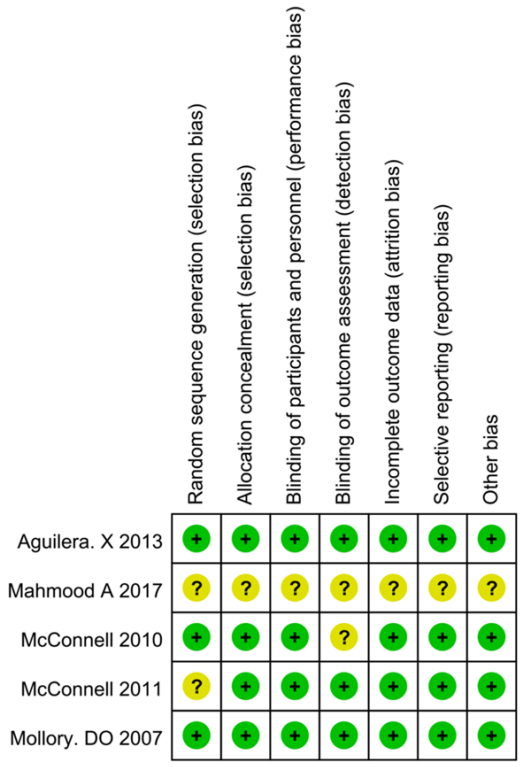

Figure 2. The risk of bias summary for the included studies.

Data extraction

The following data were extracted and recorded: first author's name; cases of topical FS and IV-TXA; mean age of patients in the topical FS and IV-TXA groups; number of male patients in the FS and IV-TXA groups; dose of TXA and volume of FS; transfusion criteria; and type of prosthesis, DVT prophylaxis and joint arthroplasty. Then, all of the outcomes were extracted and recorded in a pregenerated Microsoft® Excel sheet (Microsoft Corporation, Redmond, Washington, USA).

Quality of evidence

The quality of evidence for the outcomes was judged according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. Two independent authors evaluated five factors (risk of bias, inconsistency, indirectness, imprecision, and publication bias) that may downgrade the quality level of the evidence. The quality level of the evidence was classified into four categories: high, moderate, low or very low.

Outcome measures and statistical analyses

The main outcomes were the need for transfusion, total blood loss, hemoglobin drop and length of hospital stay. Complications (the occurrence of DVT, fever, infection and hematoma) were also reviewed to evaluate the safety of topical FS and IV-TXA. Continuous outcomes (total blood loss, hemoglobin drop and length of hospital stay) were expressed as the weighted mean difference (WMD) and 95% confidence interval (CI). Dichotomous outcomes (the need for transfusion as well as complications) were expressed as relative risk (RR) with 95% CIs. Statistical significance was set at $P<0.05$ across the trials. Stata 12.0 (Stata Corp., College Station, TX) was used for meta-analysis. Statistical heterogeneity was tested using I^2 statistic. As the doses of TXA and FS applied were different, a random-effects model was chosen to avoid heterogeneity. Publication bias was tested by the funnel plot and Begg's test.

Results

Search results

In the initial search, we identified 472 potentially relevant studies (PubMed =152, Embase =124, Web of Science =50, Cochrane Library = 50, and Google database =50). After removing the duplicates, a total of 210 papers were screened, and 203 papers were excluded because they did not meet the inclusion criteria. Thus, we ultimately included seven clinical trials (RCTs=5; and non-RCTs=2) with 646 patients (FS=346; and IV-TXA=300) in the meta-analysis [14-20]. The search and identification process is outlined in **Figure 1**. One report included two different types of FS (BSTC and Tissucol) that were compared with the TXA group [14]. These groups were analyzed separately, ultimately resulting in eight 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 between 2012 and 2017. The characteristics of the studies that were included are shown in **Table 1**. All participants in the five TKA studies and two THA studies were adults. The number of patients ranged from 20 to 100, and the mean age ranged from 64 to 71. The dose of TXA included 1 g IV [19], 2 g IV [14, 17], 10 mg IV [18], 500 mg IV [16],

Table 2. Quality assessment for non-randomized trials

Quality assessment for non-randomized trials	Xu Q 2014	Sabatini L 2014
A clearly stated aim (total score =2)	2	2
Inclusion of consecutive patients (total score =2)	1	1
Prospective data collection (total score =2)	1	2
Endpoints appropriate to the aim of the study (total score =2)	1	0
Unbiased assessment of the study endpoint (total score =2)	0	1
A follow-up period appropriate to the aims of study (total score =2)	2	2
Less than 5% loss to follow-up (total score =2)	2	2
Prospective calculation of the sample size (total score =2)	0	0
An adequate control group (total score =2)	2	1
Contemporary groups (total score =2)	1	0
Baseline equivalence of groups (total score =2)	2	2
Adequate statistical analyses (total score =2)	2	2
Total score (24)	16	15

Table 3. The Grade evidence for the outcomes

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	1				
Need for transfusion		Study population				
	55 per 1000	168 per 1000 (107 to 264)	RR 3.07 (1.95 to 4.83)	693 (8 studies)	⊕⊕⊕⊖ moderate	
		Moderate				
	23 per 1000	71 per 1000 (45 to 111)				
Total blood loss		The mean total blood loss in the intervention groups was 148.97 higher (12.38 to 285.55 higher)		552 (6 studies)	⊕⊕⊖⊖ low[1]	
Hemoglobin drop		The mean hemoglobin drop in the intervention groups was 0.19 higher (0.26 lower to 0.64 higher)		390 (3 studies)	⊕⊕⊖⊖ low[2]	
Length of hospital stay		The mean length of hospital stay in the intervention groups was 0.13 higher (0.07 lower to 0.33 higher)		465 (4 studies)	⊕⊕⊕⊖ moderate	

and 10 mg/kg IV [15, 20]. The volume of FS ranged from 4 ml to 10 ml. Only one study performed uncemented prosthesis [16], whereas the rest of the studies were performed with cemented prostheses [14, 15, 17-20].

Quality of the included studies and quality level assessment

The risk of bias of the included RCTs is outlined in **Figure 2**. The quality of non-RCTs is shown in **Table 2**. The total score of Xu et al. [17] and Sabatini L et al. [18] was 16 and 15, respectively. A summary of the quality of the evidence according to the GRADE approach is shown in **Table 3**. The GRADE level of evidence was low for total blood loss and hemoglobin drop; and moderate for the need for transfusion and length of hospital stay.

Results

Need for transfusion

Seven studies [14-20] with 646 patients provided data on patients who needed transfusions. Pooling data revealed a statistically significant difference in the patients needing transfusions between the topical FS and intravenous TXA groups (RR 3.07, 95% CI 1.95 to 4.83, *P*=0.000, **Figure 3**).

Total blood loss

A total of five studies [14-16, 19, 20] (308 patients) provided data on total blood loss. Pooled results indicated that IV-TXA was associated with less total blood loss compared with topical FS (MD=148.97, 95% CI 12.38 to 285.55, *P*=0.041, **Figure 4**). Subgroup analysis

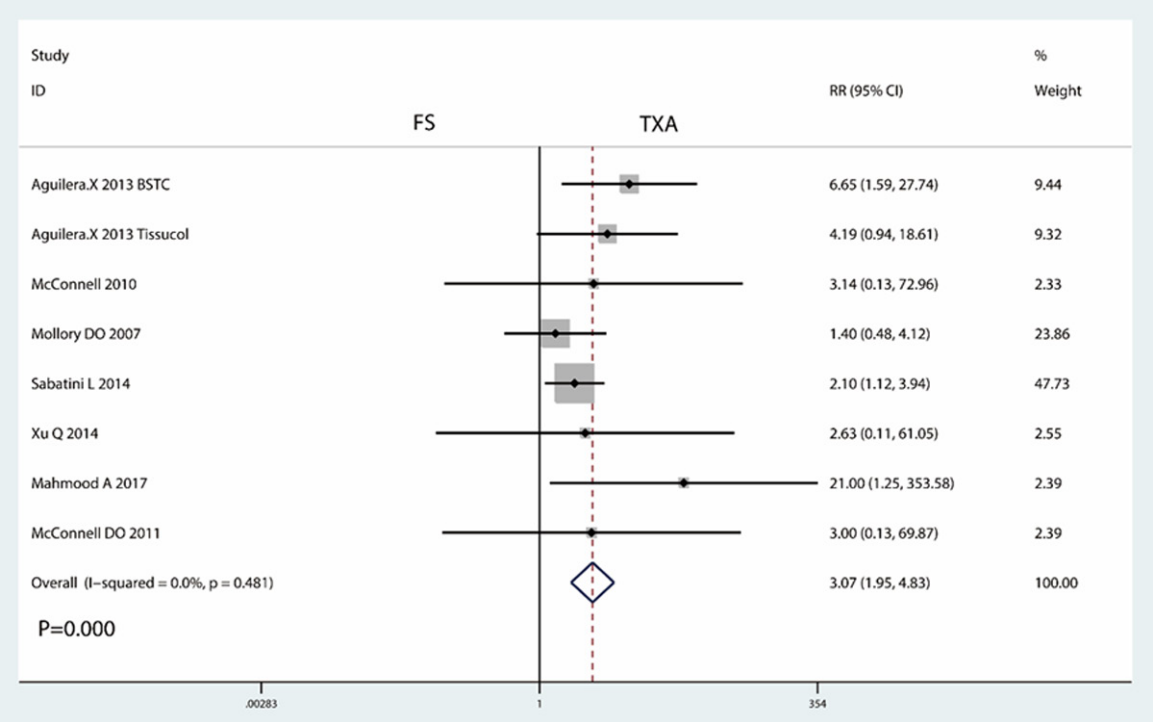

Figure 3. The risk of bias graph for the included studies.

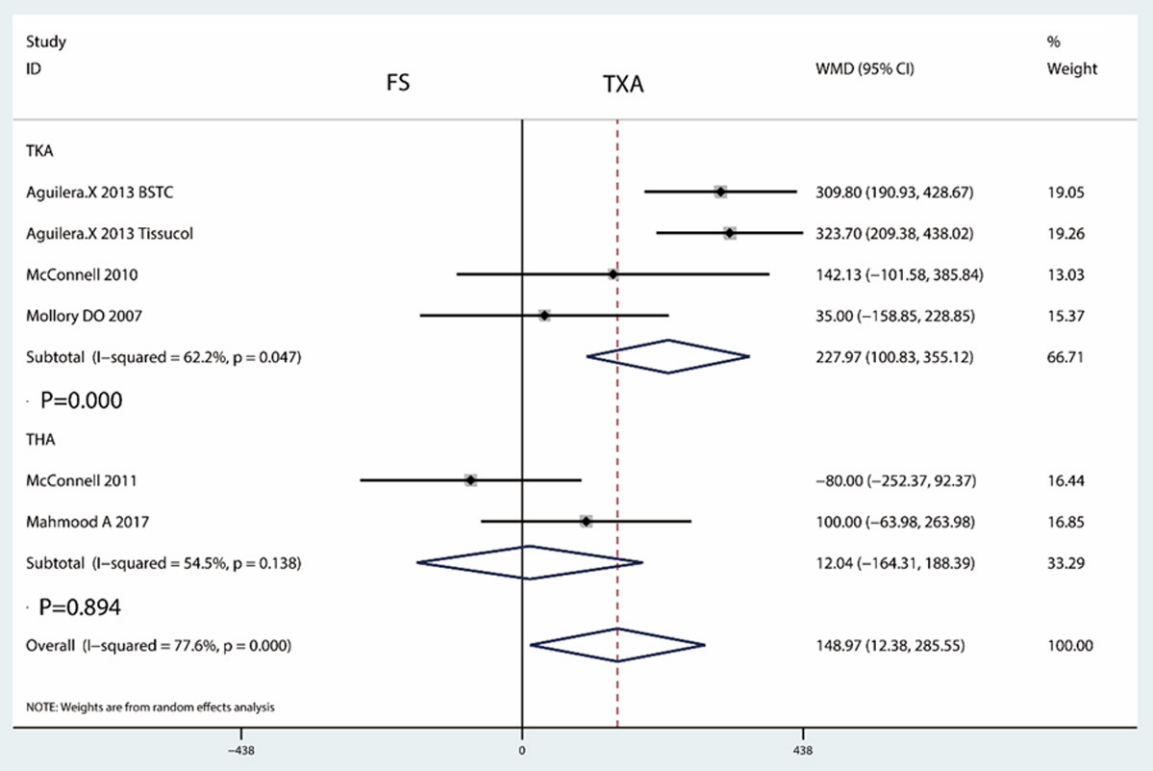

Figure 4. Forest plot comparing the need for transfusion between the two groups.

indicated that IV-TXA was associated with less total blood loss in TKA patients (MD=227.97, 95% CI 100.83 to 355.12, *P*=0.000), and no significant difference was observed in patients

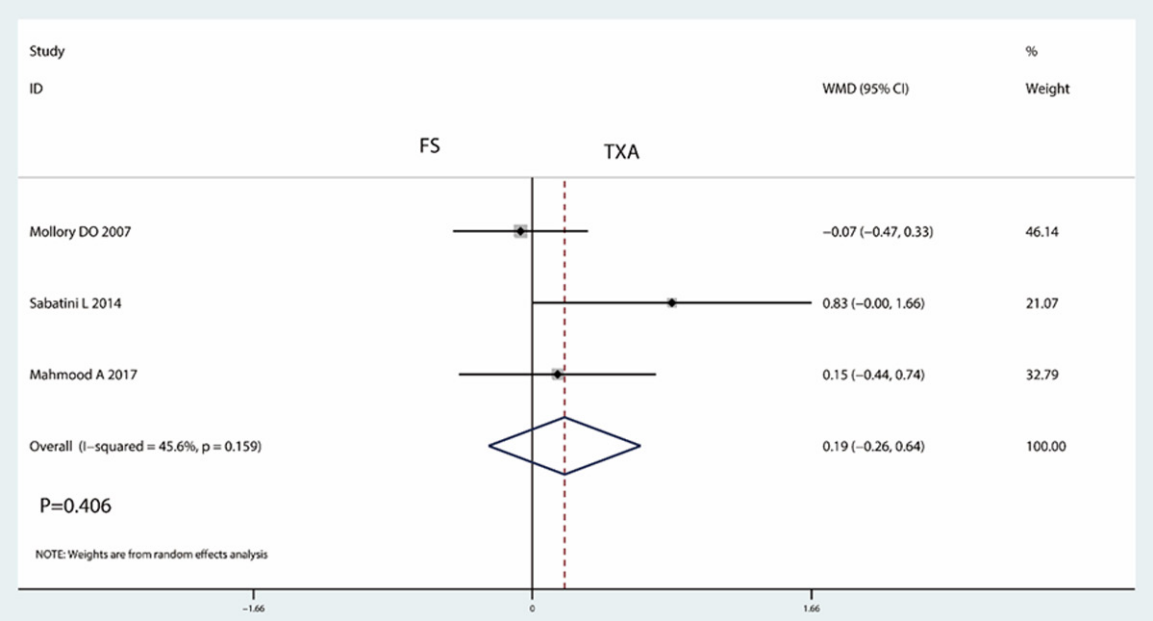

Figure 5. Forest plot comparing total blood loss between the groups.

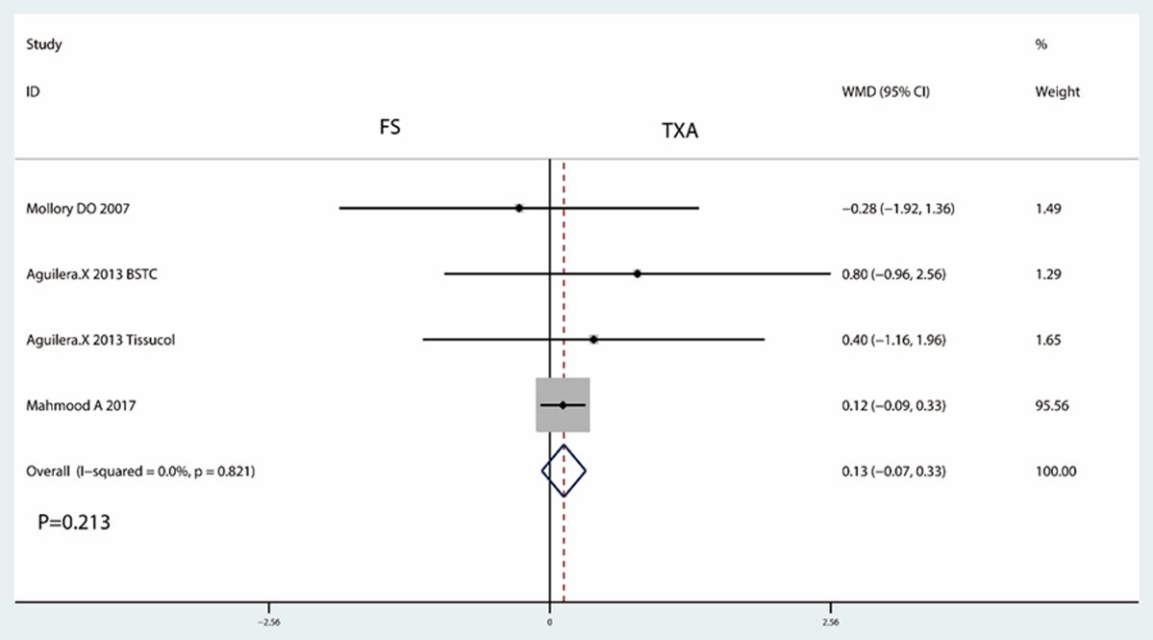

Figure 6. Forest plot comparing hemoglobin drop between the groups.

prepared for THA (MD=12.04, 95% CI -164.31 to 188.39, *P*=0.894).

Hemoglobin drop

A total of three component studies [16, 18, 19] (308 patients) provided data on hemoglobin drop. Pooled results indicated that there was no significant difference between IV-TXA and topical FS in terms of hemoglobin drop (MD=0.19, 95% CI -0.26 to 0.64, *P*=0.406, **Figure 5**).

Length of hospital stay

A total of three component studies [14, 16, 19] (465 patients) provided data on hemoglobin drop. Pooled results indicated that there was no significant difference between IV-TXA and topical FS in terms of hemoglobin drop

Table 4. The complications between the two groups

Outcomes	Studies	Heterogeneity (I^2, *P*)	Statistically method	Effect estimate (RR with 95% CI)	*P* value
DVT	5	0.0%, 0.451	Relative risk (M-H, fixed, 95% CI)	4.05 (0.46, 28.71)	0.516
Fever	3	0.0%, 0.209	Relative risk (M-H, fixed, 95% CI)	0.51 (0.20, 3.07)	0.308
Infection	2	0.0%, 0.308	Relative risk (M-H, fixed, 95% CI)	0.46 (0.25, 1.80)	0.251
Hematoma	2	0.0%, 0.140	Relative risk (M-H, fixed, 95% CI)	1.05 (0.28, 3.70)	0.095

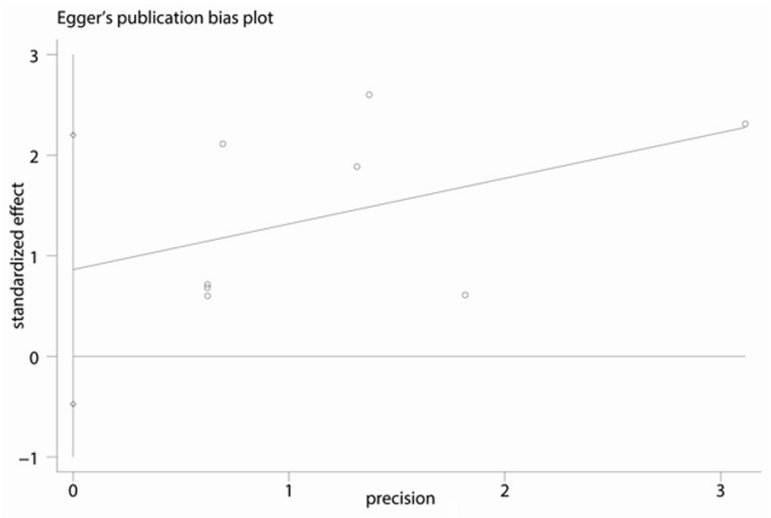

Figure 7. Forest plot comparing the length of hospital stay between the topical FS and IV-TXA groups.

(MD=0.13, 95% CI -0.07 to 0.33, *P*=0.213, **Figure 6**).

Complications

Complications related to the topical administration FG and intravenous administration of TXA are shown in **Table 4**. The meta-analysis of the two included trials showed that there were no statistically significant differences between topical FS and IV-TXA in terms of the incidence of thromboembolic events (RR 4.05, 95% CI 0.46 to 28.71, *P*=0.516), fever (RR 0.51, 95% CI 0.20 to 3.07, *P*=0.308), infection (RR 0.46, 95% CI 0.25 to 1.80, *P*=0.251) or hematoma (RR 1.05, 95% CI 0.28 to 3.70, *P*=0.095).

Publication bias

Egger's test was performed to test the publication bias for the need for transfusion. Results shown that there was no publication bias for the need for transfusion (*P*=0.256, **Figure 7**).

Discussion

The current study revealed that IV-TXA is more effective than topical FS in decreasing the need for transfusion and decreasing total blood loss in patients prepared for TJA. Moreover, no significant differences were found in terms of the risk of thromboembolic events and the length of hospital stay between the IV-TXA and topical FS groups. The major strengths of the current meta-analysis include the comprehensive search and rigorous statistical analysis.

Five RCTs and two CCTs met the inclusion criteria that were established in the meta-analysis; among the included studies, only one report was published in 2007, and the rest were all published after 2010. Although the number of studies that we included was small, the quality of the studies was relatively high. All of the included studies showed comparable baseline data.

Topical FS has been used to decrease blood loss in surgery for more than one hundred years. A previous meta-analysis reported that FS reduced blood loss by approximately 138.25 ml during TJA [7]. Another alternative for blood loss control is IV-TXA. IV-TXA can reduce the total blood loss during THA by approximately 305.27 mL compared with controls [21]. Thus, this indirect comparison indicated that IV-TXA was more effective than topical FS in reducing blood loss during TJA. The current evidence also indicated that IV-TXA decreased total blood loss by 148.97 ml (MD=148.97, 95% CI 12.38 to 285.55, *P*=0.041). The comparison between the present study and the previous meta-analysis can be seen in **Table 5**. The previous meta-analysis only found that IV-TXA was more effective at reducing the need for blood transfusion than topical FS [12].

Pooled results indicated that compared with topical FS, IV-TXA can reduce the incidence of

Table 5. The difference compared with previous meta-analysis

	Xu et al. [11].	Gao et al. [12]	Present study
No. of studies	5	5	7
No. of participants	359	359	646
Search strategies until (year)	2015	2016	2017
Outcomes			
Blood loss	(MD=116.59, 95% CI -138.29 to 371.47, *P*=0.37)	(MD=198.06; 95% CI -267.45 to 663.57; *P*=0.40)	(MD=227.97, 95% CI 100.83 to 355.12, *P*=0.000)
Blood transfusion	(RR 2.62, 95% CI 1.64 to 4.18, *P*<0.0001)	(OR=3.14; 95% CI, 1.67 to 5.90; *P*=0.0004)	(RR 3.07, 95% CI 1.95 to 4.83, *P*=0.000)
Complications	NS	NS	NS
Length of hospital stay	n.r	n.r	MD=0.13, 95% CI -0.07 to 0.33, *P*=0.213
Hemoglobin drop	n.r	n.r	(MD=0.19, 95% CI -0.26 to 0.64, *P*=0.406
Economic costs	n.r	n.r	TXA is superior than FS
Grade evidence	n.r	n.r	Yes

n.r not related, NS, not significance; TXA, tranexamic acid; FS, fibrin sealant.

transfusion after TJA by 12.4% (RR 3.07, 95% CI 1.95 to 4.83, *P*=0.000). Subgroup results indicated that statistical significance was observed only in the TKA surgical group and not in the THA surgical group. A total of two studies were included to analyze the need for transfusion after THA. More studies are required to identify the effects of IV-TXA on reducing the need for transfusion after THA. Skovgaard C et al. [22] revealed that when administered with a tourniquet, TXA and FS showed no benefit toward reducing the need for transfusion or in facilitating early functional recovery.

Another reason surgeon tended to first choose IV-TXA for blood loss control was the economic costs. Mcconnell el al. [15] reported that the cost per patient was £3.10 for IV-TXA and £390 for topical FS. Thus, IV-TXA utilization may save about £387 per patient. Choufani et al. [23] revealed that 2 patients (total =30 patients) in the FS group and 3 patients in the control group (total =30 patients) needed blood transfusions. The treatment cost for 30 patients was 13,500 €; after a savings of 187 € due to less need for blood transfusion, the treatment cost for the FS group was 13,313 € Phan et al. [24] indicated that IV-TXA was significantly less expensive as a treatment option during TJA and recommended IV-TXA for the control of blood loss in TJA.

There were several potential limitations of this meta-analysis: (1) Only seven studies were included in this meta-analysis, and the sample sizes in each trial were not large, which could affect the final results; (2) Two non-RCTs were enrolled in this meta-analysis, which could lower the evidence level; (3) The duration of follow up in some studies was unclear, and long-term follow up is needed to identify complications; and (4) The publication bias that exists in all meta-analyses will also influence the results.

Conclusion

This systematic review and meta-analysis indicated that IV-TXA was more effective than topical FS in reducing need for transfusion and reducing total blood loss during TJA. High quality RCTs and well-designed trials are still required in the future for the determination of the therapeutic dose or to detect adverse effects.

Disclosure of conflict of interest

None.

Abbreviations

IV, intravenous; TXA, tranexamic acid; FS, fibrin sealant; TJA, total joint arthroplasty; RCTs, randomized controlled trials; DVT, deep vein thrombosis; RR, relative risk; CI, confidence interval; WMD, weight mean difference; TKA, total knee arthroplasty; THA, total hip arthroplasty; MINORS, methodological index for non-randomized studies; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

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