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Review Article

The efficacy and safety of fibrin tissue adhesive to reduce blood transfusion and blood loss following total hip arthroplasty: a meta-analysis

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Abstract: Objective: This meta-analysis aimed to demonstrate the efficacy and safety of fibrin tissue adhesive versus control group or tranexamic aicd (TXA) for reducing blood loss in patients undergoing total hip arthroplasty (THA). Methods: Electronic databases: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Google databases were searched for randomized controlled trials (RCTs) comparing fibrin tissue adhesive versus placeboor TXA for patients undergoing THA. Outcomes included need for transfusion, total blood loss, blood loss in drainage, hemoglobin drop and the occurrence of deep venous thrombosis (DVT). We calculated risk ratios (RR) with a 95% confidence interval (CI) for dichotomous outcomes (need for transfusion and the occurrence of DVT) and the weighted mean difference (WMD) with a 95% CI for continuous outcomes (total blood loss, blood loss in drainage and hemoglobin drop). Review Manager 5.3.0 software was used for meta-analysis. Results: Ten clinical trials with 902 patients (fibrin tissue adhesive =396, control =384 and TXA=122) in the meta-analysis. Compared with the placebo, topical fibrin tissue adhesive was associated with less need for transfusion with no statistically significance. And fibrin tissue adhesive was associated with less total blood loss, blood loss in drainage and hemoglobin drop with statistically significance ($P<0.05$). However, these final results seem with no clinically importance. Compared with topical fibrin tissue adhesive, intravenous TXA was more effective in reducing need for transfusion and total blood loss with statistically significance ($P<0.05$). Conclusion: Based on current meta-analysis, we found no evidence to administration fibrin tissue adhesive in reducing blood loss in THA. And TXA was an relative effective and cheap alternative than fibrin tissue adhesive in THA. More RCTs were still needed to draw a definitive conclusion about the TXA in THA.

Keywords: Fibrin tissue adhesive, total hip arthroplasty, tranexamic acid, meta-analysis

Introduction

In total hip arthroplasty(THA), the overall blood loss is always underestimated as it exceeds the visible blood loss due to bleeding into the tissues or into the hip joint [1]. And the blood transfusion rates can be reached as high as 56% [2]. Blood transfusion may add extra costs and the risk of infectious disease [3]. Since 1972, the supportive use of fibrin tissue adhesive in selected surgical procedures has become current practice to control bleeding and to reduce blood loss after surgery [4]. However, there was no consensus about the efficacy of fibrin tissue adhesive in reducing blood loss in THA. Though, there were two meta-analyses published, one meta-analyses included patients for TKA and THA, and they did not perform subgroup analysis based on TKA or THA, and thus their results should be treated with caution [5]. Another meta-analysis did not include all of the published studies, the reason was that they did not included Google database and retrieval strategies were not comprehensive enough [6]. Another important issue was that tranexamic acid (TXA) was more popular than fibrin tissue adhesive. And whether fibrin tissue adhesive was more effective than TXA in patients prepared for THA was unknown. Thus, we performed a meta-analysis to summarize the existing evidence from randomized controlled trials (RCTs) to determine the effectiveness and safety of fibrin tissue adhesive for THA.

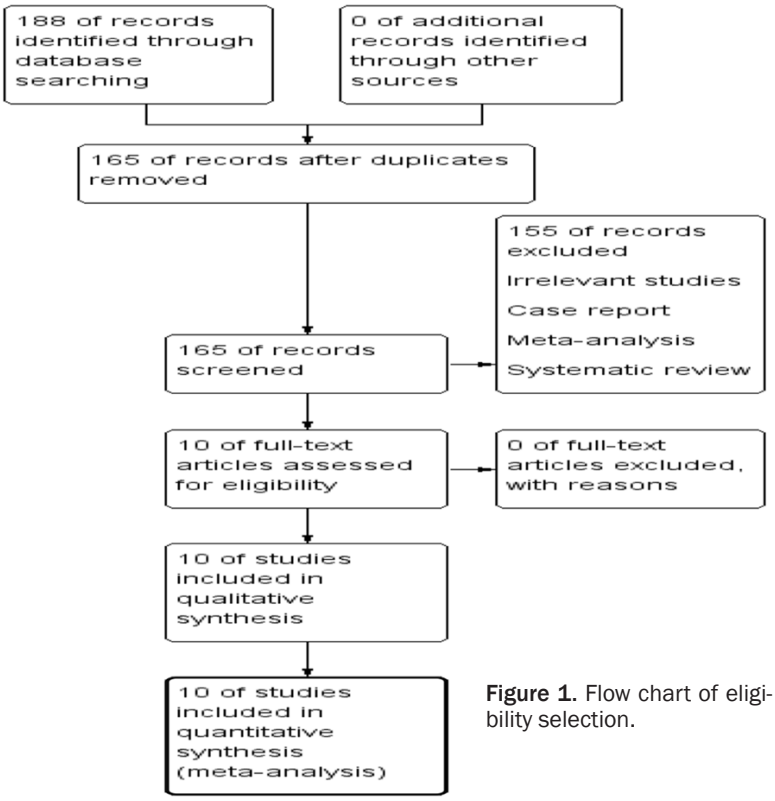

Figure 1. Flow chart of eligibility selection.

Materials and methods

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [7] and was written in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist [8].

Search strategy and study selection

The electronic databases PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Google database were systematically searched from inception to December 31, 2016. The detailed PubMed search strategy was as follows: (((((“Fibrin Tissue Adhesive”[Mesh]) OR fibrin glue) OR fibrin tissue adhesive) OR fibrin sealant)) AND (((((“Arthroplasty, Replacement, Hip”[Mesh]) OR THA) OR THR) OR total hip replacement) OR total hip arthroplasty). Meta-analysis was collected from published data and thus ethical review or approved was not necessary.

Eligibility criteria and exclusion criteria

Eligibility criteria: 1. Participants: Patients undergoing primary THA and revision THA. 2. Interventions: The comparison group was an administration of fibrin tissue adhesive. 3. Comparisons: The comparison group was with placebo or intravenous TXA (IV-TXA) group. 4. Outcomes: need for transfusion, total blood loss, blood loss in drainage, hemoglobin drop and the occurrence of deep venous thrombosis (DVT). 5. Study design: Only RCTs were included.

Exclusion criteria: 1. Any non-RCTs, quasi-RCTs, surgical registries and review papers were excluded. 2. Retrospective studies, cadaverstudies, comments, letters, editorials, protocols and guidelineswere excluded.

Data extraction and outcome measures

Two authors (L. W and Y.HW) independently extracted the author, publication year, the number of patients in intervention and control groups, the proportion of male patients and the mean age of the patients, the volume of fibrin tissue adhesive and comparison, outcomes and duration of follow-up. Any disagreement was resolved by discussion. The outcomes were need for transfusion, total blood loss, blood loss in drainage, hemoglobin drop and the occurrence of complications. If the data were not reported numerically, we extracted mean and standard deviation values from the published papers using GetData Graph Digitizer software as needed [7].

Risk of bias assessment

Two authors (J.J and D.YZ) independently evaluated the risk of bias of included RCTs according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [7]. The assessment criteria included the following 7 domains: i) random sequence generation, ii) allocation sequence concealment, iii) blinding of participants and personnel, iv) blinding of outcome assessment, v) incomplete outcome data, vi) selective outcome reporting, and vii) other biases. All do-

Table 1. The general characteristic of the included studies

Reference	No. of patients		Male (I:C, %)	Mean age, (I:C, y)	Preoperative Hb (I:C, g/dL)	Transfusion criteria	Intervention		Outcomes	Study design	Follow up	Surgery
	I	C					I	C				
Falez 2013	31	38	NS	NS	NS	NS	fibrin spray (10 ml) before wound closure (contain TXA)	Placebo	1, 2, 3, 4, 5, 6, 7	RCTs	72 hours	Primary THA
Lassen 2006	33	36	24.6:32.6	65.4:67.2	12.9:12.2	NS	Vivostat sealant (NS, contain no TXA)	Saline	1, 2, 3, 4, 7	RCTs	8 days	Primary THA
Mawatari 2006	60	60	100:85	60.3:58.4	12.3:12.6	NS	Vivostat sealant (10 ml, contain no TXA)	Saline	7	RCTs	3 year	Primary THA
Ren 2011	20	20	45.7:54.6	75.1:72.3	12.0:11.7	NS	Vivostat sealant (5 ml, contain no TXA)	Placebo	1, 2, 4, 7,	RCTs	7 days	Primary THA
McConnell 2011	22	22	31.8:43.4	NS	NS	NS	Quixil® (10 ml, contain TXA)	Arm1=Saline Arm2=TXA	1, 4, 7	RCTs	30 days	Primary THA
Randelli 2013	35	35	27.1:32.9	63.8:66.2	13.5:12.8	<8.5 g/dL	Quixil® (10 ml, contain TXA)	Saline	2, 3,4,	RCTs	2 month	Primary THA
Wang 2003	38	43	55.6:55.3	67.3:64.1	12.9:13.1	NS	Omrixil® (10 ml, contain no TXA)	Saline	4	RCTs	6 month	Primary THA
Ghoz 2015	44	45	62.1:64.6	68.2:72.9	NS	<8 g/dL	Quixil® (10 ml, contain TXA)	Saline	1, 2, 3, 4, 5, 6, 7	RCTs	2 days	Revision THA
Mahmood 2017	100	73	38.7:41.7	64.2:66.0	13.4:13.2	<8 g/dL	TISSEEL (10 ml, contain no TXA)	Arm1=Saline Arm2=TXA	1, 2, 3, 4, 5, 6, 7	RCTs	At discharge	Primary THA
Crawford 1999	13	12	51.3:53.4	67.1:70.2	12.6:13.1	NS	Quixil® (10 ml, contain TXA)	Placebo	2, 6	RCTs	7 days	Primary THA

NS, not stated, SA, spinal anesthesia, EA, epidural anesthesia, I, intervention, C, control 1, VAS at 12 h, 2, VAS at 24 h, 3, VAS at 48 h, 4, the occurrence of nausea and vomiting, 5, length of hospital stay, 6, the blood glucose, 7 the occurrence of infection, TKA, total knee arthroplasty, THA, total hip arthroplasty, TJA, total joint arthroplasty, RCTs, randomized controlled trials.

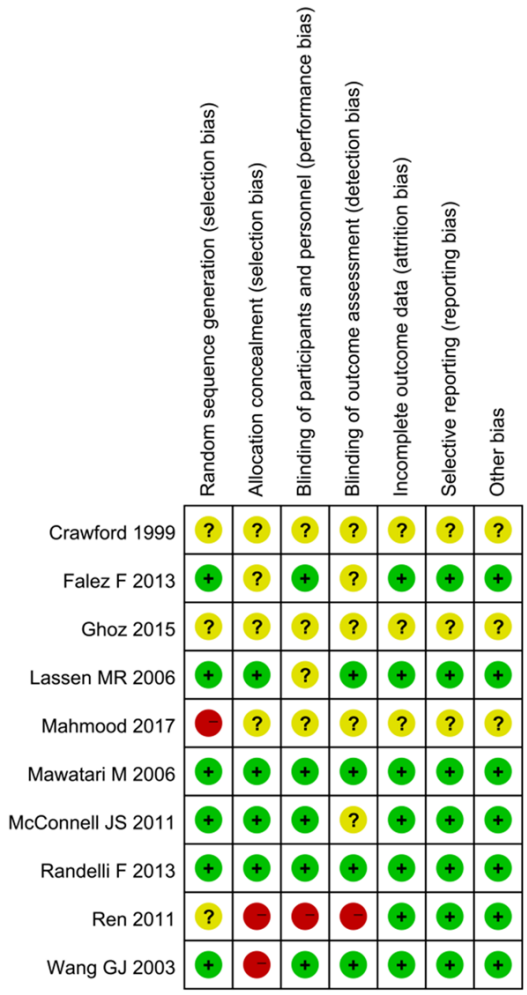

Figure 2. The risk of bias summary of the included studies. "+" represent low risk of bias, "-" represent high risk of bias, "?" represent unclear of bias.

mains were evaluated as "low", "high", or "unclear" according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.3.0) [7] and the risks of bias were drawn by the Review Manager 5.3.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Quality of evidence assessment

Two reviewers (X.F and K.JG) independently evaluated the quality of evidence assessment in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [9]. Risk of bias, inconsistency, indirectness, imprecision and publication bias were the assessment items [9, 10]. Each result was classified as high, moderate, low, or very low. GRADE Pro software was used to construct summary tables for the included studies.

Statistical analysis

For total blood loss, blood loss in drainage, hemoglobin drop, the weighted mean difference (WMD) and 95% confidence interval (CI) were calculated. For dichotomous outcomes (need for transfusion and the occurrence of complications), we calculated the risk ratio (RR) and 95% CI. Heterogeneity was considered to be statistically significant if the I^2 value was greater than 50%. A random-effect model was used for all of the calculation due to the dose and category of fibrin tissue adhesive was different. All statistical analyses were conducted using Review Manager 5.3.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and publication bias was performed by the software of Stata 12.0 (Stata Corp., College Station, TX). The subgroup analysis was conducted based on the dose of fibrin tissue adhesive (when total dose of fibrin tissue adhesive more than 5ml, we identify it was ashigh dose; and if total dose of fibrin tissue adhesive less than 5 ml, we identify it was aslow dose) and with TXA or no. A *P* value less than 0.05 was considered statistically significant. Kappa values were used to measure the degree of agreement between the 2 reviewers and were rated as follows: fair, 0.40 to 0.59; good, 0.60 to 0.74; and excellent, 0.75 or more [11].

Results

Search results

The literature search and selection process are illustrated in **Figure 1**. The initial search yielded 188 articles; 165 papers were read after excluding the duplicates. Next, 155 papers were excluded based on the inclusion criteria. Of these, we included ten clinical trials with 902 patients (fibrin sealant =396, control =384 and TXA=122) in the meta-analysis [12-21].

Study characteristics

The detailed baseline characteristics of the included studies are presented in **Table 1**. Ten studies were included in the meta-analysis. Nine articles were published in English and one study was published in Chines between the

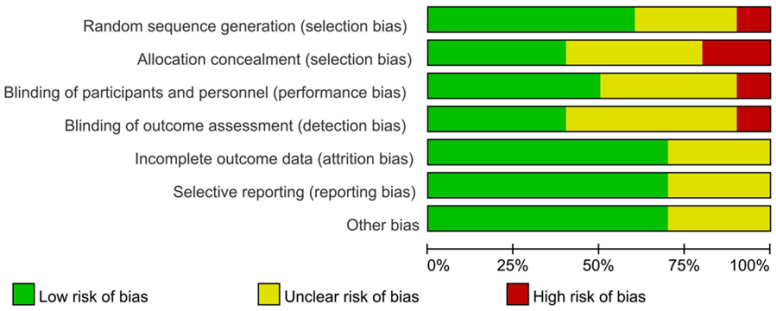

Figure 3. The risk of bias graph.

years of 1999 and 2017. The sample sizes ranged from 12 to 100 (total =902) and the mean age ranged from 60 to 75.1. The follow up ranged from 2 day to 6 month. The volume of fibrin tissue adhesive ranged from 5 ml to 10 ml. And five studies administration fibrin sealant with no TXA and the rest studies administration TXA as stabilizer [12, 15, 16, 19, 21].

Risk of bias among the included studies

Figures 2 and **3** presents the details of the risk of bias assessment for all of the included studies. Randomized sequence generation was implemented adequately in 6 studies [12-17]; 3 studies had an unclear risk of bias [18, 19, 21] and 1 study has high risk of bias [12-21]. Allocation concealment was implemented adequately in all included studies. All studies reported blinding of the participants, personnel, and outcome assessors. The overall kappa value regarding the evaluation of risk of bias of included RCTs was 0.913, indicating an excellent degree of agreement between the 2 authors.

Quality of evidence assessment

A summary of the quality of the evidence based on the GRADE approach is shown in Supplement Table 1. The GRADE level of evidence was moderate for need for transfusion, low for total blood loss and hemoglobin drop, very low for blood loss in drainage.

Need for transfusion

Seven studies [12, 13, 15-17, 19-21] including 552 patients tested the effect of fibrin tissue adhesive on the need for transfusion. Compared with the placebo, fibrin tissue adhesive were associated with a small reduction in the need for transfusion with no statistically significance (RR= 0.83, 95% CI 0.67 to 1.02, P=0.07; I^2=0%) (**Figure 4A**). Two studies reported data from 244 participants with THA and were included in this meta-analysis to estimate the effect of intravenous TXA and fibrin tissue adhesive on the need for transfusion. Compared with fibrin tissue adhesive, intravenous TXA were associated with a significantly reduction in the need for transfusion (RR=8.82, 95% CI 1.08 to 72.16, P=0.04; I^2=0%) (**Figure 4B**).

Subgroup analysis results are shown in **Table 2**. The results indicated that fibrin tissue adhesive contains TXA was more effective than fibrin tissue adhesive with no TXA (P=0.492). And high dose of fibrin tissue adhesive reduce more total blood loss than low dose.

Total blood loss

Six studies (557 participants) reported data on the volume of total blood loss. Compared with placebo, fibrin tissue adhesivewas associated with a small reduction of total blood loss by 117.84 ml (WMD=-117.84, 95% CI -214.42 to -21.26, P=0.02; I^2=38%) (**Figure 5A**). There was no significant difference between the fibrin tissue adhesive and TXA in the reduction of total blood loss (WMD=12.04, 95% CI -164.31 to 188.39, P=0.89; I^2=55%, **Figure 5B**). Subgroup analysis results are shown in **Table 2**. The results indicated that fibrin tissue adhesive contains TXA was more effective than fibrin tissue adhesive with no TXA (P=0.016) in reducing total blood loss.

Blood loss in drainage

Four studies (290 participants) reported data on the blood loss in drainage. Compared with placebo, fibrin tissue adhesive wasassociated with a small reduction of blood loss in drainage (WMD=-93.44, 95% CI -171.58 to -15.29, P=0.02; I^2=74%, **Figure 6**).

Hemoglobin drop

A total of two studies (270 patients) were included in the meta-analysis of hemoglobin

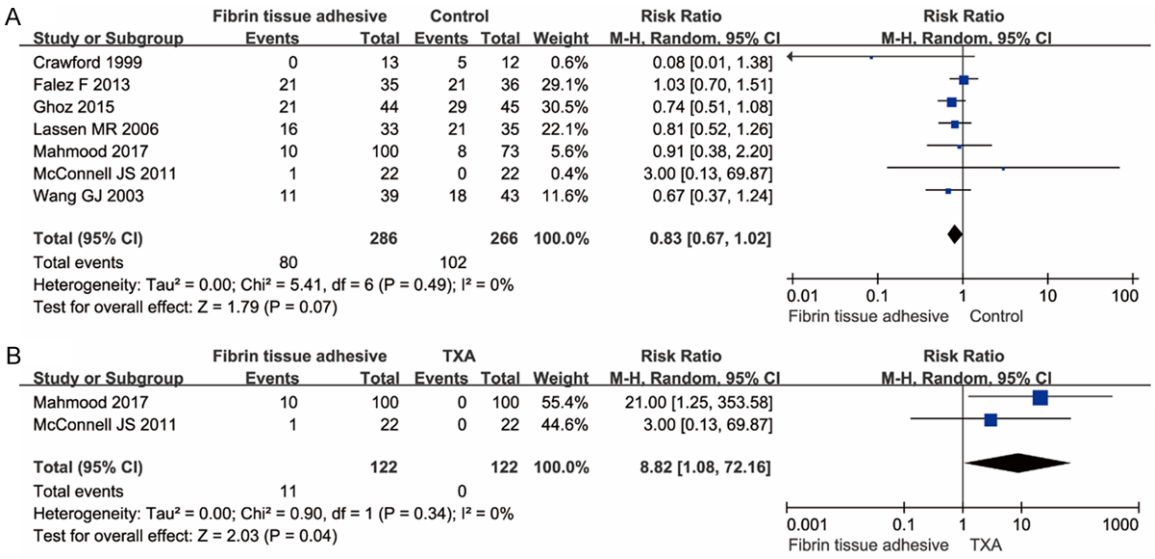

Figure 4. A. Need for transfusion between the fibrin tissue adhesive group and control group. Pooled outcome of seven studies showed no significant difference between the two groups (P=0.07). B. Need for transfusion between the fibrin tissue adhesive group and tranexamic acid group. Pooled outcome of two studies showed TXA was associated with less need for transfusion (P=0.04).

Table 2. Subgroup analysis for the need for transfusion and total blood loss

Subgroup	Number of the included studies	Relative risk		Heterogeneity		Subgroup difference, *P* value
		RR (95% CI)	*P value*	*I^2, %*	*P value*	
Need for transfusion						0.492
With TXA [12, 21, 19]	234	0.84 (0.54, 1.32)	0.453	39.3	0.176	
With no TXA [13, 15, 17, 20]	318	0.78 (0.56, 1.09)	0.142	0.0	0.883	
High dose [13, 15, 19]	306	0.87 (0.56, 1.12)	0.086	0.0	0.109	0.016
Low dose [12, 17,20, 21]	246	0.56 (0.31, 1.36)	0.097	0.0	0.256	
Total blood loss						
With TXA [13, 15, 19]	205	-131.60 (-246.60, -21.26)	0.025	52.7	0.096	
With no TXA [17, 20, 21]	352	-50.72 (-274.86, 173.42)	0.657	5.2	0.305	
High dose [13, 19, 20]	308	-155.38 (-282.16, -103.55)	0.001	25.9	0.065	0.001
Low dose [15, 17, 21]	249	-121.55 (-208.55, -76.31)	0.014	59.4	0.085	

drop. Compared with placebo, fibrin tissue adhesive was associated with a small reduction of hemoglobin drop (WMD=-0.275, 95% CI -0.51 to -0.02, P=0.03; I^2=37%) (**Figure 7**).

The occurrence of DVT

Compared with control group, fibrin tissue adhesive was not associated with the increase of the occurrence of DVT (RR=3.00, 95% CI 0.13 to 71.22, P=0.50, **Figure 8A**). Compared with topical fibrin tissue adhesive, IV-TXA was also not associated with the increase of the occurrence of DVT (RR=0.33, 95% CI 0.01 to 8.09, P=0.50, **Figure 8B**).

Discussion

This meta-analysis aimed to explore the optimal hemostasis agent for THA. Fibrin tissue adhesive and TXA were two common hemostasis agents that administration in THA for several decades. However, the efficacy and safety of fibrin tissue adhesive was still in debated and no consensus was reached. The pooled results showed that there was no significant difference between the fibrin tissue adhesive and TXA in the need for transfusion. However, TXA was effective in reducing the need for transfusion than fibrin tissue adhesive. For total blood loss, fibrin tissue adhesive was associated with a

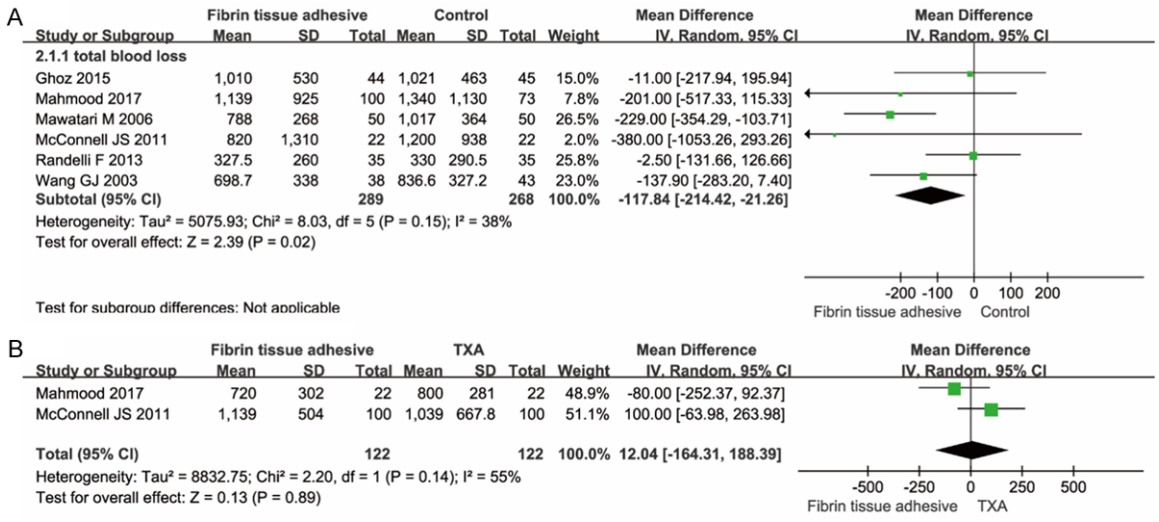

Figure 5. A. Total blood loss between the fibrin tissue adhesive group and control group. Pooled outcome of six studies showed fibrin tissue adhesive was associated with less total blood loss than control group (P=0.02). B. Total blood loss between the fibrin tissue adhesive group and tranexamic acid group. No significant difference between the total blood loss between fibrin tissue adhesive and tranexamic acid group (P=0.89).

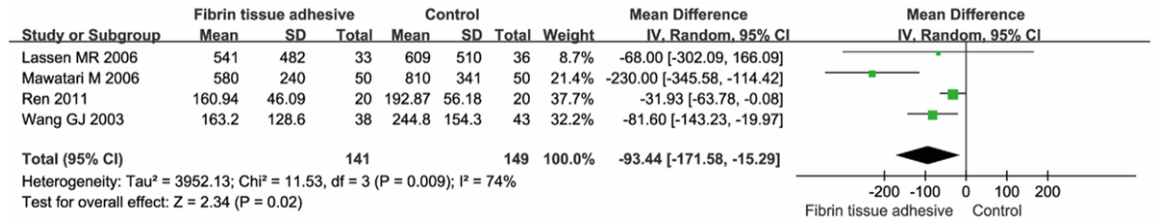

Figure 6. Forest comparing blood loss in drainage between fibrin tissue and control group.

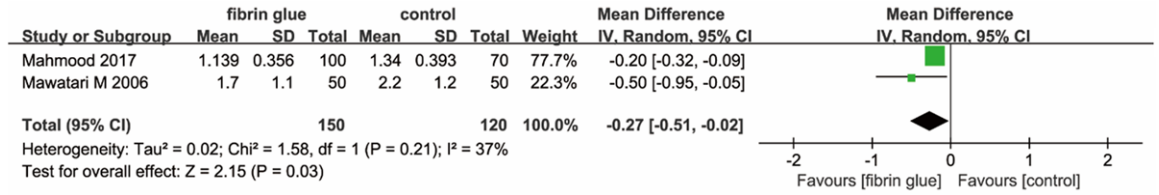

Figure 7. Forest comparing hemoglobin drop between fibrin tissue and control group.

small significant reduction of total blood loss by 117.84 ml. These volume seems with no clinically importance in clinical practice. Then, the safety of fibrin tissue adhesive and TXA were compared, no significant differences were observed in current meta-analysis. The level of evidence, which was undermined by heterogeneity and/or study design limitations, was moderate or low, indicating that the degree of benefit must be studied, although the benefit is conclusive.

A major strength of the current analysis is the comprehensive search with strict statistical calculations. Before this meta-analysis, a total of two relevant two systematic review and meta-analysis [5, 6] were published (**Table 3**). Li et al. [5] used a combined statistical analysis for TKA and THA, and this method will cause a large heterogeneity. What's more, Grade evidence for outcomes was not performed in all of the previous two studies [5, 6]. Current meta-analysis included 10 RCTs with 902 patients,

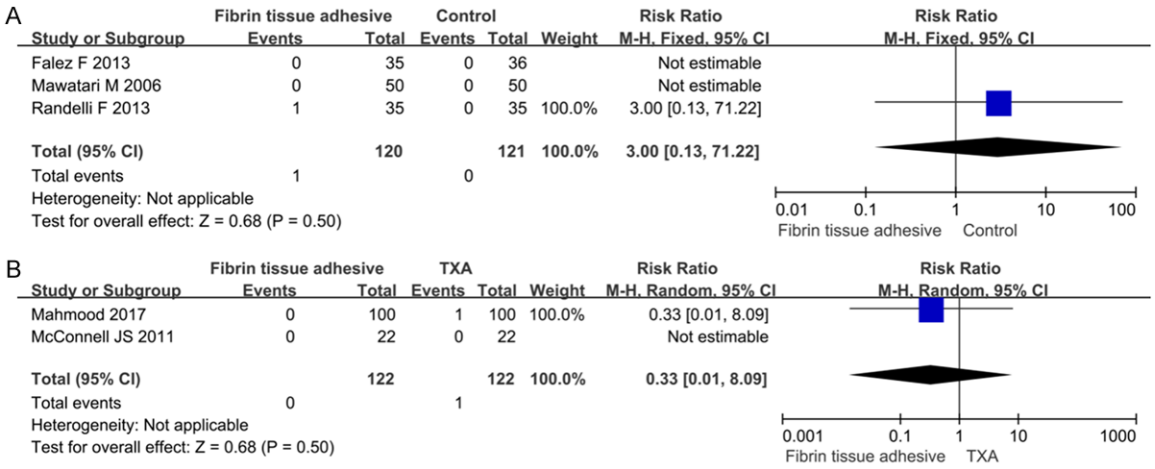

Figure 8. A. The occurrence of deep venous thrombosis between the fibrin tissue adhesive group and control group. No significant difference between fibrin tissue adhesive group and control group in terms of deep venous thrombosis (P=0.50). B. Forest plot that comparing deep venous thrombosis between fibrin tissue adhesive and tranexamic acid group. No significant difference between the total blood lossbetween fibrin tissue adhesive and tranexamic acid group (P=0.50).

which was large more than previous two meta-analysis. Compared with previous two meta-analysis, the highlight of current meta-analysis was that we revealed that TXA was more effective than fibrin tissue adhesive in THA patients. Previous two meta-analysis only compare fibrin tissue adhesive with controls in THA patients.

The current meta-analysis included all available RCTs that included comparisons of efficacy and safety of fibrin tissue adhesive in THA. Fibrin tissue adhesive and TXA were two alternative for surgeons to administration. Present meta-analysis indicated that TXA was an ideal alternative when compared with fibrin tissue adhesive. The category of fibrin tissue adhesive including commercial product (Quixil® or Omrixil®) and autologous blood centrifuge (Vivostat sealant). The difference of these products was whether these products added TXA as stabilizer. Thus, we performed a subgroup analysis that divided the fibrin tissue adhesive into two groups: with TXA and with no TXA. Results indicated that fibrin tissue adhesive with TXA was associated with less total blood loss than fibrin tissue adhesive with no TXA. Skovgaard et al. [22] conducted a RCT and final results werein accordance with our results. Fibrin tissue adhesive as a local hemostatic in TKA showed no benefit in reducing drain output and blood loss. Khan et al. [23] conducted a review and final conclusion was fibrin tissue adhesive has this potential, but is not more potent than TXA. Maheshwari et al. [24] revealed that no additional benefit with use of a fibrin tissue adhesive to decrease peri-operative blood loss during primary TKA. All of the reference studies were the products with no addition of TXA.

Another important factor that mainly concern is the cost of the fibrin sealants in the THA. A Quixil fibrin spray set costs between 450€ and 675,00€ [25]. One non-RCT reported that the cost of additional 31 units of fibrin sealant was 9743€, whereas the cost saving achieved by using 11 fewer blood transfusion units was only 3484€. Thus, patients will increase extra costs about 6259€ for one patient. TXA proved to be cost-effective with an average cost of R$ 61.35 (currently US$16) per year of life saved [26]. Thus, TXA was more cost-effective than topical fibrin tissue adhesive. However, there was no direct comparison the cost analysis between fibrin tissue adhesive and TXA. Firm conclusion may be drawn from the direct cost analysis.

Our meta-analysis also has several potential limitations: (1) patient treatment with different types and volume of fibrin tissue adhesive; (2) marked heterogeneity among the included studies in total blood loss and hemoglobin drop, reflecting the inconsistent benefit patients acquired from fibrin tissue adhesive, although these analyses were performed using a random effects model; and (3) the follow-up in the included studies was relative short. Thus, some

Table 3. Current meta-analysis compared with previous meta-analysis

	Li et al. [5]	Wang et al. [6]	Current study
No. of RCTs	5	6	10
No. of participants	405	405	902
Search strategy until (year)	2015	2016	2017
Outcomes			
Need for transfusion	RR=0.65, 95% CI 0.53 to 0.79	RD=0.12,95% CI: 0.22 to 0.03	RR=0.83, 95% CI 0.67 to 1.02
Total blood loss	MD=-127.63, 95% CI -203.61 to -51.65	MD=-153.77, 95% CI: 287.21 to 20.34)	MD=-117.84, 95% CI -214.42 to -21.26
Blood loss in drainage	MD=-425.47, 95% CI -462.82 to -388.13	n.r.	MD=-93.44, 95% CI -171.58 to -15.29
Hemoglobin drop	n.r.	n.r.	MD=-0.275, 95% CI -0.51 to -0.02
The occurrence of DVT	n.r.	RD=0.01, 95% CI: 0.02 to 0.04	RR=3.00, 95% CI 0.13 to 71.22
Quality of Evidence Assessment	n.r.	n.r.	Yes
Supplement instruction			Compared fibrin tissue adhesive with TXA

adverse events such as infection with hepatitis or other infectious disease may be underestimated. Finally, some data for comparisons were not originally available but were calculated by estimation, potentially leading to other bias.

Conclusions

In conclusion, the present meta-analysis demonstrated that fibrin tissue adhesive has limited effects in reducing peri-operative blood loss in THA patients. And direct comparison between TXA and fibrin tissue adhesive indicated that TXA may be more effective than fibrin tissue adhesive. Furthermore, commercial fibrin tissue adhesive with TXA was more effective than fibrin tissue adhesive with no TXA. Considering the limitations of the current meta-analysis, the conclusions regarding the effects of TXA and fibrin tissue adhesive should be interpreted cautiously; more RCTs are warranted before making final recommendations.

Disclosure of conflict of interest

None.

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Supplement Table 1. Grade evidence file for the need for transfusion, total blood loss, blood loss in drainage, hemoglobin drop and the occurrence of DVT

Need for transfusion						
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	Transfusion rate				
New Outcome	Study population		RR 0.83 (0.67 to 1.02)	552 (7 studies)	⊕⊕⊕⊖ moderate[1]	
	383 per 1000	318 per 1000 (257 to 391)				
	Moderate					
	419 per 1000	348 per 1000 (281 to 427)				
Intervention: total blood loss						
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	Blood loss				
Total blood loss-total blood loss	The mean total blood loss - total blood loss in the intervention groups was 117.84 lower (214.42 to 21.26 lower)			557 (6 studies)	⊕⊕⊖⊖ low[1]	
Intervention: blood loss in drainage						
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	Drain out				
Drain out	The mean drain out in the intervention groups was 93.44 lower (171.58 to 15.29 lower)			290 (4 studies)	⊕⊖⊖⊖ very low[1]	
Intervention: Hemoglobin drop						
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	Hemoglobin drop				
Hb drop	The mean hemoglobin drop in the intervention groups was 0.27 lower (0.51 to 0.02 lower)			270 (2 studies)	⊕⊕⊖⊖ low[1]	

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No explanation was provided. CI: confidence interval.