

The Efficacy and Safety of Fibrin Sealant Versus Tranexamic Acid Administration in Patients Undergoing Hip Arthroplasty: A Meta-analysis

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Abstract

Purpose

The efficacy and safety of topical fibrin sealant (FS) compared with tranexamic acid (TXA) to reduce blood loss after total hip arthroplasty (THA) is not clear. A meta-analysis was conducted to evaluate the efficacy and safety of topical FS versus topical or intravenous TXA for treatment of primary THA.

Method

We searched electronic databases, including PubMed, Embase, and the Cochrane Library to identify studies up to March 2020. The references included in articles were also checked for additional potentially-relevant studies. The language of publication was limited to English. The endpoints included the mean difference (MD) of blood loss, hemoglobin value, and odds ratios (ORs) of transfusion requirements and thrombotic events. Our meta-analysis was performed according to the Guidelines of the Cochrane Reviewer's Handbook and the PRISMA statement. The data of the included studies were analyzed using RevMan 5.3.

Results

A total of four studies (two randomized controlled trials and two non-randomized controlled trials) met the inclusion criteria. Our meta-analysis demonstrated that TXA administration led to significantly different outcomes in terms of transfusion rate (RD = -0.12, 95% CI (-0.23, -0.00), $P = 0.05$, $I^2 = 74\%$) and postoperative hemoglobin levels (WMD = -0.47, 95% CI (-0.74, -0.21), $P = 0.0005$, $I^2 = 3\%$) compared with topical application of FS in patients undergoing THA. No significant difference was seen in total calculated blood loss (WMD = -86.22, 95% CI (-99.13, -73.31), $P < 0.00001$, $I^2 = 96\%$) or complication rate (RR = 0.98, 95% CI (-99.13, -73.31), $P = 0.45$, $I^2 = 0\%$) between the two groups.

Conclusions

TXA administration can effectively decrease the transfusion rate and result in higher postoperative hemoglobin levels without increasing the rate of infection.

Introduction

Total hip arthroplasty (THA) is considered to be the most effective surgical treatment for patients with severe hip disease[1-2]. In spite of the satisfactory results of THA, because patients suffer blood loss during the perioperative period, surgery carries risks of postoperative anemia and blood transfusion, leading to longer hospital stays and higher medical costs[3-4]. Therefore, reducing perioperative blood loss and minimizing the risk of allogeneic transfusion have attracted a great deal of attention from orthopedists performing THA surgery[5-6]. Many measures have been taken to minimize perioperative blood loss, including drug intervention, autologous donation, perioperative hemodilution, and minimally-invasive surgery[7].

Fibrin sealant (FS) forms fibrin that adheres to the wound surface and is formed from human fibrinogen by the action of thrombin. Previous studies have demonstrated that it can effectively reduce perioperative blood loss, postoperative blood transfusion rate and hemoglobin decline[8-9]. Meanwhile numerous studies have shown that TXA can effectively reduce blood loss and blood transfusion rate during THA[10-11]. Moreover, meta-analysis of pooled results indicate that TXA reduces blood loss with no increase in the risk of thrombotic events[12-15]. Previously, a meta-analysis has been performed on the comparison of topical fibrin sealants and intravenous TXA for reducing blood loss during total knee arthroplasty[16]. Although the two pharmacological interventions are effective in reducing blood loss, the best for use in THA, in terms of efficacy and safety of the two interventions, remains controversial. Since we were unable to find a meta-

analysis of the two pharmacological interventions in THA, to the best of our knowledge this is the first meta-analysis to compare the efficacy and safety of fibrin sealants and TXA in THA.

Materials And Methods

This study was performed according to the Guidelines of the Cochrane Reviewer's Handbook and the PRISMA statement.

Search Strategy

We searched the electronic databases PubMed, Embase and the Cochrane Library, from the database inception to February 2020. The studies included were those which compared FS and TXA for reducing blood loss in patients undergoing THA. In potentially relevant studies, the references of the included articles were also checked. The language of publication was limited to English. The key words and medical subject headings (MeSH) used in search methods were "fibrin sealant", "fibrin glue" "tranexamic acid", and "total hip arthroplasty", combined using Boolean operators. The search results are shown in Fig. 1.

Inclusion Criteria and Study Selection

Studies were included in the meta-analysis if: 1) patients underwent primary unilateral THA; 2) data were from randomized controlled trials (RCTs) or non-randomized controlled trials (non-RCTs); 3) the pharmacological intervention considered was the use of FS versus TXA; 4) outcome measures included blood loss, hemoglobin level, number of patients receiving allogeneic blood transfusions, incidence of thromboembolic events (DVT and PE), and wound infection. comments, editorials, reviews, studies with insufficient data and patients with bleeding disorders were excluded.

Data extraction and quality assessment

Two authors (DB and HHN) independently scanned the titles and abstracts of the included studies. Subsequently, the full text of any study that met the inclusion criteria was selected. If there was a disagreement, a senior auditor (ZZ) was consulted to resolve the problem. Another two authors (FYY and DB) independently extracted data from the included studies. Corresponding authors were consulted for details if the data were incomplete. The following data were extracted and recorded: first author names, publication year, age, sex, other baseline characteristics, intervention procedures, sample size and outcome parameters. Weighted mean difference (WMD) and relative risk (RR) with a 95% confidence interval (95%CI) were used to describe the endpoints.

The same two authors (FYY and HHN) assessed the quality of each randomized trial according to the Cochrane Handbook for Systematic Reviews of Interventions. If there was a disagreement, it was decided as before by consulting the corresponding author (DB). A "Risk of Bias" table included the following elements: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting and other bias. Quality assessment was then carried out based on this "risk of bias" table.

Statistical analysis

Data analysis was performed using RevMan 5.3 software (Revman; The Cochrane collaboration, Oxford, United Kingdom). The chi-square test was used to assess the significance of heterogeneity[17]. If the I^2 value $\geq 50\%$ and $P < 0.1$, it suggested a high degree of heterogeneity[18]. When there was high heterogeneity among studies, a random-effects model was applied for the current meta-analysis. Otherwise, the fixed effects model was used. Only a *CI* was provided in two studies[19-20], the SD was calculated using the following formula where U refers to the upper limit of the *CI*, u to the mean, s to the SD and n to the number of study participants in each group.

$$U-u=s/\sqrt{n)^2}$$

When $P < 0.05$ was considered significant. Sensitivity analysis was used to find potential sources of significant heterogeneity.

Results

Study selection process

The electronic search originally identified 26 citations. Seventeen studies were excluded after reading the title and abstract. For the remaining nine we screened the full text, and eventually, four studies[19-22] involving 180 patients were included. The included studies involved 98 patients in the FS group and 81 patients in the TXA group. All included studies were published between 2011 and 2019. Participant numbers ranged from 40 to 54. The characteristics of the included studies are shown in Table 1. 10ml topical FS was applied in two studies. The application of FS in two other studies includes 2 mL was sprayed after prosthesis was implanted and 2 mL after fascia lata closure and one 10 mL fibrin sealant was applied prior to closure of the arthrotomy. The application of TXA is different in the included studies, including 10mg/kg intravenous TXA at the start of the surgical procedure, 1 mg TXA intravenously on induction of anesthesia, 1 g of IV TXA prior to skin incision and 1 g of topical TXA at the end of the surgery. Two studies applied general anesthesia, while another study applied intra-spinal anesthetic.

Risk of bias assessment

All included studies provided clear inclusion and exclusion criteria. In two[20-21] of the included RCTs, the randomization allocation was generated from a computer and random number table. Jordan *et al.*[21] provided details of the double blinding for intervention and the blinding of clinical investigators. A summary of methodological quality assessment is provided in Figure 2. Each risk of bias item is presented as a percentage in all the included studies, and the proportion of each risk of bias item at different levels is given in Figure 3. For the two non-RCTs, the MINORS scores were 20 and 18. The methodological quality assessment is shown in Table 2.

Total calculated blood loss

Data of total calculated blood loss was provided in three studies[19,21-22]; the pooled outcomes demonstrated that there were no significant differences between the FS group and the TXA group during THA [WMD = -86.22, 95% CI (-99.13, -73.31), $P < 0.00001$, $I^2 = 96\%$, Fig. 3] in the presence of statistical heterogeneity ($I^2 = 95\%$).

Postoperative hemoglobin level

The data of postoperative hemoglobin level was reported in three studies[20-22]. The current meta-analysis showed that there was a significant difference in postoperative hemoglobin level between the FS group and the TXA group during the THA [WMD = -0.47, 95% CI (-0.74, -0.21), $P = 0.0005$, $I^2 = 3\%$, Fig. 4]. Moreover, There was little statistical heterogeneity ($I^2 = 3\%$).

Blood transfusion rate

Blood transfusion rate data were provided in three studies[20-22]. The meta-analysis demonstrated that there were no significant differences in blood transfusion rate [RD = -0.12, 95% CI (-0.23, -0.00), $P = 0.05$, $I^2 = 74\%$, Fig. 5] between the two groups in the absence of statistical heterogeneity ($I^2 = 74\%$).

Postoperative complication rate

Three studies[19,21-22] were available with information regarding postoperative complications. The pooled results demonstrated that topical FS was associated with the same rate of postoperative complications as TXA administration [RR = 0.98, 95% CI (-99.13, -73.31), $P = 0.45$, $I^2 = 0\%$ Fig. 6]. There was little statistical heterogeneity ($I^2 = 0\%$).

Discussion

The most important finding of this meta-analysis was that patients undergoing THA who received topical application of FS had higher blood transfusion rates and sustained lower hemoglobin levels compared with application of TXA in the early postoperative period. However, the total calculated blood loss showed no significant differences between the two groups. Furthermore, our meta-analysis demonstrated that there was no significant difference in the rate of complications between the topical FS group and the TXA group during the THA.

TXA has been widely used to reduce blood loss and transfusion rates in THA and TKA[23-24]. Moreover, several clinical trials and meta-analyses have demonstrated that topical FS is effective and safe in reducing blood loss and transfusion in hip and knee surgery[25-27]. A previous meta-analysis compared the effect of topical FS and intravenous administration of TXA on blood loss after TKA, and its pooled results indicated that TXA use resulted in a significantly lower incidence of blood transfusion and higher hemoglobin level. However, there was no significant difference in blood loss or in the rate of complications between the two groups. Whether the two pharmacological interventions have the same results in THA as during TKA is still controversial. Several clinical trials on the application of topical FS and TXA in THA have been implemented[19-22]. Kearns *et al.*[22] concluded that the use of TXA significantly reduced blood-transfusion requirements and preserved higher hemoglobin levels in patients undergoing THA compared with topical FS. Mahmood *et al.*[20] conducted a clinical trial that obtained similar outcomes. In contrast, McConnell *et al.*[19] did not find a significant difference in blood loss or transfusion rate between FS and TXA groups. Our meta-analysis results indicated that there was a lower blood transfusion rate and a higher hemoglobin level in the TXA group.

Due to the large exposure of the surgical area and the activation of fibrinolysis, perioperative bleeding is a significant concern in major orthopedic surgery, which often results in anemia[28-30]. Acute anemia can lead to myocardial infarction and heart failure. Therefore, in order to reduce blood loss and improve safety during THA, the surgical significance of TXA is widely recognized, especially in joint replacement. A series of randomized clinical trials have been implemented to study the relative benefits and potential risks of using TXA. Severe anemia is frequently corrected by means of allogeneic blood transfusion. In the current meta-analysis, patients treated with TXA had higher postoperative hemoglobin levels than FS-treated patients. However, the current meta-analysis demonstrated that there was no significant difference in total blood loss between the two groups. The method used to calculate blood loss in the included studies was not the same, which may lead to the calculated blood loss differing from the actual amount. In the study by McConnell *et al.*[19] the method of blood loss calculation was chosen in light of previous work. The total blood loss consisted of swabs and suction drainage, which can lead to substantial underestimation of the actual loss. Whether a blood transfusion is required depends on the postoperative hemoglobin level[31]. We believe that the higher requirements for blood transfusion in patients treated with FS were associated with lower postoperative hemoglobin levels. Mahmood *et al.*[20] and Jordan *et al.*[22] reported that the use of TXA can reduce the total amount of blood loss in patients undergoing THA compared to the application of FS, although the difference was not statistically significant. Nevertheless, the outcome of one included study[21] indicated that blood loss was significantly reduced in the group receiving TXA compared to the group receiving FS. Mahmood *et al.*[19] reported that 2 mL of FS was sprayed around the short external rotators after the prosthesis was implanted and the hip reduced, and a further 2 mL in superficial layers after fascia lata closure in the FS group. However, patients treated with TXA received 1 mg TXA intravenously on induction of anesthesia. Obviously, different methods were used to apply the hemostatic measures and calculate total blood loss, which may be one reason why no significant reduction in blood loss was observed in the patients receiving TXA compared with those patients receiving FS.

Perioperative complications in THA include deep vein thrombosis (DVT), pulmonary embolism (PE), wound infection, hematoma, periprosthetic fracture, and dislocation. Generally speaking, DVT and PE are common postoperative complications and can even lead to the risk of death in TKA and THA[32]. In our study, we were unable to carry out a meta-analysis of the incidence of DVT and PE owing to the small sample size and insufficient data, but only performed a meta-analysis of the overall complication rate. We found no significant difference in the complication rate between the group receiving TXA compared with the group receiving FS. Moreover, numerous studies and meta-analyses have indicated that topical FS or intravenous/topical administration of TXA does not increase the prevalence of DVT or PE during THA[27,33-36]. Wound infection is also a complication of THA, and in spite of the low prevalence of infection, it is a devastating complication. However, due to the small sample size and insufficient data in the included study, we could not conduct a meta-analysis to draw an exact conclusion. Moreover, subgroup analyses of the different complications were not carried out owing to the lack of sufficient data required for further confirmation.

There were several limitations to this meta-analysis: (1) two of the included studies were non-RCTs. As we all know, due to the large selection bias of non-RCTs, our meta-analysis result may involve a great deal of heterogeneity.(2) The included studies were not the same in terms of surgical time, technique, methods of intervention, and postoperative measures. (3) Due to the small sample size and insufficient data of each primary study, as well as the significant heterogeneity in postoperative hemoglobin decline and complication rate, we did not carry out subgroup analysis to draw a firm conclusion. (4) The endpoints for evaluating the efficacy of THA, including duration of hospital stay, functional scores, rehabilitation, range of motion, cost and postoperative swelling, were not analyzed because these data were not included in each primary study. (5) Due to the limitation of retrospective studies, the outcome may have a less robust analysis. (6) There was publication bias.

Conclusions

TXA administration appeared to be associated with lower transfusion rate and higher hemoglobin levels compared with topical FS for blood management in patients undergoing THA. The topical application of FS and TXA administration have a similar effect in decreasing blood loss without increasing the risk of complications, including DVT, PE and wound infection. However, due to the limitations of the included studies, larger, high-quality RCTs are required to draw confident conclusions from the findings of the current meta-analysis.

Declarations

Ethics approval and consent to participate

This is a meta-analysis, There is no relevant problems exist.

Consent for publication

Not applicable.

Availability of data and material

Supporting data is available.

Competing interests

Both authors declare that they have no competing interests

Funding

Not applicable.

Authors' contributions

DB designed the study and developed the retrieval strategy. DB and FYY searched and screened the summaries and titles. FYY drafted the article. All authors read and approved the final draft.

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Tables

Table 1. The characteristics of included studies

Study	Cases (F/T)	Study type	Male patients (F/T)	Anesthesia	FS Group	TXA Group	Outcome measures
McConnell 2011	22/22	RCT	5/7	Regional-general	10 mL of topical FS	10mg/kg intravenous TXA at the start of the surgical procedure	☐☐
Mahmood 2017	100/100	CCT	40/51	general anesthesia	2 mL was sprayed after prosthesis was implanted and 2 mL after fascia lata closure.	1 mg TXA intravenously on induction of anesthesia	☐☐☐☐
Kearns 2017	80/80	CCT	36/30	NR	one 10 mL fibrin sealant was applied prior to closure of the arthrotomy.	1 g of IV TXA prior to skin incision	☐☐☐☐
Jordan 2019	56/52	RCT	14/11	intra-spinal anesthetic	10 ml of FS	1 g of topical TXA at the end of the surgery	☐☐☐☐

☐ total calculated blood loss; ☐ postoperative hemoglobin level; ☐ blood transfusion rate; ☐ postoperative complications.

F: fibrin sealant group; T: tranexamic acid group; FS = fibrin sealant; TXA = tranexamic acid; RCT: randomized controlled trial; CCT: case control trial, NR = no report.

Table 2. Quality assessment for non-randomized trials

Quality assessment for non-randomized trials	Mahmood 2017	Kearns 2017
A clearly stated aim	2	2
Inclusion of consecutive patients	2	2
Prospective data collection	0	0
Endpoints appropriate to the aim of the study	2	2
Unbiased assessment of the study endpoint	2	0
A follow-up period appropriate to the aims of study	2	2
Less than 5% loss to follow-up	2	2
Prospective calculation of the sample size	0	0
An adequate control group	2	2
Contemporary groups	0	0
Baseline equivalence of groups	2	2
Adequate statistical analyses	2	2
Total score	18	16

Figures

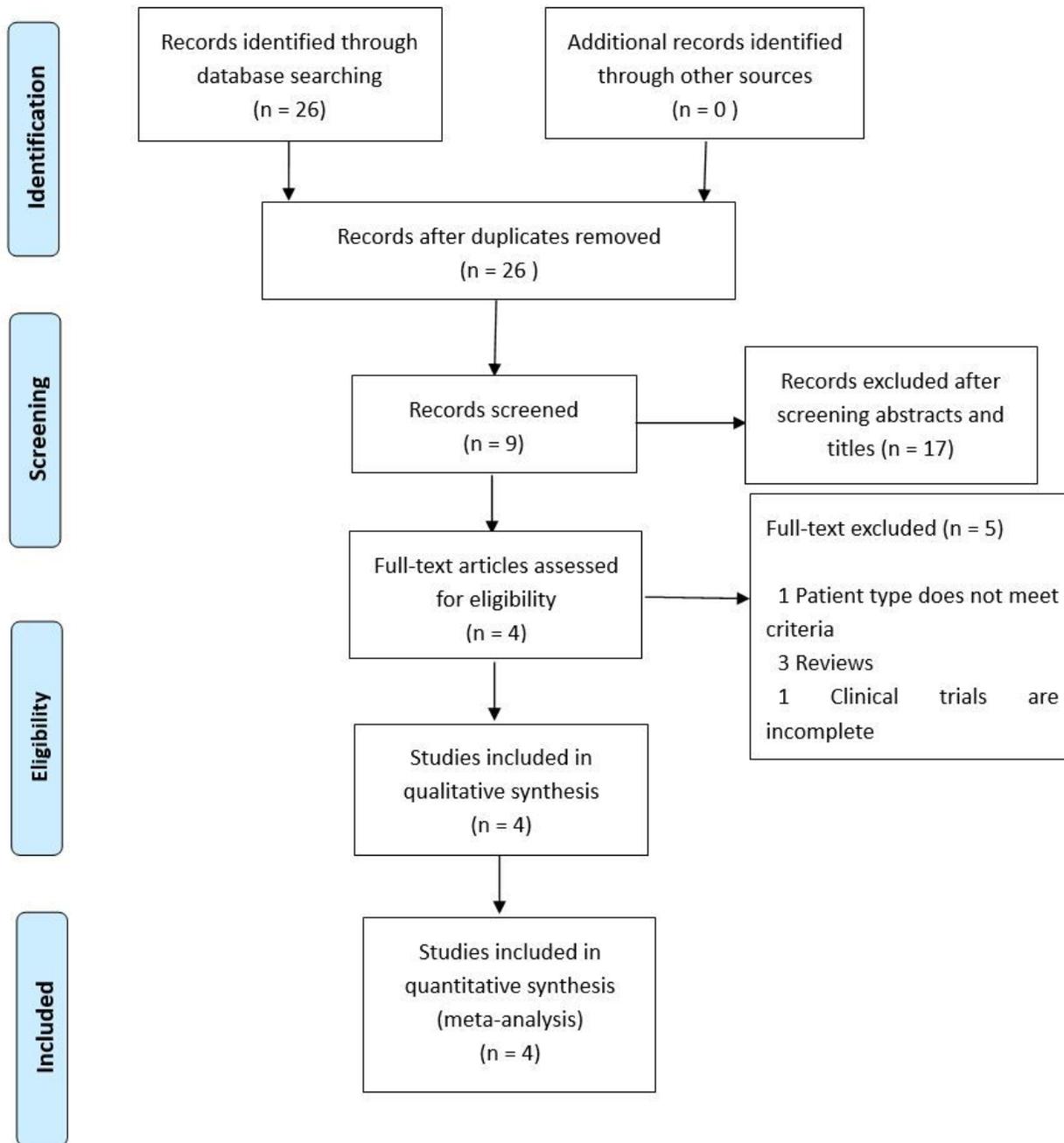


Figure 1

Flowchart of literature screening

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Jordan 2019	+	+	+	+	+	+	?
McConnell 2011	+	+	+	+	+	+	?

Figure 2

Methodological quality of the randomized controlled trials

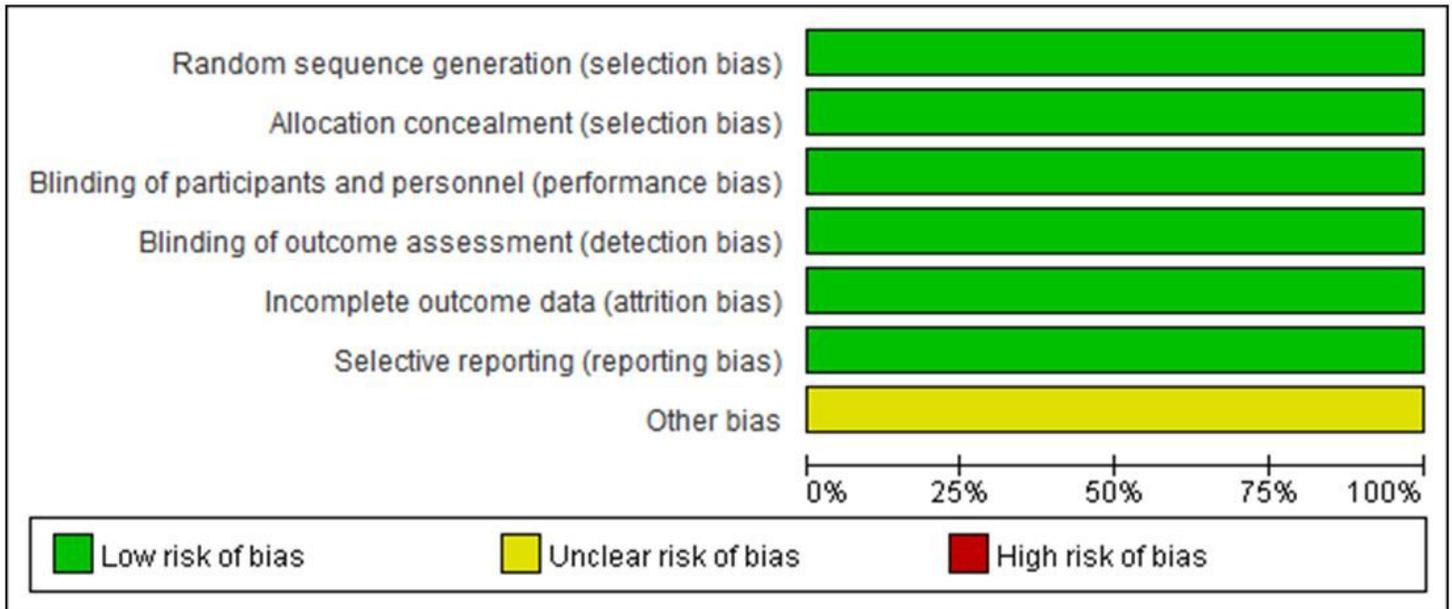


Figure 3

Risk of bias

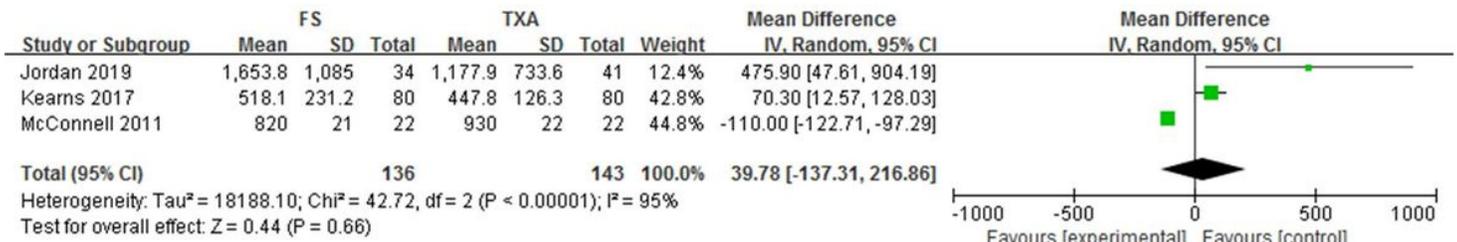


Figure 4

Meta-analysis for the comparison of total blood loss between the two groups.

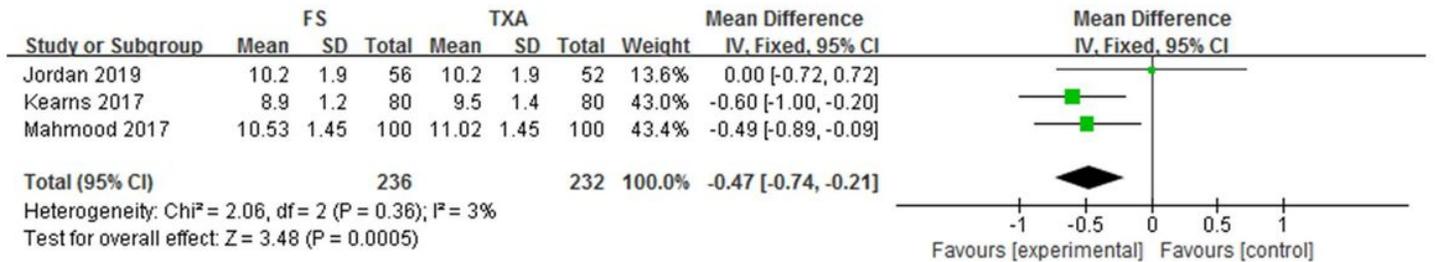


Figure 5

Meta-analysis for the comparison of postoperative hemoglobin level between the two groups.



Figure 6

Meta-analysis for the comparison of the blood transfusion rate between the two groups.



Figure 7

Meta-analysis for the comparison of postoperative complication rate between the two groups.

Supplementary Files

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