


Peri-Articular Injection of Tranexamic Acid Reduce Blood Loss and Transfusion Requirement During Total Knee Arthroplasty: A Meta-analysis

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Abstract

Background: The aim of this meta-analysis was to evaluate the efficacy and safety of peri-articular injection of tranexamic acid (TXA) during total knee arthroplasty (TKA) from clinical controlled trials. **Method:** Eligible scientific articles published prior to October 2021 were retrieved from the PubMed, Springer, ScienceDirect and Cochrane Library databases. The statistical analysis was performed with RevMan 5.1. **Result:** 2 RCTs and 3 non-RCTs met the inclusion criteria. Meta-analysis showed significant differences in terms of hemoglobin reduction (MD = -1.04, 95% CI: -1.33 to -.76, $P < .00001$), total blood loss (MD = -342.80.70, 95% CI: -437.52 to -248.08, $P < .00001$), drainage volume (MD = -297.24, 95% CI: -497.26 to -97.23, $P = .004$) and blood transfusion rate (OR = .30, 95% CI: .14 to .62, $P = .001$) were found in the control group. No postoperative infection and deep venous thrombosis were found between 2 groups. **Conclusion:** Peri-articular injection of TXA can effectively decrease perioperative blood loss and blood transfusion rate without increasing the incidence of postoperative complications during TKA.

Keywords

total knee arthroplasty, tranexamic acid, peri-articular, injection, meta-analysis

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Introduction

Total knee arthroplasty (TKA) is a successful treatment to relieve pain and improve postoperative knee function.¹ However, substantial blood loss is associated with the surgical procedure, ranging from 1000 mL to 2000 mL.² It has been reported that 10-38% of patients require blood transfusion after TKA.³ Allogenic blood transfusions result in the risk of adverse effects and increase medical cost.⁴

Tranexamic acid (TXA) is a synthetic amino acid derivative that promotes hemostasis by competitively blocking the lysine-binding site of plasminogen.⁵ To date, administration of TXA has been well established in the literature to reduces blood loss and transfusion

requirements during TKA.^{6,7} Recently, a new local administration method of TXA, periarticular injection (PAI),

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was introduced. Mao et al⁸ reported that the direct injection of TXA solution into the soft tissue around the joint cavity that is vulnerable to postoperative bleeding is expected to decrease bleeding more effectively. Several studies⁹⁻¹² have reported that PAI of TXA effectively reduces blood loss and allogenic blood transfusions during TKA. However, whether PAI is safe and efficient in TKA remains controversial. Therefore, we performed a meta-analysis with a large sample to evaluate the efficacy and safety of PAI of TXA in TKA from clinical controlled trials.

Materials and Methods

Search Strategy

This meta-analysis was conducted in accordance with the relevant Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Potentially relevant scientific articles published from the inception of the electronic databases to October 2021 were retrieved from the PubMed, Springer, ScienceDirect and Cochrane Library databases. A final check that no relevant articles were missed was conducted by searching manually all references of included studies and by performing citation tracking on the included articles. There were no restrictions on language of publication. The keywords used for the search were “total knee arthroplasty”, “tranexamic acid” and “peri-articular”.

Inclusion Criteria

Studies were considered eligible for inclusion if they met the following criteria: (1) the patients were treated with primary TKA; (2) the experimental group was treated via the PAI of TXA and the control group was treated with placebo or null; (4) the clinical outcomes included hemoglobin reduction, total blood loss, postoperative drainage volume, blood transfusion requirements and postoperative complications; and (5) the study was a published comparative trial, including randomized controlled trials (RCTs) and non-RCTs. Two independent reviewers screened the titles and abstracts of all studies identified by the search strategy. A third reviewer resolved any disagreements.

Exclusive Criteria

We excluded articles that were (1) duplicate articles or articles having the same patients, content and results; (2) case reports, conference reports, theoretical research, systematic reviews, meta-analyses, expert comments, and economic analyses; and (3) studies whose outcomes that were not relevant.

Data Extraction

Predefined data collection form was developed to extract data from the eligible studies by 2 independent reviewers. The

following information was extracted: the author's name, publication date, the intervention measures, patient demographics and the outcome measures. Other relevant parameters were also extracted from the individual studies. Corresponding authors of included studies were contacted via email for relevant information if the available data were insufficient.

Quality Assessment

The methodological quality of the RCTs was assessed by the modification of the generic evaluation tool described in the Cochrane handbook for systematic reviews of interventions.¹³ The methodological quality of the non-RCTs was evaluated using the methodological index for non-randomized studies (MINORS).¹⁴

Data Analysis and Statistical Methods

The statistical analysis was performed using Review Manager 5.1 (The Cochrane Collaboration, Oxford, United Kingdom). Heterogeneity of the mean difference across studies was checked using the chi-squared test and I^2 statistic. If significant ($P < .1$ or $I^2 > 50\%$), a random effects model was used to estimate the overall effect sizes and a sensitivity analysis was performed to investigate the potential sources of heterogeneity. Otherwise, fixed-effects model was adopted. The continuous data are expressed as mean differences (MDs) and 95% confidence intervals (CIs). The odds ratio (OR) and 95% CIs were calculated for the dichotomous data.

Results

Search Results

A total of 53 studies were identified as potentially relevant literature reports. There were no additional studies identified through other sources. After carefully scanning the titles, 48 studies were excluded. Eventually, 3 non-RCTs and 2 RCTs and were eligible for data extraction and meta-analysis. The process of study selection was showed in [Figure 1](#).

Characteristics of the Included Studies

The detailed characteristics of included studies are presented in [Table 1](#). In each study, the baseline characteristics of the 2 groups were similar. A placebo (normal saline) was given in 1 trial, and 4 studies reported that the control group were null.

Risk of Bias Assessment

The methodological quality of the RCTs were displayed in [Figure 2](#). The inclusion and exclusion criteria were clearly

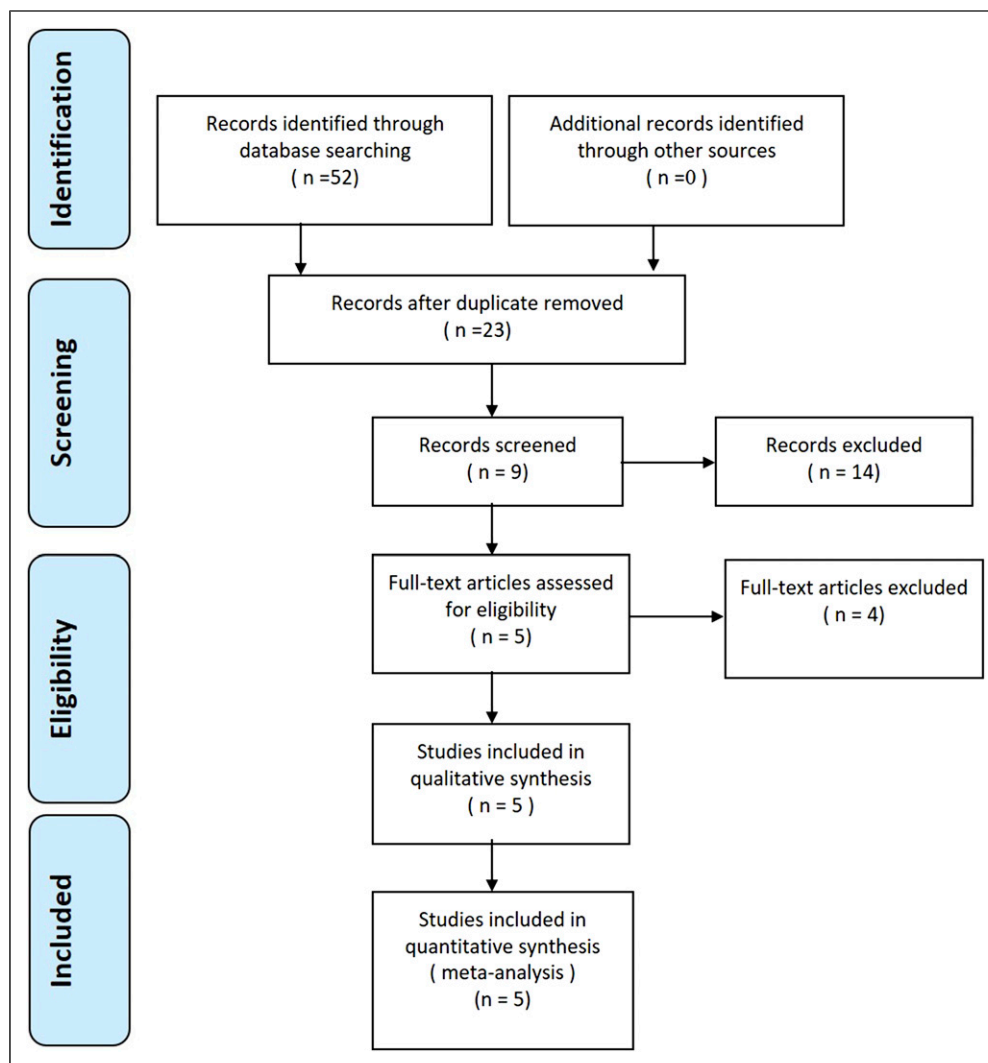


Figure 1. Flowchart of the study selection process.

Table 1. Characteristics of included studies.

Author	Group	Cases (n)	Mean Age (year)	Female (n)	Dosage	DVT prophylaxis
Hirose 2019	TXA	44	75.1±7.9	31	25 mg/mL	NS
	C	44	73.0±10.9	34		
Mao 2016	TXA	49	68.5±7.4	41	2g	Rivaroxaban
	C	42	69.6±5.7	32		
Pinsornsak 2021	TXA	36	65.6±7.5	34	15 mg/kg	Aspirin
	C	36	68.6±7.4	32		
Yozawa 2018	TXA	44	75.1±7.9	31	25 mg/mL	NS
	C	44	73.0±10.9	34		
Zhang 2019	TXA	53	66	37	1g	LMWH
	C	55	68.5	43		

TXA: tranexamic acid, C: control, DVT: deep venous thrombosis, LMWH: low molecular weight heparin, NS: not state.

	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
Pinsornsak 2021	+	+	+	+	+	+	+
Zhang 2019	+	+	+	+	+	+	+

Figure 2. The summary of bias risk of randomized controlled trials.

described in all RCTs. All included RCTs reported methodology for randomization, concealment of allocation and blinding. Unclear bias was not reported due to incomplete outcome data or selective outcomes. All included non-RCTs were evaluated by the MINORS, and their scores ranged from 20 to 22 (Table 2).

Outcomes of the Meta-analysis

Hemoglobin reduction. Hemoglobin reduction was documented in 3 studies. Present meta-analysis demonstrated that the hemoglobin drop in the PAI group was lower than that in the control group (MD = -1.04 , 95% CI: -1.33 to $-.76$; $P < .00001$; Figure 3).

Total Blood Loss

Four studies stated total blood loss. Present meta-analysis demonstrated that total blood loss in the PAI

group was lower than that in the control group (MD = -342.80 , 95% CI: -437.52 to -248.08 ; $P < .00001$; Figure 4).

Drainage Volume

Drainage volume was assessed in 2 studies. Present meta-analysis demonstrated that the drainage volume in the PAI group was lower than that in the control group (MD = -297.24 , 95% CI: -497.26 to -97.23 ; $P = .004$; Figure 5).

Blood Transfusion Rate

Three studies reported postoperative blood transfusion rate. Present meta-analysis demonstrated that the blood transfusion rate in the PAI group was lower than that in the control group (OR = $.30$, 95% CI: $.14$ to $.62$; $P = .001$; Figure 6).

Table 2. Quality assessment for non-randomized trials.

Quality Assessment for Non-randomized Trials	Hirose 2019	Mao 2016	Yozawa 2018
A clearly stated aim	2	2	2
Inclusion of consecutive patients	2	2	2
Prospective data collection	2	0	2
Endpoints appropriate to the aim of the study	2	2	2
Unbiased assessment of the study endpoint	2	2	2
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	0	0	0
An adequate control group	2	2	2
Contemporary groups	2	2	2
Baseline equivalence of groups	2	2	2
Adequate statistical analyses	2	2	2
Total score	22	20	22

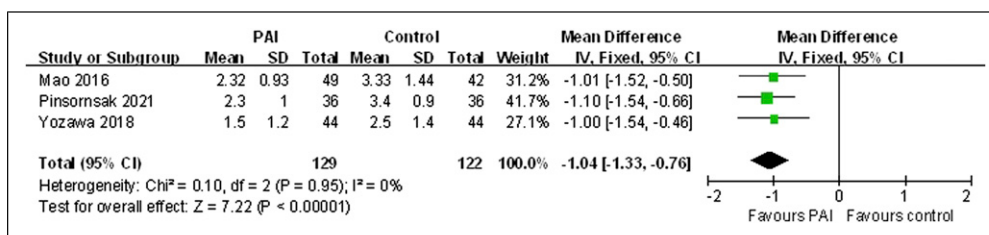


Figure 3. Forest plot showing hemoglobin drop.

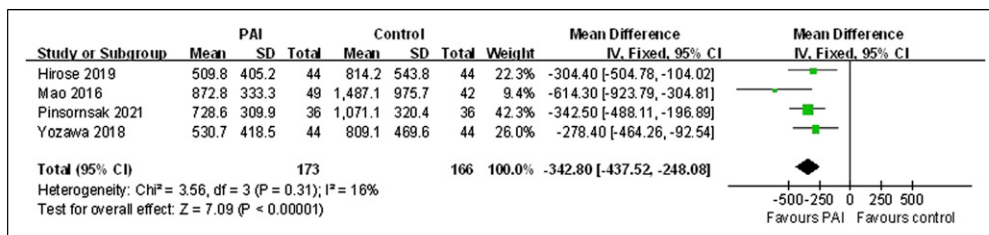


Figure 4. Forest plot showing total blood loss.

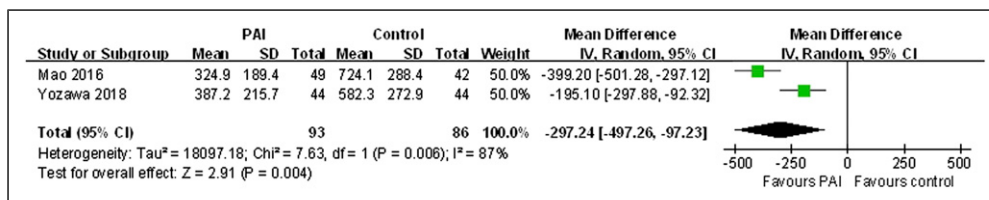


Figure 5. Forest plot showing drainage volume.

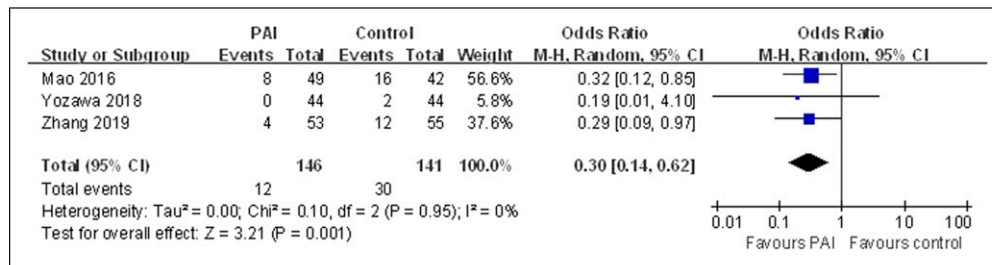


Figure 6. Forest plot showing blood transfusion requirement.

Other Outcomes

All included studies reported that none of the patients had symptomatic DVT postoperatively. Four of included studies reported that there was no infection in 2 groups.

Discussion

The most important finding of current meta-analysis was that PAI of TXA during TKA would reduce total blood loss, hemoglobin reduction, blood transfusion rate and drainage volume without increasing risk incidence of infection or DVT. Furthermore, no TXA-related adverse effect was discovered. To our knowledge, the present study is the first quantitative meta-analysis to evaluate the efficacy and safety of PAI of TXA during TKA.

Reducing perioperative blood loss during TKA is 1 of the most important goals today to accelerate patients' recovery. TXA was reported to effectively reduce blood loss and transfusion requirements during TKA in intravenous or topical administration.^{6,7} PAI allow TXA solution directly injected into the soft tissue around the joint cavity that is vulnerable to postoperative bleeding.⁸ Besiris et al¹⁵ found that PAI of TXA after TKA is superior to reduce hemoglobin reduction, transfusion rate and length of hospital stay when compared with IAI route. Present meta-analysis indicated that PAI of TXA could significantly decrease the drainage volume and total blood loss.

Postoperative anemia is related to a longer length of hospital stay, wound complications, poor functional recovery and even death, especially for geriatric patients.¹⁶ It has been reported that 10-38% of patients require blood transfusion after primary TKA to correct postoperative anemia.³ A randomized controlled trial study by Pinsornsak et al¹¹ compared hemoglobin reduction between patients who received PAI of TXA or not during TKA. They observed that the PAI of TXA group had significantly lower hemoglobin reduction than the control group. Mao et al⁸ and Yozawa et al⁹ reported similar results. The pooled results demonstrated significant differences in the transfusion rate and hemoglobin reduction between the TXA group and the control group.

DVT is a common complication after TKA which may develop to pulmonary embolism and even death.¹⁷ Although administration of TXA in TKA has been proven does not increase the risk for DVT, the effects of TXA on thromboembolic events and mortality remain uncertain.¹⁸ None of DVT was reported in all the included studies. Pinsornsak et al¹¹ reported that PAI of TXA resulted in significantly lower serum TXA levels postoperatively when compared with others route. They concluded that PAI of TXA may be safer to high risk patients for thromboembolic events.

The limitations of present meta-analysis include the relatively low numbers for sample size. In addition, another limitation is the lack of high-quality evidence in several articles. Furthermore, we found several results with heterogeneity. However, we cannot perform further analysis by subgroup analysis due to insufficient data on this topic.

Conclusion

Peri-articular injection of TXA can effectively reduce perioperative blood loss and blood transfusion rate without increasing the incidence of postoperative complications during TKA.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' Note

YL, DS, PT, ZJL, GJX, and XF contributed to conception and design of this study. Study selection and data extraction of the finally included studies were done by YL and DS, PT and XF independently assessed the methodological quality of each

included study. YL and DS, PT, ZJL, GJX, and XF contributed to preparation of the manuscript. The final version of the article was approved by all the authors.

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