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META ANALYSIS

Comparison between peri-articular injection and intra-articular injection of tranexamic acid during total knee arthroplasty: A meta-analysis

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ABSTRACT

Objectives: In this meta-analysis, we aimed to compare the efficacy and safety of peri-articular injection (PAI) and intra-articular injection (IAI) of tranexamic acid (TXA) in total knee arthroplasty (TKA).

Patients and methods: We performed a comprehensive literature search from electronic databases such as Springer, Web of Science, PubMed, Cochrane Library databases, and ScienceDirect up to October 2021. The language of identified articles was not restricted. The keywords used for the search strategy included: "tranexamic acid", "total knee arthroplasty", "peri-articular injection" and "intra-articular injection".

Results: Two randomized-controlled trials (RCTs) and four non-RCTs with a total of 491 patients met the inclusion criteria. Of the patients, 242 patients were in the PAI group and 249 patients were in the IAI group. No significant difference was observed between the two groups in hemoglobin drop, postoperative drainage volume, total blood loss, blood transfusion requirements, or units of blood transfused. There was no significant difference between the two groups regarding postoperative infection or deep venous thrombosis.

Conclusion: The PAI of TXA is comparable to IAI of TXA in decreasing postoperative blood loss during TKA.

Keywords: Intra-articular injection, meta-analysis, peri-articular injection, total knee arthroplasty, tranexamic acid.

Total knee arthroplasty (TKA) has been proven to be a successful surgical procedure to correct deformity, relieve pain, and restore knee function. However, about 10 to 38% of patients following TKA require blood transfusion ranging between 1,000 mL and 2,000 mL for massive postoperative blood loss.[1,2] Blood transfusion may lead to transfusion-related complications and increase the medical burden.[3,4]

Tranexamic acid (TXA), a synthetic lysine analogue, can competitively inhibit the activation of plasmin binding protein and plasminogen has been commonly utilized to reduce blood loss during TKA.[5,6] Multiple studies have reported that the intravenous (IV), oral or topical administration of TXA significantly decreases postoperative blood loss and transfusion rates during TKA.[7-10] However, the IV and the oral administration of TXA may lead to systemic adverse effects and is contraindicated in patients with several comorbidities, such as a history of cardiac and cerebrovascular disease, deep vein thrombosis (DVT) and renal failure.[11] The intra-articular injection (IAI)

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of TXA has been recommended to avoid these adverse effects.[12]

Recently, peri-articular injection (PAI) of TXA introduced by Pinsornsak et al.[13] is as a new local administration method to reduce blood loss in TKA. Theoretically, TXA solution directly injected into the soft tissue around the joint cavity that is vulnerable to postoperative bleeding is expected to reduce bleeding more effectively.[14] Several studies have compared the efficacy of PAI with IAI in TKA. However, they reported inconsistent results and whether PAI is effective and safe in TKA still remains controversial. In this meta-analysis, we, therefore, aimed to compare the efficacy and safety of PAI and IAI with TXA during TKA.

PATIENTS AND METHODS

Search strategy

This meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We performed a comprehensive literature search from electronic databases such as Springer, Web of Science, PubMed, Cochrane Library databases, and Science Direct up to October 2021. We also checked the references of the identified articles to find other relevant articles. The language of identified articles was not restricted. The keywords used for the search strategy included: "tranexamic acid", "total knee arthroplasty", "peri-articular injection" and "intra-articular injection".

Inclusion criteria

Studies were selected for inclusion if they met the following criteria: *(i)* study design: published randomized-controlled trials (RCTs) and non-RCTs; *(ii)* study population: patients with primary TKA treatment; *(iii)* intervention: the experimental group received PAI of TXA therapy and the control group received IAI of TXA therapy; and *(iv)* outcome measurements: hemoglobin (Hb) drop, total blood loss, blood transfusion requirements, postoperative drainage volume and postoperative complications. Two independent reviewers assessed the eligibility of identified articles. A third reviewer resolved any disagreement between the reviewers.

Exclusion criteria

Studies were excluded for the following reasons: *(i)* duplicate articles or articles including the same patients, content and results; *(ii)* theoretical research, case reports, meta-analyses, systematic reviews, expert comments, economic analyses and conference reports; and *(iii)* studies with non-relevant outcomes.

Data extraction

Data extraction was performed independently from the included articles by two reviewers. The following information was extracted: the first author's name, the publication year, country conducted in, the size of the sample, intervention, the comparable baselines, the follow-up time and the computed endpoints in each study. Endpoints include total blood loss, blood transfusion requirement, units of blood transfused, postoperative drainage, Hb drop, DVT and infection. Other relevant information were also extracted from included studies. If there were incomplete data, we contacted the corresponding author through e-mail for details.

Quality assessment

The methodological quality of the RCTs were assessed with a modification of the generic evaluation tool described in the Cochrane handbook for systematic reviews of interventions.[15] Every RCT's bias assessment checklist involved the following items: *(i)* randomization sequence generation; *(ii)* allocation concealment; *(iii)* blinding of personnel and participants, findings appraisal blinding; *(iv)* incomplete outcome data; and *(v)* selective reporting. The methodological quality of non-RCTs was evaluated by the methodological index for non-RCT studies (MINORS).[16] Every non-RCT's bias assessment checklist involved 12 items: *(i)* a clearly stated aim; *(ii)* inclusion of consecutive patients; *(iii)* prospective data collection; *(iv)* endpoints appropriate to the aim of the study; *(v)* unbiased assessment of the study endpoint; *(vi)* a follow-up period appropriate to the aims of study; *(vii)* less than 5% loss to follow-up; *(viii)* prospective calculation of the sample size; *(ix)* an adequate control group; *(x)* contemporary groups; *(xi)* baseline equivalence of groups; and *(xii)* adequate statistical analyses. Two authors independently performed the methodological quality assessment. Disagreements in methodological assessment were solved by discussion, and a third reviewer was consulted, if necessary.

Statistical analysis

Statistical analysis was performed using the RevMan version 5.1 software (Cochrane Collaboration, Oxford, UK). The I2 values and p values were used to estimate the level of heterogeneity. When I2 <50%, p>0.1, heterogeneity could be accepted and the fixed-effects model was used for data analysis.

Otherwise, significant heterogeneity was considered, and a random-effects model was used for the data analysis. Subgroup analysis was performed to investigate the sources of significant heterogeneity. For continuous variables, mean differences (MDs) and 95% confidence intervals (CIs) were calculated. For dichotomous outcomes, risk differences (RDs) and 95% CIs were calculated.

RESULTS

Search results

A total of 46 studies were retrieved from the selected data base search. No additional study was identified through other sources. After carefully reviewing the titles and abstract, 40 studies were excluded. Finally, two RCTs[17,18] and four non-RCTs[14,19-21] were included for data extraction and meta-analysis. The detailed search process is summarized in Figure 1.

Characteristics of the included studies

General information of included studies is shown in Table I. The baseline characteristics of two groups in all studies were comparable.

Risk of bias assessment

The methodological quality of the RCTs is shown in Figure 2. Inclusion and exclusion criteria were clearly stated in all RCTs. All RCTs stated randomized sequence generation, allocation concealment, and blind method. Unclear bias was not found due to incomplete outcome data or selective outcomes. The MINORS was used to assess the quality of the non-RCTs. Their scores ranged from 20 to 22, indicating relatively high quality (Table II). Prospective calculation of the sample size was not performed in all non-RCTs. One of non-RCTs did not prospectively perform data collection.

Outcomes of the meta-analysis

Hemoglobin drop

Hemoglobin drop was defined as the difference between the lowest Hb concentration level preoperatively and postoperatively. The Hb drop was recorded in three studies. A total of 223 patients were involved to evaluate Hb drop, of whom 118 were in PAI group and 105 in IAI group. The Hb drop in the PAI group was similar to that in the IAI group (MD=-0.00, 95% CI -0.51 to 0.51; p=1.00) (Figure 3).

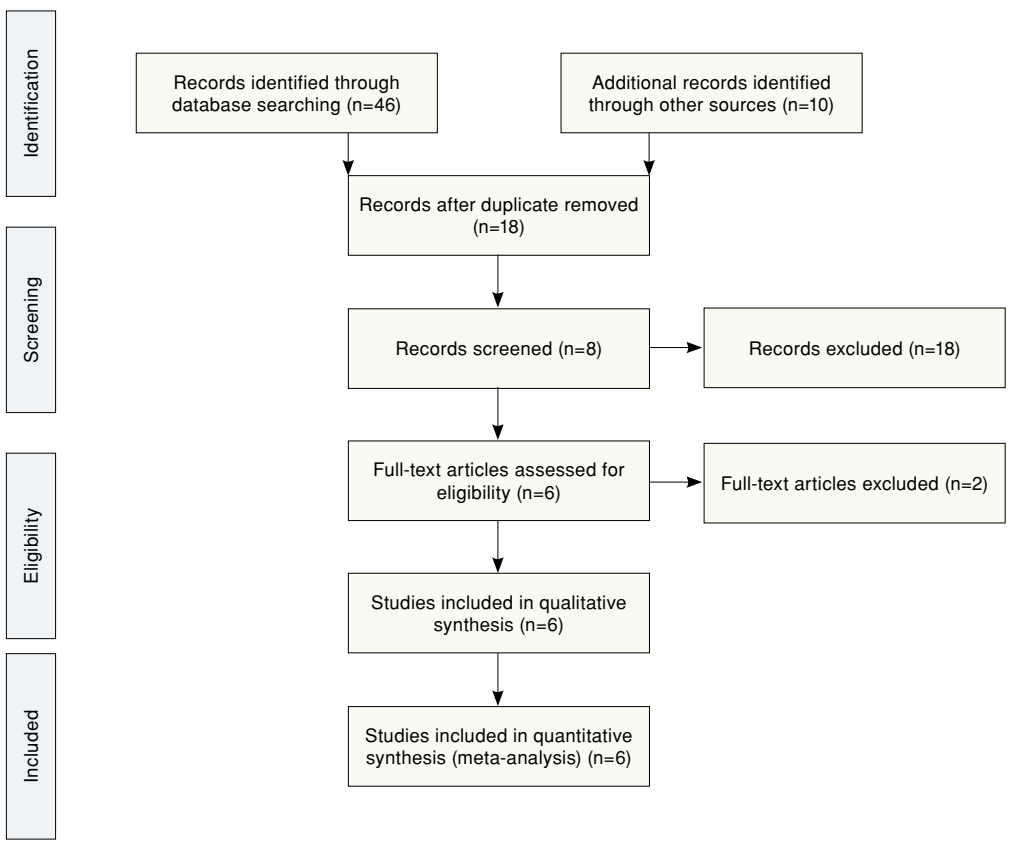

FIGURE 1. Study flowchart.

TABLE I
Characteristics of included studies

Author	Year	Country	Language of publication	Group	Cases (n)	Mean age (year)	Female (n)	Dosage	Tourniquet use	Transfusion criteria	DVT prophylaxis
Besiris et al.[19]	2020	Greece	English	PAI	33	72.1±6.1	54 in	1.5 g	Yes	NS	LMWH
				IAI	33	72.3±7.1	total	1.5 g			
Lin et al.[20]	2021	China	English	PAI	50	70.5±1.3	18	1 g	Yes	Hb <8 mg/dL	LMWH
				IAI	50	70.5±1.3	18	1 g			
Mao et al.[14]	2016	China	English	PAI	49	68.5±7.4	41	2 g	Yes	Hb <8 mg/dL	Rivaroxaban
				IAI	36	69.7±7.2	31	2 g			
Pinsornsak et al.[17]	2021	Thailand	English	PAI	36	65.6±7.5	34	15 mg/kg	Yes	Hb <8 g/dL	Aspirin
				IAI	36	68.4±8.2	33	2 g			
Sivasubramanian et al.[21]	2021	Singapore	English	PAI	21	65.5	12	1 g	Yes	Hb <8.5 g/dL	NS
				IAI	42	66.8	22	1 g			
Zhang et al.[18]	2019	China	English	PAI	53	66	37	1 g	Yes	Hb <8 mg/dL	LMWH
				IAI	52	68.5	38	1 g			

DVT: Deep venous thrombosis; PAI: Peri-articular injection; IAI: Intra-articular injection; NS: Not state; LMWH: Low-molecular-weight heparin.

Total blood loss

Total blood loss was calculated using a previously reported method[22] in three studies. In all, 262 patients were assessed for total blood loss, with 138 and 124 allocated to PAI and IAI groups, respectively. The total blood loss in the PAI group was similar to that in the IAI group (MD=-1.90, 95% CI -44.16 to 40.37; p=0.93) (Figure 4).

Drainage volume

Drainage volume was reported in three studies. The number of patients was 290, with 152 allocated to PAI group and 138 to IAI group. The drainage volume in the PAI group was similar to that in the IAI group (MD=-32.05, 95% CI -135.51 to 71.41; p=0.54) (Figure 5).

Blood transfusion requirement

Blood transfusion requirement was documented in four studies. A total of 319 patients were contained to evaluate blood transfusion requirement, 158 and 163 in the PAI and IAI groups, respectively. The blood transfusion requirement in the PAI group was similar to that in the IAI group (RD=-0.05, 95% CI -0.16 to 0.06; p=0.40) (Figure 6).

Units of blood transfused

The units of blood transfused were assessed in two studies. A total of 138 patients were evaluated

FIGURE 2. The summary of bias risk of randomized-controlled trials.

TABLE II
Quality assessment for non-randomized trials

Quality assessment for non-randomized trials	Besiris et al.[19] 2020	Lin et al.[20] 2021	Mao et al.[14] 2016	Sivasubramanian et al.[21] 2021
A clearly stated aim	2	2	2	2
Inclusion of consecutive patients	2	2	2	2
Prospective data collection	2	0	0	0
Endpoints appropriate to the aim of the study	2	2	2	2
Unbiased assessment of the study endpoint	2	2	2	2
A follow-up period appropriate to the aims of study	2	2	2	2
Less than 5% loss to follow-up	2	2	2	2
Prospective calculation of the sample size	0	0	0	0
An adequate control group	2	2	2	2
Contemporary groups	2	2	2	2
Baseline equivalence of groups	2	2	2	2
Adequate statistical analyses	2	2	2	2
Total score	22	20	20	20

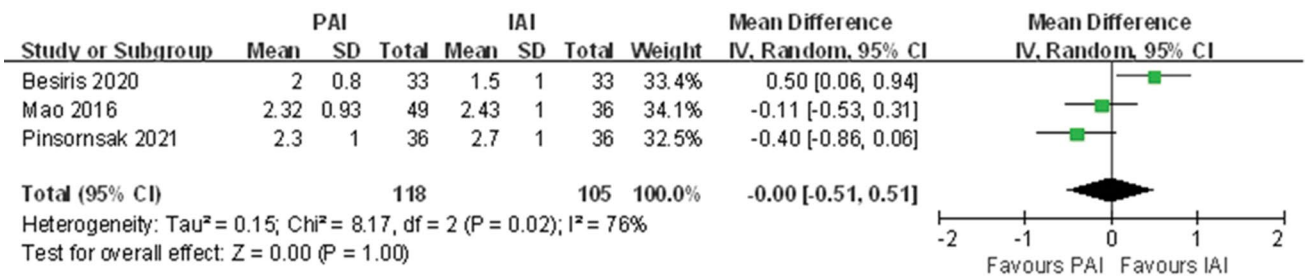

FIGURE 3. Forest plot showing hemoglobin drop.

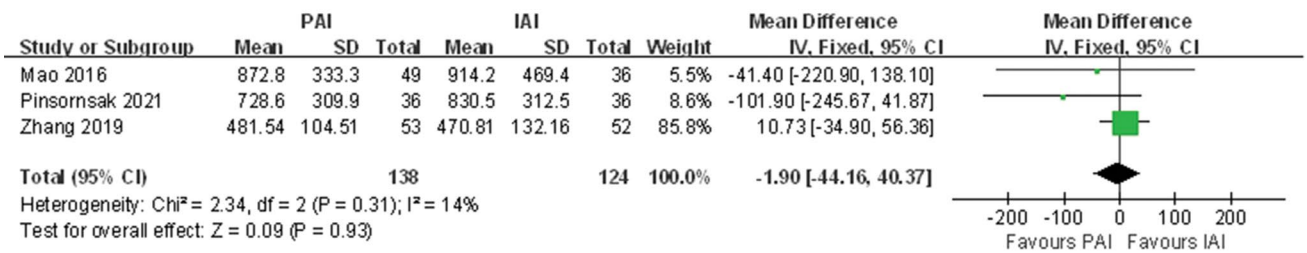

FIGURE 4. Forest plot showing total blood loss.

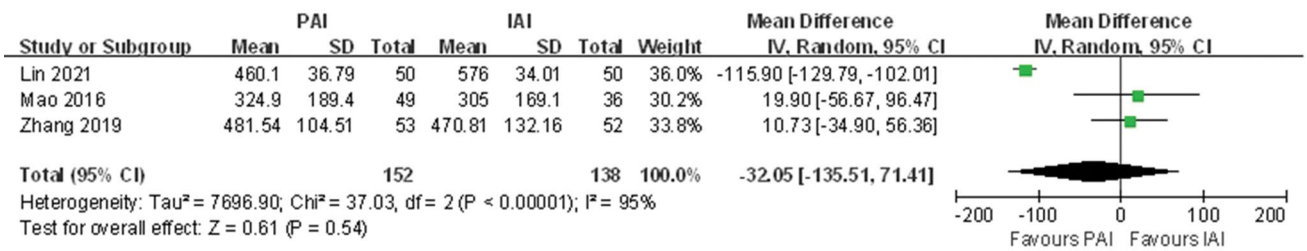

FIGURE 5. Forest plot showing drainage volume.

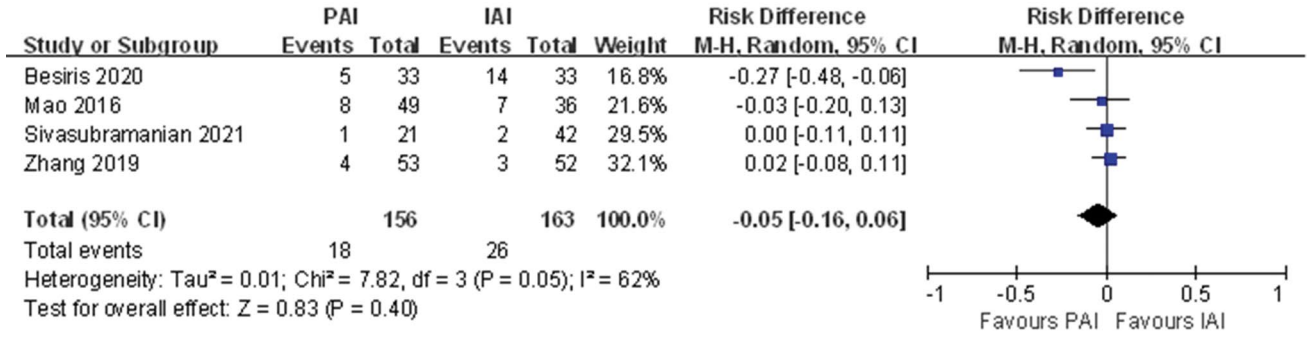

FIGURE 6. Forest plot showing blood transfusion requirements.

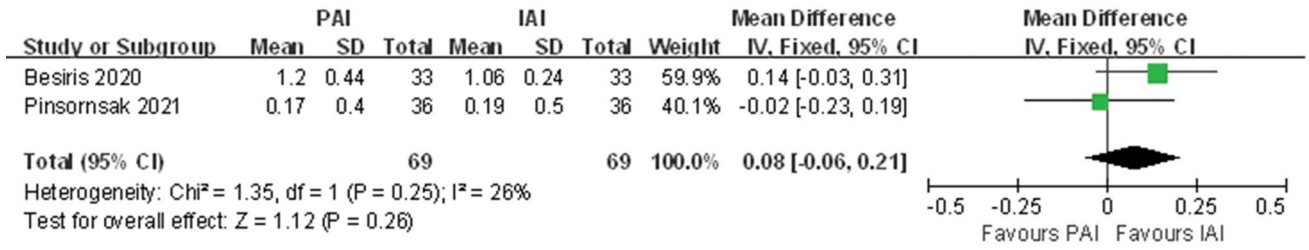

FIGURE 7. Forest plot showing blood transfusion units.

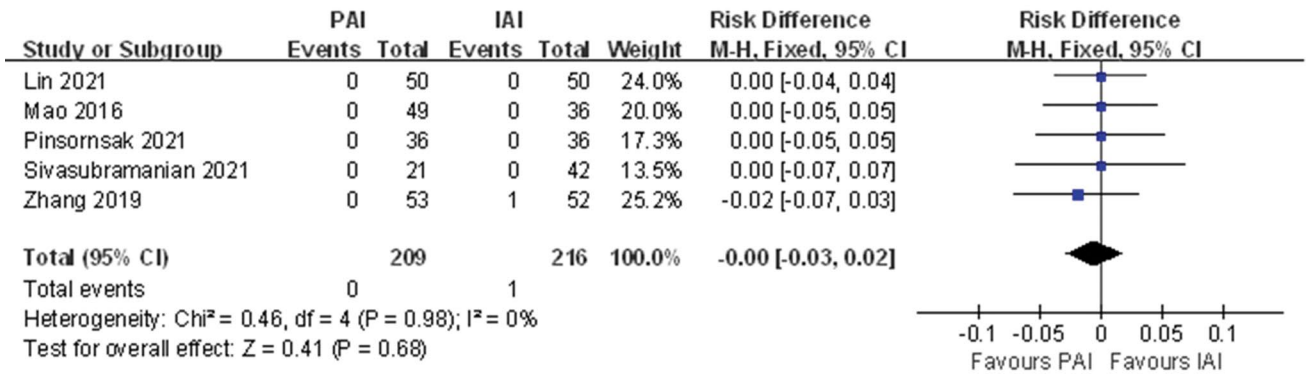

FIGURE 8. Forest plot showing deep vein thrombosis.

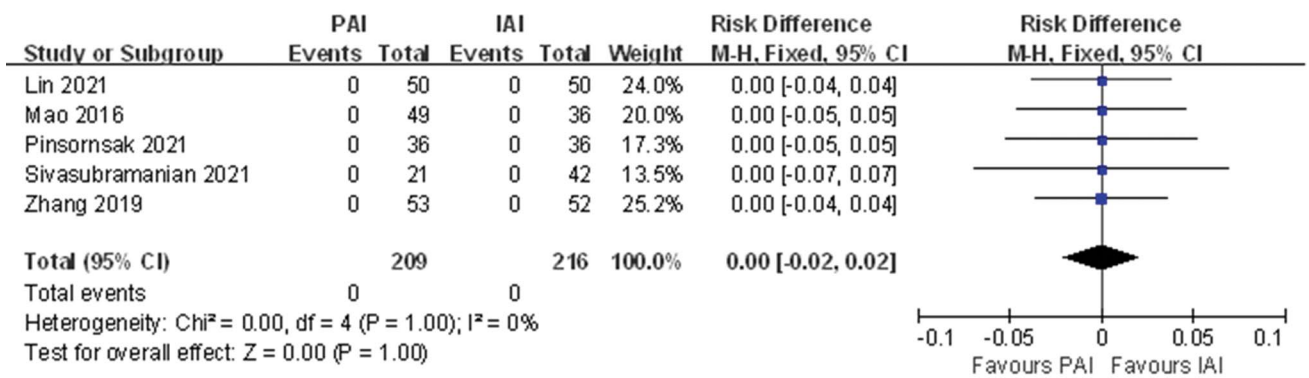

FIGURE 9. Forest plot showing infection.

for units of blood transfused, of whom 69 and 69 in the PAI and IAI groups, respectively. The units of blood transfused in the PAI group were similar to those transfused in the IAI group (MD=0.08; 95% CI -0.06 to 0.21; p=0.26) (Figure 7).

Deep venous thrombosis

The DVT data were available in five studies, of which 0 out of 209 in the PAI group and 1 out of 216 in the IAI group experienced DVT. No significant difference was found between the two groups (RD=-0.00, 95% CI -0.03 to 0.02; p=0.68) (Figure 8).

Infection

Infection was reported in five studies, of which 0 out of 209 in the PAI group and 0 out of 216 in the IAI group experienced DVT. No significant difference was found between the two groups (RD=0.00; 95% CI -0.02 to 0.02; p=1.00) (Figure 9).

DISCUSSION

In this meta-analysis, six studies were included. We attempted to compare the efficacy and safety of the PAI and IAI of TXA acid during TKA from clinical controlled trials. In this meta-analysis, we found that the PAI of TXA was comparable to the IAI of TXA in decreasing postoperative blood loss during TKA without complications.

Considerable postoperative blood loss following TKA leads to anemia and can necessitate the need for RBC transfusion. Local applications of TXA have already proven effective in reducing blood loss following TKA.[6] Pinsornsak et al.[17] conducted a RCT to evaluate PAI and IAI of TXA administration and reported that both PAI and IAI, compared to no intervention, reduced Hb drop and estimated total blood loss. They found that PAI of TXA was as effective as IAI of TXA in decreasing postoperative blood loss in TKA. This meta-analysis demonstrated that PAI showed similar total blood loss, drainage volume, and Hb drop as IAI. Zhang et al.[18] and Mao et al.[14] reported that postoperative drainage volume of PAI and IAI were similar. On the contrary, Lin et al.[20] found that postoperative drainage volume of the PAI group were significantly lower than those of the IAI group. Theoretically, compared to IAI, PAI may avoid TXA solution leakage and improve the permeation of TXA into the deeper soft tissues of the knee joint.[14] The PAI of TXA may be more advantageous in decreasing postoperative blood loss following TKA.

Postoperative anemia, particularly for geriatric patients, is related to a longer length of hospital stay, poor functional recovery, wound complications and even death.[3] Recently, Besiris et al.[19] reported results from 66 TKA patients who received IAI or PAI of TXA. Their study demonstrated that the PAI of TXA resulted in lower transfusion rates and shorter length of hospital stay. They concluded that the PAI of TXA administration was superior to the IAI of TXA. Mao et al.[14] confirmed that TXA solution directly injected into the soft tissue around the joint cavity that is vulnerable to postoperative bleeding was expected to reduce bleeding more effectively. However, the present meta-analysis revealed that PAI showed transfusion rates and number of units transfused similar to those of IAI. We conclude that the PAI of TXA has the same effects on preventing blood transfusion as IAI.

Deep vein thrombosis is a major concern after TKA, particularly for patients who receive TXA. Although multiple studies[8,23] have provided evidence that the IV or IAI of TXA does not increase the risk of DVT following TKA, the effects of TXA administration on thromboembolic events and mortality remain uncertain.[24] Recently, a randomized study of PAI-TXA compared to IAI-TXA demonstrated a comparable reduction in blood loss after TKA17. Pinsornsak et al.[17] compared the serum levels between IAI-TXA and PAI-TXA at 2 h and 24 h postoperatively. Their study suggested that the PAI of TXA (15 mg/kg) resulted in significantly lower serum TXA levels than the IAI of TXA (2 g), perhaps due to the continued absorption of TXA in the IAI group. Therefore, PAI of TXA could be an alternative to IAI, limiting the systemic absorption of TXA, particularly in patients at risk for thrombotic events.

The limitations of the present meta-analysis should be noted. The meta-analysis was limited to only six articles published, and the number of patients included in this meta-analysis was relatively small. In addition, methodological weakness of prospective calculation of the sample size exists in all non-RCTs and may have decreased the level of evidence. Finally, postoperative Visual Analog Scale scores and length of hospital stay were incomplete and we failed to conduct a meta-analysis on these parameters.

In conclusion, PAI of TXA is comparable to IAI of TXA in decreasing postoperative blood loss during TKA. Due to the limited quality of the current evidence, more high-quality RCTs with large sample sizes are required.

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Ethics Committee Approval: No ethical approval was required, as all data in this meta-analysis were derived from previously published research. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Contributed to conception and design of this study: Y.L., Y.M.L., P.T., Z.J.L., G.J.X., and X.F.; Study selection and data extraction of the finally included studies were done independently assessed the methodological quality of each included study: by Y.L. and Y.M.L., P.T. and X.F.; Contributed to preparation of the manuscript: Y.L. and Y.M.L., P.T., Z.J.L., G.J.X. and X.F.; The final version of the article was approved by all the authors.

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