

# The efficacy and safety of anti-fibrinolytic agents in blood management following peri-acetabular osteotomy

## A meta-analysis

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### Abstract

**Background:** Blood management after peri-acetabular osteotomy (PAO) has become a serious problem. We performed a meta-analysis to evaluate the efficacy and safety of antifibrinolytics for blood management after PAO.

**Methods:** PubMed, OVID, Embase, ScienceDirect, and Web of Science were searched up to January, 2018 without restrictions on publication date and language. We also searched the relevant publication sources. The research was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. Randomized controlled trials (RCTs) and non-RCTs were included in our study. Weighted mean differences, risk difference, and 95% confidence intervals were calculated. We assessed statistical heterogeneity for each outcome with the use of a standard chi-square test and  $I^2$  statistic. The data were extracted by 2 of the co-authors independently and were analyzed by RevMan5.3. Primary outcomes were total blood loss, postoperative hemoglobin decline, and transfusion rates. Secondary outcomes were length of a hospital stay and postoperative complications.

**Results:** Four studies including 1 RCT and 3 non-RCTs were included in our study. The present meta-analysis indicated that antifibrinolytics was associated with a significant reduction of the total blood loss, postoperative hemoglobin decline, transfusion rates, and length of a hospital stay compared with control groups. No significant differences were identified in terms of the incidence of postoperative complications.

**Conclusion:** Intravenous antifibrinolytics was efficacious in reduction of total blood loss, postoperative hemoglobin decline, and length of a hospital stay after PAO without increasing the risk of thromboembolic complications. More high-quality RCTs with long follow-up period were necessary for proper comparisons of the efficacy and safety of antifibrinolytics with placebo.

**Abbreviations:** DVT = deep vein thrombosis, PAO = peri-acetabular osteotomy, PE = pulmonary embolism, RCTs = randomized controlled trials.

**Keywords:** aminocaproic acid, blood loss, meta-analysis, peri-acetabular osteotomy, tranexamic acid

## 1. Introduction

Peri-acetabular osteotomy (PAO) is a successful surgical procedure for the treatment of symptomatic hip dysplasia, which is mainly performed on young patients.<sup>[1]</sup> However, PAO is associated with substantial perioperative bleeding due to a series of pelvic osteotomies around the acetabulum, which increases morbidity.<sup>[2]</sup> It was reported that total blood loss could be up to 4 L.<sup>[3]</sup> Blood management has become a serious problem. Various

methods have been tried to minimize the perioperative blood loss including minimal invasive procedures, controlled hypotensive anesthesia, and the use of various blood-salvaging techniques<sup>[4,5]</sup>; however, allogeneic transfusion rate was reported as high as 82%.<sup>[6]</sup>

Antifibrinolytic agents such as tranexamic acid and amidocaproic acid were well-documented for reducing perioperative blood loss, and were widely used in various surgical procedures including cardiac, orthopaedic, and general surgery.<sup>[7-9]</sup> These drugs can block the binding sites of the enzymes or plasminogen and thus stop plasmin formation.<sup>[10,11]</sup> Guerreiro et al<sup>[12]</sup> reported intravenous tranexamic acid reduced intraoperative and postoperative blood loss and thus reduced the need of allogenic blood transfusion in total knee arthroplasty. Sucher et al<sup>[13]</sup> indicated that intraoperative use of aminocaproic acid did not appear to increase the risk of postoperative complication in total hip arthroplasty. Compared with total joint arthroplasties, PAO was associated with more blood loss and higher transfusion rates. However, only small numbers of the articles have focused on the antifibrinolytic agents for blood management after PAO. No guideline for blood management has been proposed, and standardized blood conservation protocols remains controversial. Therefore, we performed a systematic review and meta-analysis to evaluate the efficacy and safety of antifibrinolytics for blood management after PAO. The purpose of the study was to determine whether antifibrinolytics was associated with the

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The authors declare that they have no competing interests.

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following: less total blood loss; less hemoglobin decline; fewer blood transfusion rates; and increased risk of thromboembolic complications compared with the control groups.

## 2. Materials and methods

Ethical approval for this study was deemed unnecessary because it was a review of existing literature and did not involve any handling of individual patient's data.

### 2.1. Search methodology

Two reviewers independently searched PubMed, OVID, Embase, ScienceDirect, and Web of Science. All databases were searched up to January, 2018, without restrictions on publication date and language. The following terms were used to search the databases: "hip dysplasia," "peri-acetabular osteotomy," "aminocaproic acid OR tranexamic acid," and "blood loss OR transfusion." Search terms were combined using the Boolean operators "AND" or "OR." Reference lists of relevant articles were manually searched to identify additional trials.

### 2.2. Inclusion and exclusion criteria

Studies were considered eligible when they met following criteria: published clinical randomized controlled trials (RCTs) and non-RCTs; patients undergoing PAOs, intervention groups received intravenous infusion of antifibrinolytic agents for blood management and control group received placebo or nothing; studies with at least 1 of the following outcomes: total blood loss, postoperative hemoglobin decline, transfusion rates, length of a hospital stay, and postoperative complications such as infection, deep venous thrombosis (DVT), or pulmonary embolism (PE). Studies would be excluded from present meta-analysis for incomplete data, case reports, conference abstract, or review articles.

### 2.3. Study selection

Two investigators independently selected articles according to the criteria described above. The full text was scanned to determine whether articles fit the inclusion criteria. We resolved disagreements by discussion until a consensus was reached. If no consensus was reached, a third investigator was consulted.

### 2.4. Data extraction

Two investigators independently extracted the data from the eligible studies that met the inclusion criteria. A double-check procedure was performed to test the accuracy of the extracted data. The information extracted from the studies were as follows: first author names, publishing year, study design, sample size, age, sex, intervention of each groups, transfusion trigger, duration of follow-up, and outcomes measures. Primary outcomes were total blood loss, postoperative hemoglobin decline, and transfusion rates. Secondary outcomes were length of a hospital stay and postoperative complications. Corresponding authors were consulted to obtain incomplete outcome data.

### 2.5. Data analysis

We performed all meta-analysis using the Revman5.3 software. For continuous outcomes, the number of patients, means, and standard deviations were pooled to a weighted mean difference (WMD) and a 95% confidence interval (CI). For dichotomous

outcomes, the risk difference (RD) and the 95% CI were assessed. The assessment for statistical heterogeneity was calculated using the chi-square and  $I^2$  tests. A fixed-effects model was used when  $I^2 < 50\%$  and  $P > .05$ ; otherwise, the random-effects model was adopted. Because no more than 10 studies were included in the meta-analysis, publication bias was not detected.

### 2.6. Quality assessment

A quality assessment of each RCT was performed according to the Cochrane Handbook for Systematic Reviews of Interventions. Two authors independently evaluated the risk of bias of the included RCTs based on the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias.

The Methodological Index for Non-Randomized Studies (MINORS) scale was used to assess non-RCTs with scores ranging 0 to 24. A reviewer author was the adjudicator when no consensus can be reached.

The evidence grade was assessed using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group including the following items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The recommendation level of evidence was classified into the following categories: high, which means that further research is unlikely to change confidence in the effect estimate; moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate; low, which means that further research is likely to significantly change confidence in the effect estimate and to change the estimate; and very low, which means that any effect estimate is uncertain. GRADE pro Version 3.6 software is used for the evidence synthesis.

## 3. Results

### 3.1. Search result

A total of 422 studies related to antifibrinolytics and PAO were reviewed. After reading the titles and abstracts, 418 studies were excluded from the present meta-analysis. One RCT<sup>[14]</sup> and 3 non-RCTs<sup>[15-17]</sup> which were published between 2015 and 2016 eventually satisfied the eligibility criteria for this study. There were 210 participants in the intervention groups and 201 patients in the control groups. The search process was conducted as presented in Fig. 1.

### 3.2. Study characteristics

The sample size ranged from 85 to 137 and average age ranged from 24 to 32 years. In these studies, the intervention groups received intravenous antifibrinolytics for blood management and the control groups received no antifibrinolytics. General guidelines for postoperative blood transfusion were based on the postoperative hemoglobin level and clinical signs of symptomatic anemia. Duration of follow-up ranged from 1 to 4 months. Every patient received standard antifibrinolytic therapy which was described in Table 1.

### 3.3. Risk of bias

Seven aspects of the RCT related to the risk of bias were assessed, following the instructions in the Cochrane Handbook for Systematic Reviews of Interventions (Table 2). Wingerter

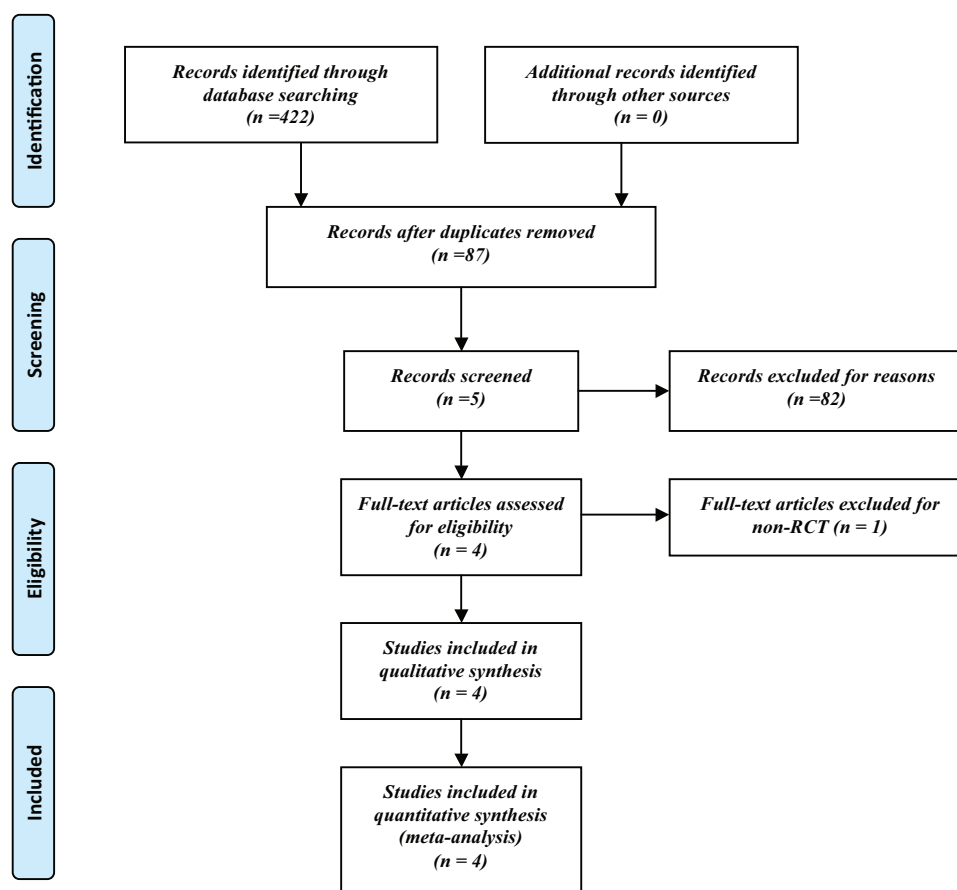


Figure 1. Flow diagram showing details of literature search.

et al<sup>[14]</sup> performed randomization from computers and used sealed envelopes for allocation concealment. Double blinding to the surgeons and participants was reported; however, assessor was not blinded. Low risk of bias due to incomplete outcome data was detected. The MINORS scale was used to assess non-RCTs by assigning scores ranging from 0 to 24, which was shown in Table 3.

### 3.4. Outcomes for meta-analysis

**3.4.1. Total blood loss.** All studies<sup>[14–17]</sup> reported the total blood loss after PAO. Statistical heterogeneity was observed in our study ( $\chi^2=8.05$ ,  $df=3$ ,  $I^2=62.7\%$ ,  $P=.000$ ); therefore, a random-effect model was applied. We found that there was significant difference between the antifibrinolytic groups and control groups regarding the total blood loss (WMD =  $-311.01$ , 95% CI  $-478.56$  to  $-143.46$ ,  $P=.0003$ ; Fig. 2).

**3.4.2. Hemoglobin decline.** All studies<sup>[14–17]</sup> showed the postoperative hemoglobin decline after PAO. There was significant heterogeneity ( $\chi^2=9.92$ ,  $df=3$ ,  $I^2=69.8\%$ ,  $P=.019$ ); therefore, a random-effects model was adopted. The result of meta-analysis indicated that there was significant difference between 2 groups regarding the postoperative hemoglobin decline (WMD =  $-0.437$ , 95% CI  $-0.709$  to  $-0.165$ ,  $P=.002$ ; Fig. 3).

**3.4.3. Transfusion rates.** Transfusion rates after PAO were reported in all studies.<sup>[14–17]</sup> There was no significant heterogeneity ( $\chi^2=3.36$ ,  $df=3$ ,  $I^2=10.6\%$ ,  $P=.340$ ) and a fixed-effects

model was used. The present meta-analysis revealed that there was significant difference between 2 groups in terms of transfusion rates (RD =  $-0.240$ , 95% CI  $-0.314$  to  $-0.165$ ,  $P=.000$ ; Fig. 4).

**3.4.4. Length of a hospital stay.** All studies<sup>[14–17]</sup> reported the length of a hospital stay. A fixed-effects model was adopted because no significant heterogeneity was identified ( $\chi^2=4.37$ ,  $df=3$ ,  $I^2=31.3\%$ ,  $P=.224$ ). Significant difference in the length of a hospital stay was found between the 2 groups (WMD =  $-0.222$ , 95% CI  $-0.439$  to  $-0.005$ ,  $P=.045$ ; Fig. 5).

**3.4.5. Incidence of venous thromboembolism.** All studies<sup>[14–17]</sup> showed the postoperative thromboembolic complications including DVT and PE. A fixed-effect model was adopted. There was no significant difference between groups regarding the incidence of venous thromboembolism (Fig. 6).

**3.4.6. Subgroup analysis.** Subgroup analysis was performed according to the type of the included studies. The pooled results indicated that intravenous antifibrinolytics can reduce total blood loss, hemoglobin decline, transfusion rates, and length of stay after PAO (Fig. 7).

## 4. Discussion

To the best of our knowledge, this was the first meta-analysis to evaluate the efficacy and safety of intravenous antifibrinolytics for reducing perioperative blood loss and transfusion rates after

**Table 1**  
Trials characteristics.

Author	Study design	Surgical type	Cases (E/P)	Mean age (E/P)	Male patient (E/P)	Experiential group	Control group	Blood transfusion trigger	Follow-up
Wassilew et al, 2015 <sup>[17]</sup>	Non-RCT	PAO	48/48	27/32	6/6	A continuous infusion of TXA at a rate of 10 mg/kg/h	No-TXA	A hemoglobin level ≤80 g/L	4 mos
Wingerter et al, 2015 <sup>[14]</sup>	RCT	PAO	44/41	27/28	6/9	1 g TXA infused intravenously during 10 min before skin incision and an additional 1 g intravenously at wound closure	No-TXA	A hematocrit ≤26%	2 mos
Bryan et al, 2016 <sup>[16]</sup>	Non-RCT	PAO	68/69	24/28	10/12	Intravenous TXA 1 g at the time of incision and 1 g at the time of closure	No-TXA	A hemoglobin level ≤70 g/L	2 mos
McLawnhorn et al, 2016 <sup>[15]</sup>	Non-RCT	PAO	50/43	24/25	3/1	Intravenous EACA 10 g over 30 min followed by 5 g over 3 h	No-EACA	A hemoglobin level ≤70 g/L	1 mo

E=experiential, EACA=epsilon-aminocaproic acid, P=placebo, PAO=periacetabular osteotomy, RCT=randomized controlled trial, TXA=tranexamic acid.

PAO. The most important finding of the present meta-analysis was that intravenous antifibrinolytics was associated with a significant reduction in total blood loss, hemoglobin decline, transfusion rates, and length of a hospital stay compared with controls. Additionally, no increased risk of the postoperative complications was found.

Blood management after PAO has become a serious clinical problem. This was of great importance because now PAO was more commonly performed with concomitant procedures to correct associated intra-articular pathology. Atwal et al<sup>[2]</sup> reported an average total blood loss of 2191 mL in PAOs. Pulido et al<sup>[5]</sup> showed that 20% of patients required allogeneic

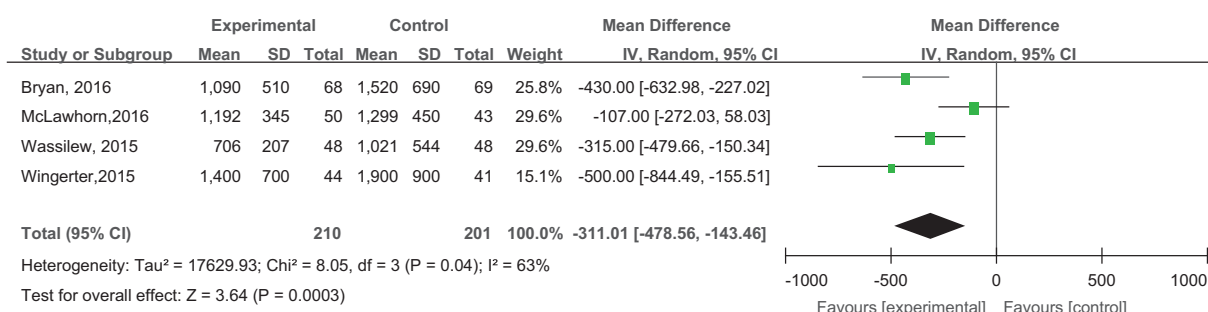
**Table 2**  
Methodological quality of the randomized controlled trials.

	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
Wingerter, 2015	+	+	+	?	+	?	?

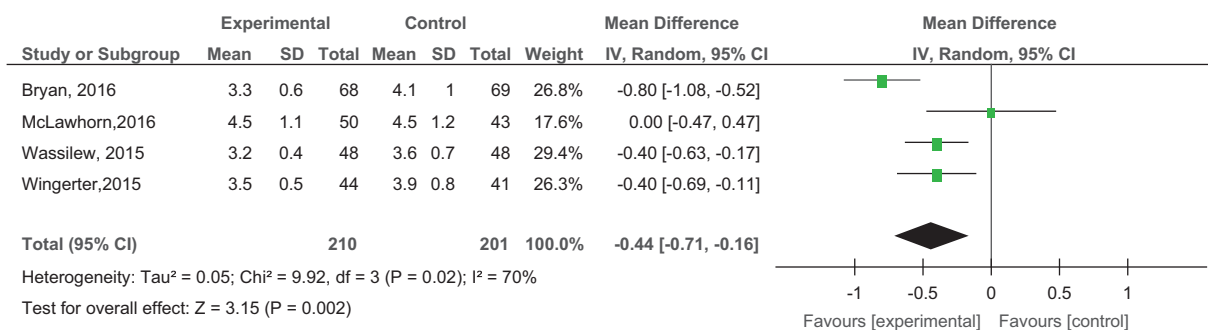
**Table 3**

**Methodological quality of the included non-RCT.**

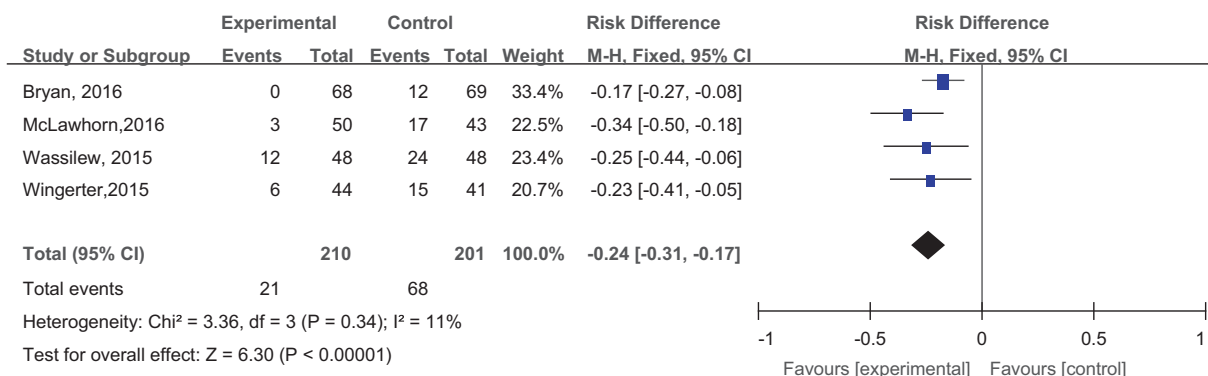
Quality assessment for nonrandomized trials	Wassilew et al, 2015 <sup>[17]</sup>	Bryan et al, 2015 <sup>[16]</sup>	McLawhorn et al, 2016 <sup>[15]</sup>
A clearly stated aim	2	2	2
Inclusion of consecutive patients	2	2	2
Prospective data collection	2	2	2
Endpoints appropriate to the aim of the study	2	2	2
Unbiased assessment of the study endpoint	0	0	0
A follow-up period appropriate to the aims of study	2	2	2
Less than 5% loss to follow-up	2	2	2
Prospective calculation of the sample size	2	2	1
An adequate control group	2	2	2
Contemporary groups	1	0	2
Baseline equivalence of groups	2	2	2
Adequate statistical analyses	2	2	2
Total score	21	20	21



**Figure 2.** Forest plot diagram showing effect of antifibrinolytics on total blood loss.



**Figure 3.** Forest plot diagram showing effect of antifibrinolytics on hemoglobin decline.



**Figure 4.** Forest plot diagram showing effect of antifibrinolytics on transfusion rates.

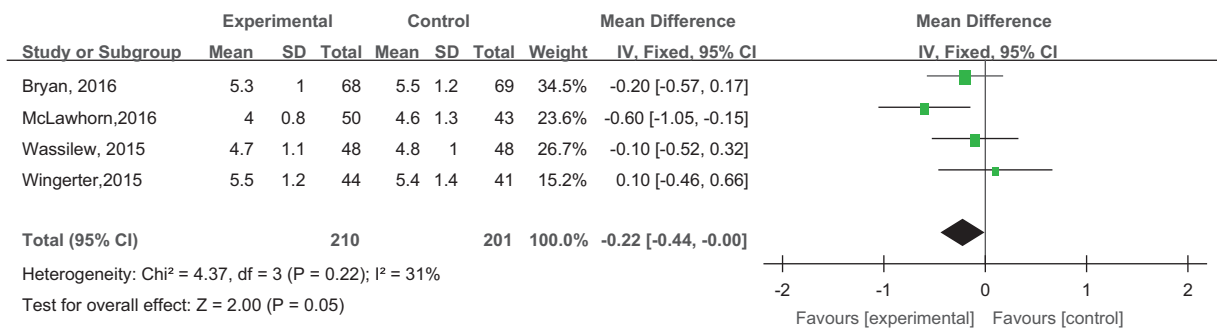


Figure 5. Forest plot diagram showing effect of antifibrinolytics on length of a hospital stay.

transfusion with an average transfusion amount of 2.14 units. The most dramatic single change has come with the introduction of antifibrinolytic medications. Clinical trials have reported that antifibrinolytic agents can block the interaction of plasminogen and plasmin by competing with the lysine residues on the surface of fibrin and inhibits fibrinolysis.<sup>[18]</sup> Previous meta-analysis have confirmed antifibrinolytics was associated with a worthwhile total blood loss and transfusion requirements without adverse effects for patients undergoing arthroplasties.<sup>[19,20]</sup> There was a higher volume of blood loss in PAO, and blood management was more serious and challenging compared with arthroplasties. It was reported that PAO was associated with a total blood loss ranging from 300 to 4500 mL.<sup>[2,21,22]</sup> Based on the previous experience and search for safe blood conservation strategies for

PAO, question was posed that if antifibrinolytics was effective in reducing blood loss and postoperative hemoglobin decline. Four articles with 452 patients were included in our study; the results of meta-analysis indicated that the use of intravenous antifibrinolytics led to a decreased total blood loss and hemoglobin decline.

Patients were often affected by postoperative anemia and associated with increasing mortality and morbidity. Previous study showed 20% allogeneic transfusion rate and an overall rate of 90% autologous transfusion for patients with PAO.<sup>[5]</sup> However, allogeneic blood transfusion was associated with several potential adverse effects including transmission of infection, anaphylactic reaction, and hemolysis.<sup>[23-25]</sup> Minimizing transfusion requirement facilitated recovery and reduced the

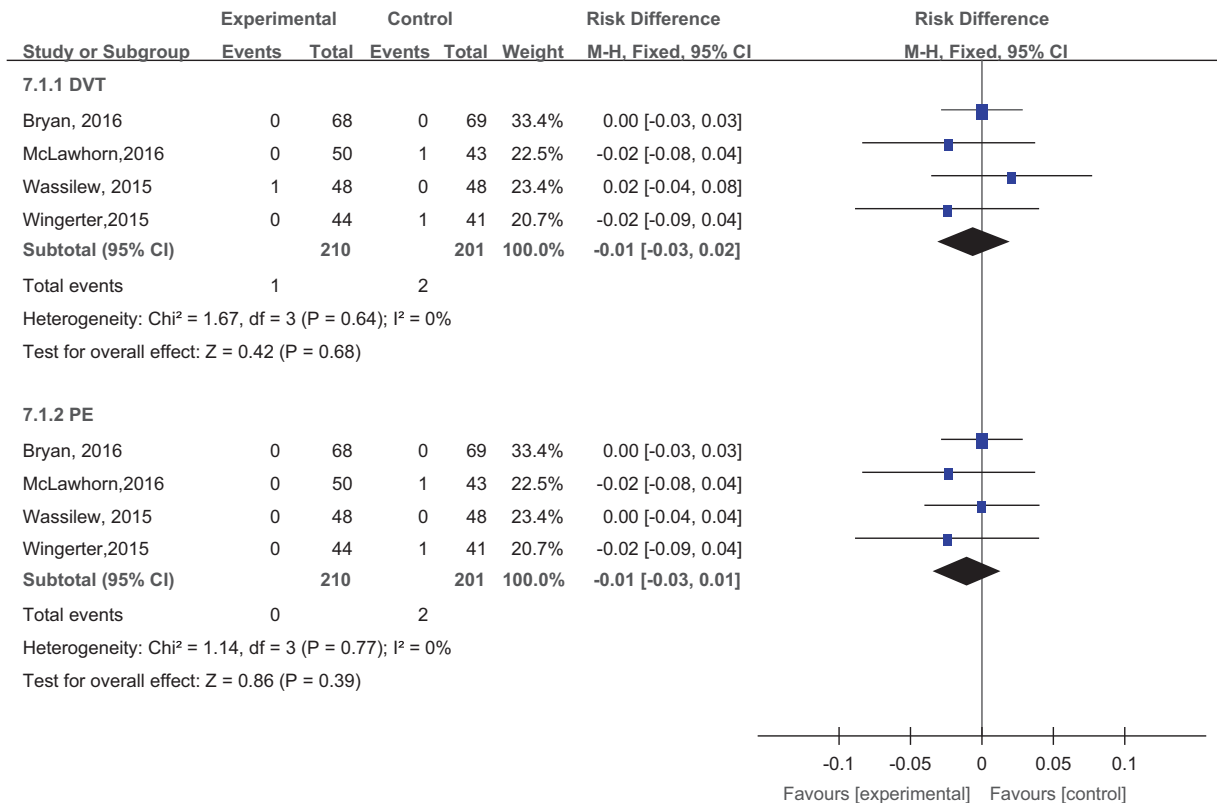


Figure 6. Forest plot diagram showing effect of antifibrinolytics on the risk of thromboembolic complications.

Variables	Studies (n)	Patients (n)	P	WMD or RD (95% CI)	Heterogeneity P-value (I <sup>2</sup> )	Model
Total blood loss						
Non-RCTs	3	326	0.003	-277.562[-460.33, -94.80]	0.04 (69%)	random
Hemoglobin decline						
Non-RCTs	3	326	0.03	-0.44[-0.83, -0.05]	0.008 (79%)	random
Transfusion requirements						
Non-RCTs	3	326	<0.01	-0.24[-0.32, -0.16]	0.18 (42%)	fixed
LOS						
Non-RCTs	3	326	0.02	-0.28[-0.52, -0.04]	0.24 (30%)	fixed

Figure 7. Subgroup analysis.

risk of complications. Use of antifibrinolytics has become a popular blood conservation strategy, especially in the field of orthopedics. However, there remains controversial regarding the use of antifibrinolytics for reducing the transfusion rates in patients undergoing PAO, and there is a requirement for an evidence base to help orthopedists make clinical decisions. Meta-analysis was used as the main statistical method in the study. It could strengthen statistical power and enlarge sample size by combining published articles. The present meta-analysis showed that the intravenous antifibrinolytics was associated with a significant reduction in the transfusion rates.

Blood sparing was not the only concern when evaluating the effectiveness of antifibrinolytics. Polkowski et al<sup>[26]</sup> reported that 2 of the 134 patients were diagnosed with clinical symptoms of DVT. There were no symptoms of PE. Zaltz et al<sup>[27]</sup> showed that the crude incidence of clinically symptomatic venous thromboembolism was 9.4 per 1000 procedures. A concern among surgeons using antifibrinolytic medication was a theoretical prothrombotic effect and increased risk of thromboembolic complications. Several published meta-analyses have shown that intravenous antifibrinolytics did not appear to increase the risk of DVT or PE in total joint arthroplasties.<sup>[28]</sup> Although no significant difference in thromboembolic events was found between groups, we acknowledged that the article was underpowered with respect to the safety outcomes. More multicenter RCTs with long-term follow-up were needed. Additionally, we found that antifibrinolytics was associated with a decreased length of hospital stay due to the -paring effects, and our research team recommended the use of antifibrinolytics. Further investigation should focus on the comparison of tranexamic acid and aminocaproic acid in PAO, and also the optimal dose.

Our meta-analysis has several potential limitations: we included non-RCTs with small sample size, which lowered the evidence level; methodological weakness existed in all included studies; functional outcome was not included in our study, due to the limited articles; no included studies showed the platelets count and INR among patients, which may affect our results; short-term follow-ups may lead to an underestimation of complications; and all included RCTs were English publications; thus, publication bias was unavoidable.

## 5. Conclusions

Intravenous antifibrinolytics was efficacious in reduction of total blood loss, postoperative hemoglobin decline, and length of a hospital stay after PAO without increasing the risk of thromboembolic complications. More high-quality RCTs with

long follow-up period were necessary for proper comparisons of the efficacy and safety of antifibrinolytics with placebo.

## Author contributions

Hongzhuan Tan designed the study. Zhaozhao Wu and Ying Liang collected the data and calculation. Mian Wang wrote the manuscript. All authors read and approved the final manuscript.

**Writing – original draft:** Mian Wang.

**Conceptualization:** Hongzhuan Tan.

**Data curation:** Zhaozhao Wu.

**Software:** Ying Liang.

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