Medicine®

OPEN

Is combined topical and intravenous tranexamic acid superior to single use of tranexamic acid in total joint arthroplasty?

A meta-analysis from randomized controlled trials

Liqing Yang, MD*, Shuai Du, MD, Yuefeng Sun, MD

Abstract

Background: To compare the efficacy and safety of the combined application of both intravenous and topical tranexamic acid (TXA) versus the single use of either application in patients with total knee and hip arthroplasty (TKA and THA).

Methods: Potentially relevant studies were identified from electronic databases including Medline, PubMed, Embase, ScienceDirect, and the Cochrane Library. Randomized control trials (RCTs) of patients prepared for total joint arthroplasty that compared combined TXA with placebo were retrieved. The primary endpoint was hemoglobin decline or postoperative hemoglobin level, blood loss, drainage volume, transfusion requirements. The secondary outcomes were length of stay (LOS), and operation time as well as surgery-related adverse effects, such as wound infection, deep vein thrombosis (DVT), and pulmonary embolism (PE). After testing for publication bias and heterogeneity between studies, data were aggregated for random-effects models when necessary.

Results: Five RCTs that included 604 patients met the inclusion criteria. The present meta-analysis indicated significant differences existed in the total blood loss (mean difference [MD] = −134.65, 95% CI: −191.66 to −77.64, $P < .0001$), postoperative hemoglobin level (MD = 0.74, 95% CI: 0.39–1.10, $P < .0001$), drainage volume (MD = −47.44, 95% CI: −64.55 to −30.33, $P < .00001$), and transfusion rate (risk difference [RD] = −0.06, 95% CI: −0.10 to −0.02, $P = .006$) between groups.

Conclusion: Combined administration of TXA in TKA and THA was associated with significantly reduced total blood loss, postoperative hemoglobin decline, drainage volume, and transfusion requirements. Well-designed, high-quality RCTs with long-term follow-up are still required.

Abbreviations: DVT = deep venous thrombosis, LOS = length of stay, PE = pulmonary embolism, RCT = randomized controlled trials, THA = total hip arthroplasty, TKA = total knee arthroplasty, TXA = tranexamic acid.

Keywords: blood loss, meta-analysis, total knee and hip arthroplasty, tranexamic acid

1. Introduction

Total knee arthroplasty and hip arthroplasty (TKA and THA) are effective surgical procedure for treatment of end stage osteoarthritis. However, joint arthroplasty surgeries are usually associated with perioperative substantial blood loss and high transfusion requirement.[1,2] Various strategies have been attempted to minimize blood loss including allogenic blood transfusion, drug intervention, and autologous donation.[3] Allogenic blood transfusion is associated with side events, such as disease transmission, hemolytic reaction, and cardiovascular dysfunction, resulting in a financial burden and potentially life-threatening effects on patients.[4]

Recent studies have focused on the tranexamic acid (TXA) in reducing perioperative blood loss in total joint arthroplasty. Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules.[5] Previous articles have demonstrated that it was effective and safe for patients who received intravenous administration or topical application of TXA. In addition, meta-analyses of high-quality randomized control trials (RCTs) showed that TXA was associated with significant reduced blood loss and transfusion requirements.[6,7]

Despite this previous research, whether the combined application of TXA is superior to a single use remains unclear due to a lack of published studies and the inclusion of small sample sizes. Therefore, we performed the present systemic review and meta-analysis to evaluate the efficiency and safety of the combined application of intravenous and topical tranexamic acid compared with the single use of either application in patient with TKA and THA. We included only high quality RCTs that compared the efficacy and safety of combined application of intravenous and topical tranexamic acid with the single use of

either application in patients with TKA and THA, in which the experimental group received combined intravenous and topical application of TXA and the control group received a single application of TXA or normal saline.

2. Methods

This systematic review was reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The study was approved by the ethics committee of Shengjing Hospital.

2.1. Search strategy

We searched the electronic databases including Medline (1966–2016.2.28), PubMed (1966–2016.2.28), Embase (1980–2016.2.28), ScienceDirect (1985–2016.2.28), and the Cochrane Library. The key words used in search methods including "total knee replacement OR arthroplasty," "total hip replacement OR arthroplasty," and "tranexamic acid," "blood loss," or "blood transfusion." The search results were showed in Fig. 1. The references of the included literatures were also checked for potentially relevant studies. We placed no restrictions on the publication language. The search process was performed as presented in Fig. 1. The register number is CRD42016110660.

2.2. Inclusion criteria and study selection
2.2.1. Participants:. Only published articles enrolling adult participants that with a diagnosis of end-stage of osteoarthritis and prepared for unilateral TKA or THA.

2.2.2. Interventions:. The intervention group received combined application of TXA for postoperative blood management.

2.2.3. Comparisons:. The control group received single routine of TXA.

2.2.4. Outcomes:. Total blood loss, transfusion rate, hemoglobin decline, and postoperative complications such as wound infection, deep vein thrombosis (DVT), and pulmonary embolism (PE).

2.2.5. Study design:. Clinical randomized control trials (RCTs) were regarded as eligible in our study. Articles would be excluded from current meta-analysis for incomplete data, case reports, conference abstract, or review studies. Two reviewers independently scanned the abstracts of the potential articles identified by the above searches. Subsequently, the full text of the studies that met the inclusion criteria was screened, and a final decision was made. A senior author had the final decision in any case of disagreement regarding which studies to include.

2.3. Date extraction

The included studies were examined by 2 investigators and key data were extracted including first author name, published year, baseline characteristics, surgical procedures, dose of TXA, samples size, and transfusion trigger. The primary outcomes were total blood loss, hemoglobin decline, and transfusion requirements. The secondary outcomes were postoperative complications, such as superficial infection, DVT, or PE.
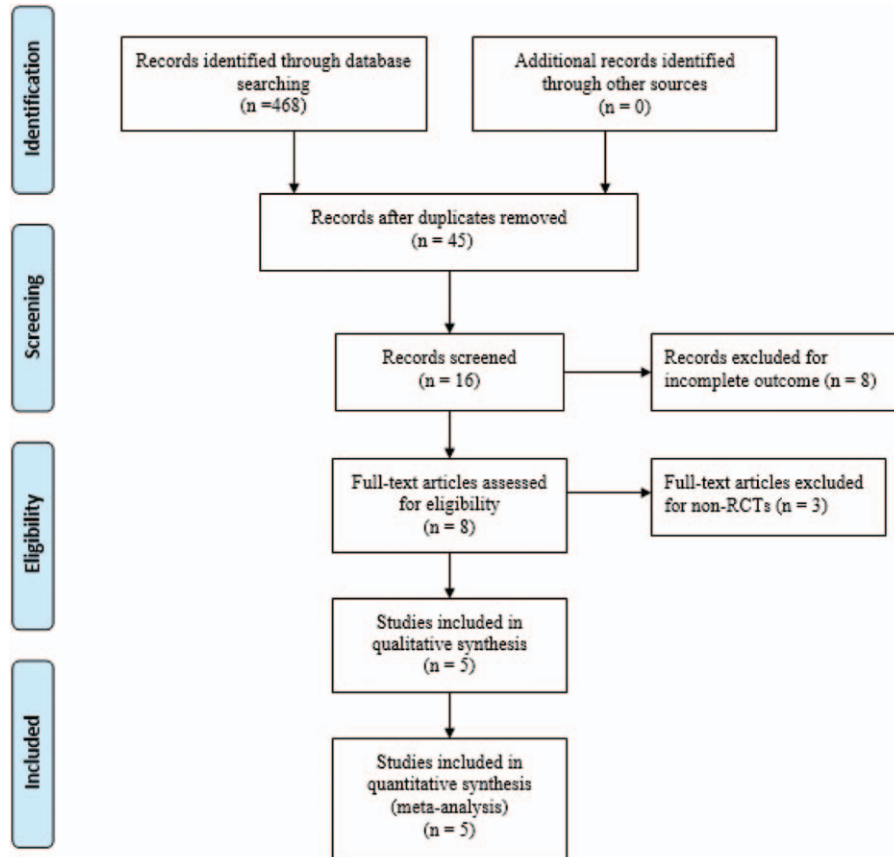

Figure 1. Search results and the selection procedure.

2.4. Assessment of methodological quality

A quality assessment of each randomized trial was performed by 2 reviewers based on the Cochrane Handbook for Systematic Reviews of Interventions. Disagreement was resolved by consulting a senior reviewer. We created a "risk of bias" table that included the following elements: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting, and other bias.[6,7] The quality of the evidence for the main outcomes in present meta-analysis was evaluated using the Recommendations Assessment, Development and Evaluation (GRADE) system including the following items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The recommendation level of evidence is 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. Publication bias is a tendency on average to produce results that appear significant, because negative or near neutral results are almost never published. Publication bias may exist in all meta-analyses. Selective reporting is a strong bias that prevents correct conclusions arising from hypothesis tests, this bias is a specific form of selection bias whereby only interesting or relevant examples are cited. Therefore, the meta-analysis results should be considered appropriate.

2.5. Data analysis and statistical methods

The data were pooled using RevMan 5.1 (The Cochrane Collaboration, Oxford, UK). After extracting the data from the included studies, we exported the means, SDs, and sample sizes of groups into RevMan 5.1 to determine the heterogeneity. Statistical heterogeneity was assessed based on the P and I^2 values using the standard Chi-square test. When $I^2 \geq 50\%$ or $P < .1$, significant heterogeneity was indicated and a random-effects model was applied for the meta-analysis. Otherwise, a fixed-effects model was used. Dichotomous outcomes (i.e., transfusion requirements) were expressed as risk differences (RDs) with 95% confidence intervals (CIs). For continuous outcomes (i.e., transfusion requirements), mean differences (MDs) and 95% confidence intervals (CIs) were calculated. A subgroup analysis was conducted when significant heterogeneity was detected to find the source if possible. Various surgical procedures may cause significant heterogeneity. Therefore, we only included studies with the same surgical procedure to find the source of heterogeneity.

3. Results

3.1. Search result

A total of 468 studies were identified through the initial search. By scanning the abstracts, 463 reports that did not meet inclusion criteria were excluded from the current meta-analysis. No gray literature was included. Finally, 5 RCTs[8–12] published between 2014 and 2015 were included in the present meta-analysis; these studies included 302 patients in the experimental groups and 302 patients in the control groups. All included studies were indexed in PubMed and published in English.

3.2. Study characteristics

The sample sizes ranged from 80 to 184 patients. Only studies that included patients with end-stage knee arthritis or osteonecrosis of the femoral head were included in the present meta-analysis. In these studies, the experimental groups received combined intravenous and topical TXA and the control groups received a single application of TXA or normal saline. The characteristics of the included studies are reported in Table 1.

Table 1

Cohort characteristics.

Studies	Study design	Patient Cases (E/C)	Patient Mean age (E/C)	Patient Female patient (E/C)	Surgical methods	TXA intervention	Prophylactic antithrombotic	Comparison	Main outcome measures
Huang et al[8]	RCT (method unreported) and controlled blind parallel study with a follow up of 1–3 mo	92/92	65.4/64.7	55/62	TKA	E: 1.5 g topical injection + 1.5 g i.v.	LMWH, 6000 IU	1. Total blood loss	
								2. Hemoglobin decline 3. Transfusion rate 4. Dragine volume	1. $P=.067$ 2. $P=.031$ 3. $P=.028$ 4. $P=.011$
Lin et al[9]	RCT (computer generated) and controlled nonblind parallel study with a follow up of 3 mo	40/40	70.7/71.0	30/33	TKA	E: 1 g topical injection + 1 g i.v. C: 1 g topical injection	Rivaroxaban, 10 mg	1. Total blood loss 2. Hemoglobin decline 3. Transfusion rate 4. Dragine volume	1. $P<.001$ 2. $P<.001$ 3. $P<.001$ 4. $P<.001$
Jain et al[12]	RCT (computer generated) and controlled blind parallel study with a unreported follow up	59/60	68.3/70.0	39/36	TKA	E: pre-op. 15 mg/kg i.v. + post-op. 10 mg/kg i.v. + 2 g topical injection	Aspirin, 75 mg	1. Total blood loss	
						C: pre-op. 15 mg/kg i.v. + post-op. 10 mg/kg i.v.		2. Hemoglobin decline	1. $P=.001$
								3. Transfusion rate	2. $P=.001$ 3. $P=.036$
Xie et al[10]	RCT (method unreported) and controlled nonblind parallel study with a follow up of 3 mo	70/70	60.5/59.5	48/50	THA	E: 1 g topical injection + 2 g i.v. C: 1.5 g i.v.	Enoxaparin, 6000 IU	1. Total blood loss	1. $P=.001$
								2. Transfusion rate	2. $P=.016$
Karaaslan et al[11]	RCT (computer generated) and controlled blind parallel study with a follow up of 2 y	41/40	65.9/65.6	32/35	Bilateral TKA	E: 15 mg/kg topical injection + 10 mg/kg i.v.	LMWH, 4000 IU	1. Transfusion rate	1. $P<.05$

C = control group, E = experiment group, i.v. = intravenous injection, LMWH = low molecular weight heparin, RCT = randomized controlled trials.

Statistically similar baseline characteristics were observed between groups.

3.3. Risk of bias

The Cochrane Handbook for Systematic Review of Interventions was consulted to assess risk of bias of the RCTs. All RCTs provided clear inclusion and exclusion criteria and described their randomization methodology, and 3 studies[9,11,12] described the use of computer-generated randomization. Two studies[8,10] reported allocation concealment by closed envelope or other techniques. Double blinding was reported in 3 RCTs,[8,11,12] however, none of the included studies attempted to blind the assessors. An intention—to-treat analysis was not performed in any of the RCTs; therefore a potential risk of type II statistical error existed. No unclear bias due to incomplete outcome data or selective outcome reporting was identified in the RCTs. The methodological quality assessment is summarized in Table 2. Each risk of bias item is presented as the percentage across all included studies, which indicates the proportion of different levels of risk of bias for each item (Table 3).
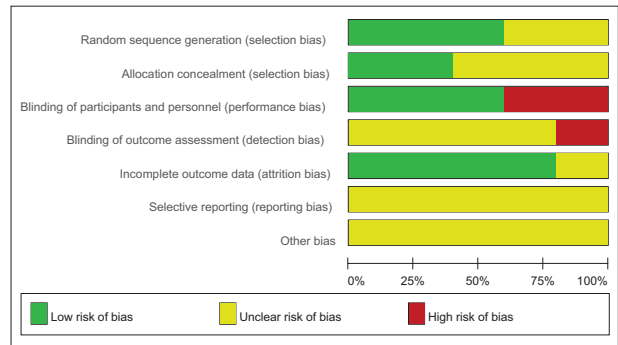
3.4. Evidence level

All outcomes in this meta-analysis were evaluated using the Recommendations Assessment, Development and Evaluation (GRADE) system. The evidence quality for most outcome was

Table 3
Risk of bias.

high (Table 4) which means further research is very unlikely to change our confidence in the estimate of effect. Therefore, we highly recommended the combined use of TXA for reducing blood loss in patients with TKA and THA.

3.5. Outcomes for meta-analysis

3.5.1. Total blood loss.
Four articles[8–10,12] reported the outcomes of total blood loss following the operation. A random-effects model was used because significant heterogeneity was found among the studies ($\chi^2 = 6.02$, $df = 3$, $I^2 = 50\%$, $P = .11$). The pooled results demonstrated that total blood loss was significantly higher in the control groups than in the experimental groups (MD = −134.65, 95% CI: −191.66 to −77.64, $P < .0001$; Fig. 2).

3.5.2. Postoperative hemoglobin level.
Two studies[9,11] reported the outcomes of postoperative hemoglobin level. A fixed-effects model was used because no significant heterogeneity was found among the studies ($\chi^2 = 0.9$, $df = 1$, $I^2 = 0\%$, $P = .34$). The pooled results demonstrated that the postoperative hemoglobin level was significantly higher in the experimental groups than in the control groups (MD = 0.74, 95% CI: 0.39–1.10, $P < .0001$; Fig. 3).

3.5.3. Hemoglobin decline.
Three studies[8,9,12] reported the outcomes of hemoglobin decline following the operation. A random-effects model was used because significant heterogeneity existed among these studies ($\chi^2 = 16.16$, $df = 2$, $I^2 = 88\%$, $P = .0003$). The pooled results demonstrated that the hemoglobin decline was significantly higher in control groups than in the experimental groups (MD = −0.44, 95% CI: −0.79 to −0.09, $P = .01$; Fig. 4).

3.5.4. Transfusion rate.
The transfusion rates were reported in 5 studies.[8–12] A fixed-effects model was applied because no significant heterogeneity was found among these studies ($\chi^2 = 2.35$, $df = 4$, $I^2 = 0\%$, $P = .67$). A significant difference was detected in the transfusion rate between the 2 groups (RD = −0.06, 95% CI: −0.10 to −0.02, $P = .006$; Fig. 5).

3.5.5. Drainage volume.
The drainage volume was provided in 2 studies.[8–9] A fixed-effects model was used because no significant heterogeneity was found among these studies ($\chi^2 = 1.07$, $df = 1$, $I^2 = 7\%$, $P = .30$). The drainage volume was significantly higher in control groups than in the experimental groups (MD = −47.44, 95% CI: −64.55 to −30.33, $P < .00001$; Fig. 6).

Table 2
Methodological quality of the randomized controlled trials.

Table 4

The GRADE evidence quality for main outcome.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Combined groups	Single groups	Relative (95% CI)	Quality	Importance
		Quality assessment					No of patients		Effect		
Total blood loss (follow-up 1–3 mo; better indicated by lower values)											
4	Randomized trials	No serious limitations	Serious	No serious indirectness	No serious imprecision	None	261	262	MD = −134.65, 95% CI: −191.66 to −77.64	Moderate	Critical
Transfusion rate (follow-up 1–48 mo; better indicated by lower values)											
5	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	14/302	31/302	RD −0.06 (0–0)	High	Critical
Hemoglobin level (follow-up 3–48 mo; better indicated by lower values)											
2	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	81	80	MD = 0.74, 95% CI: 0.39–1.10	High	Important
Hemoglobin decline (follow-up 1–48 mo; better indicated by lower values)											
3	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	191	192	MD = −0.44, 95% CI: −0.79 to −0.09	High	Important
Operation time (follow-up 1–48 mo; better indicated by lower values)											
4	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	243	242	MD = 0.22, 95% CI: −4.65 to 5.08	High	Not important
Length of stay (follow-up 1–48 mo; better indicated by lower values)											
3	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	203	202	MD = −0.09, 95% CI: −0.23 to 0.04	High	Not important
Infection (follow-up 1–3 mo; better indicated by lower values)											
3	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	237	235	RD 0 (0.03–0.03)	High	Important
DVT (follow-up 1–48 mo; better indicated by lower values)											
5	Randomized trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	237	235	RD 0 (−0.02 to 0)	High	Important

CI = confidence interval, DVT = deep venous thrombosis, MD = mean difference, RD = risk difference.

3.5.6. Operation time. The operation time was reported in 4 studies.[8–11] A random-effects model was used because significant heterogeneity was found among the pooled data ($\chi^2 = 12.79$, $df = 3$, $I^2 = 77\%$, $P = .006$). No significance difference in the operation time was observed between the 2 groups (MD = 0.22, 95% CI: −4.65 to 5.08, $P = .09$; Fig. 7).

3.5.7. LOS. Three studies reported the lengths of the hospital stays for the groups.[8,10,11] A fixed-effects model was used because no significant heterogeneity was identified in the pooled results ($\chi^2 = 3.87$, $df = 2$, $I^2 = 48\%$, $P = .14$). No significant difference in the LOS was observed between the 2 groups (MD = −0.09, 95% CI: −0.23 to 0.04, $P = .17$; Fig. 8).
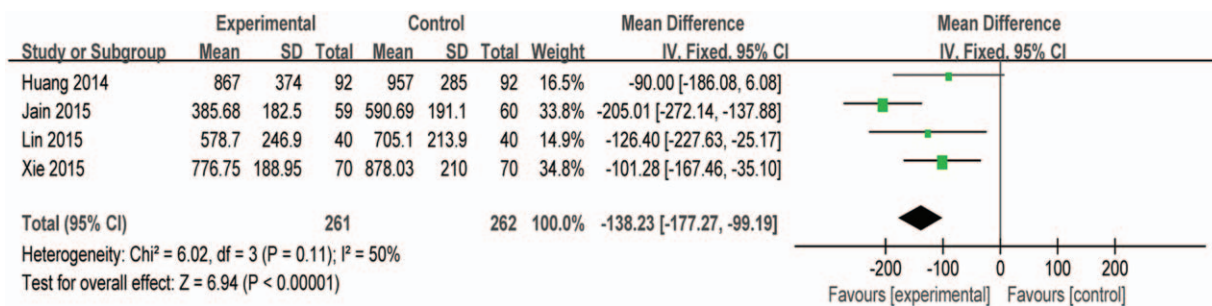

Figure 2. Forest plot diagram showing effect of combination TXA on total blood loss. TXA = tranexamic acid.
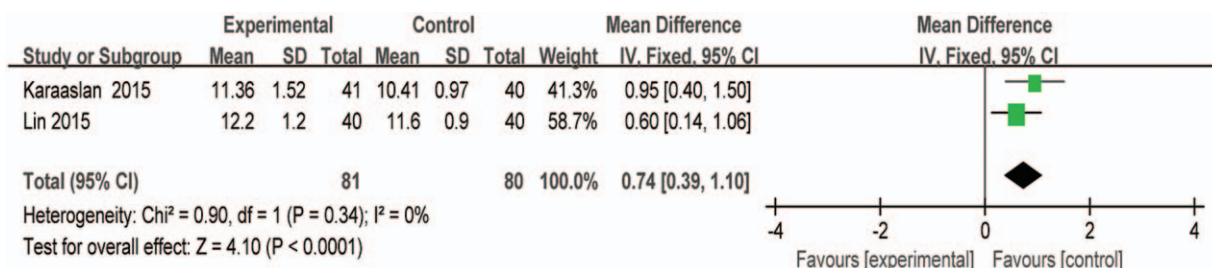

Figure 3. Forest plot diagram showing effect of combination TXA on postoperative hemoglobin level. TXA = tranexamic acid.
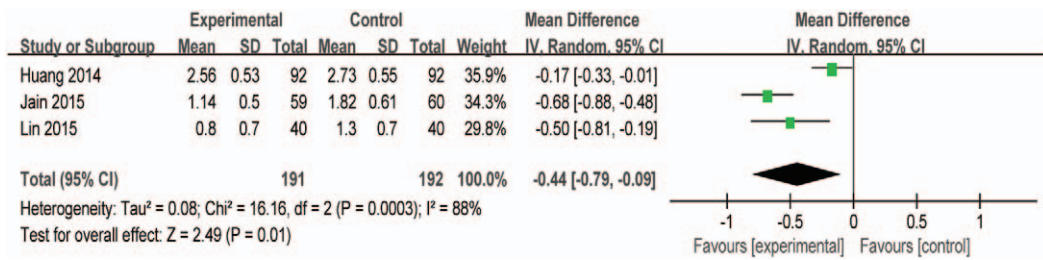
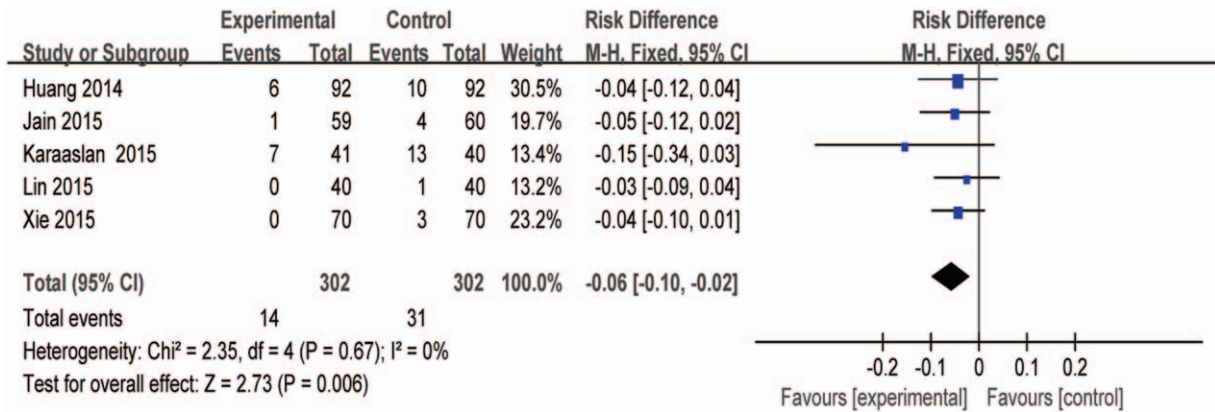**Figure 4.** Forest plot diagram showing effect of combination TXA on hemoglobin decline. TXA=tranexamic acid.

Figure 5. Forest plot diagram showing effect of combination TXA on transfusion rate. TXA=tranexamic acid.
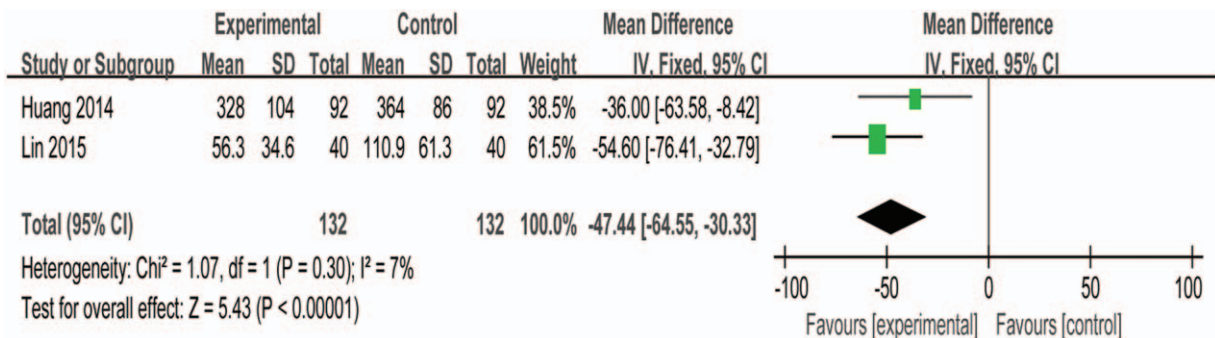

Figure 6. Forest plot diagram showing effect of combination TXA on drainage volume. TXA=tranexamic acid.
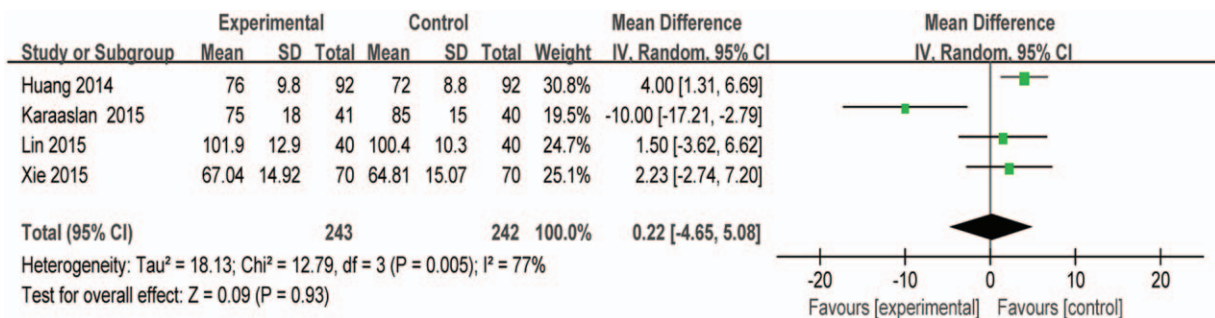

Figure 7. Forest plot diagram showing effect of combination TXA on operation time. TXA=tranexamic acid.
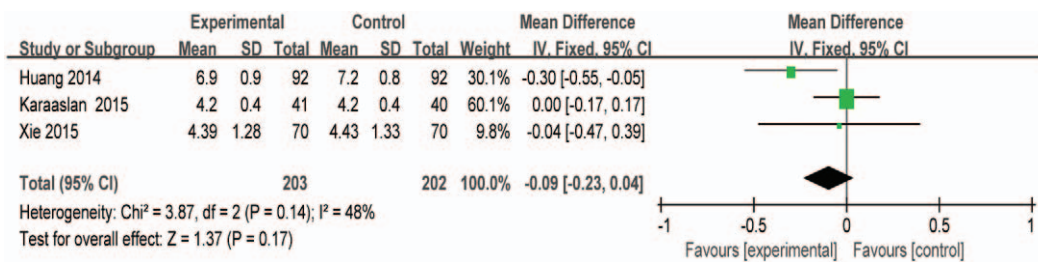
Figure 8. Forest plot diagram showing effect of combination TXA on length of stay. TXA = tranexamic acid.
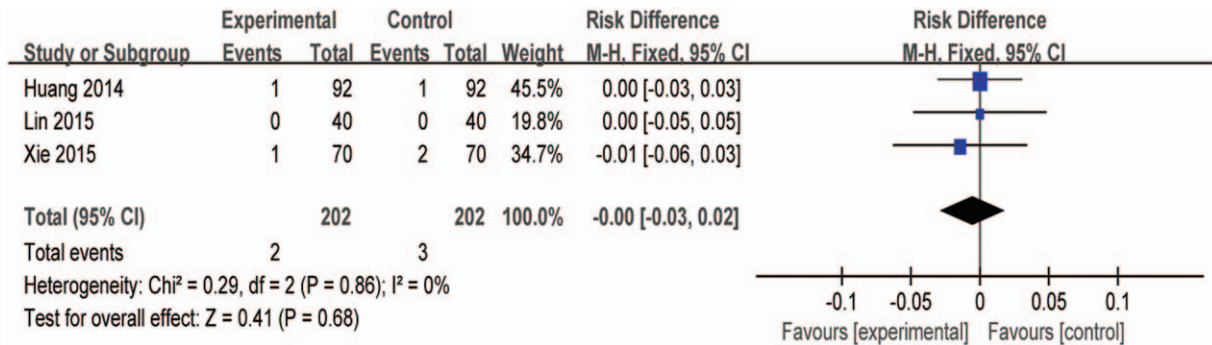

Figure 9. Forest plot diagram showing effect of combination TXA on risk of superficial infection. TXA = tranexamic acid.

3.5.8. Superficial infection. The superficial infection incidence was reported in 3 studies.[8–10] A fixed-effects model was used because no significant heterogeneity was found among these studies ($\chi^2 = 0.29$, $df = 2$, $I^2 = 0\%$, $P = .86$). No significant difference in the incidence of superficial infection was found between the 2 groups (RD = −0.00, 95% CI: −0.03 to 0.02, $P = .68$; Fig. 9).

3.5.9. DVT. Five articles[8–12] reported the incidence of DVT following joint replacement. A fixed-effects model was used due to the low significant heterogeneity among these studies ($\chi^2 = 1.92$, $df = 4$, $I^2 = 0\%$, $P = .75$). No significant difference was found between the groups (RD = −0.00, 95% CI: −0.02 to 0.02, $P = 1.00$; Fig. 10).

3.5.10. PE. PE was reported in 5 studies.[8–12] A fixed-effects model was used because no significant heterogeneity was found among the studies ($\chi^2 = 0.00$, $df = 4$, $I^2 = 0\%$, $P = 1.00$). No significant difference was found in the PE incidence between the 2 groups (RD = 0.00, 95% CI: −0.01 to 0.01, $P = 1.00$).

3.5.11. Subgroup analysis for total blood loss. A subgroup analysis was performed to assess total blood loss. Only studies in which unilateral TKA was performed were included. A fixed-effects model was used because no significant heterogeneity was found among these groups ($\chi^2 = 4.18$, $df = 2$, $I^2 = 52\%$, $P = .12$), maybe the surgical design led to the heterogeneity. A significant difference was observed between the 2 groups (MD = −157.96, 95% CI: −206.31 to −109.61, $P < .00001$; Fig. 11).
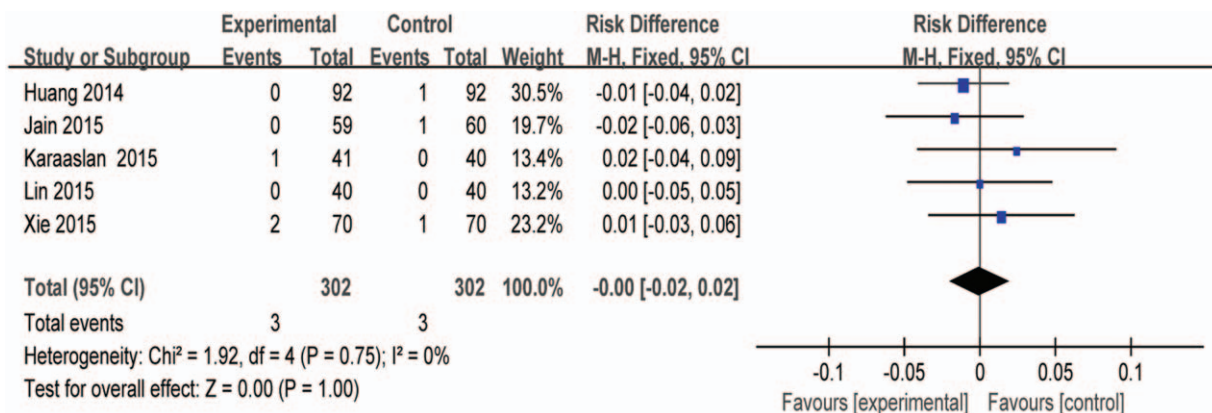

Figure 10. Forest plot diagram showing effect of combination TXA on risk of DVT. DVT = deep venous thrombosis, TXA = tranexamic acid.
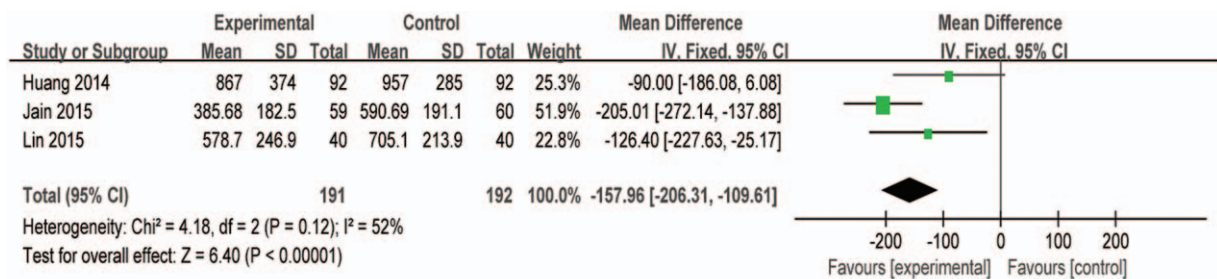
Figure 11. Subgroup analysis for total blood loss.

4. Discussion

The most important finding of the meta-analysis was that the combined application of intravenous and intraarticular TXA in patients with TKA and THA was associated with a significantly reduced postoperative hemoglobin decline, transfusion requirements, and drainage volume compared with the single application. Moreover, no increased risk of the incidence of infection, DVT and or PE was identified. The combined application of TXA was not associated with a prolonged operation time or length of stay.

Substantial articles have demonstrated that the use of TXA was associated with excellent outcomes for patients undergoing total joint arthroplasty.[13–15] Zeng et al[16] indicated that combined application of TXA can significantly minimize the total blood loss and transfusion rates.[17] Lin et al[9] also provided similar finding. In our study, only RCTs which compared combined and single use of TXA in reducing blood loss in total joint arthroplasty were included in our study and we found that combined intravenous and topical application of TXA could significantly decrease total blood loss and transfusion requirements. Subgroup analysis was performed in terms of total blood loss and we only included patients who undergoing TKA. Results studies were consistent with the findings of our meta-analysis.

Previous clinical studies have reported that joint arthroplasty without antifibrinolytics was associated with substantial bleeding ranging from 700 to 1800 mL[18–21] and 10.2% to 19%[22–25] of them received transfusions. Allogenic blood transfusion is associated with side events, such as disease transmission, hemolytic reaction, and cardiovascular dysfunction, resulting in a financial burden and potentially life-threatening effects on patients.[4] Various studies have focused on the hemostatic effects of TXA in orthopedic surgery.[26,27] The present meta-analysis indicated that there was significant difference between combined and single use groups regarding the transfusion requirements and postoperative hemoglobin level in patients with total joint arthroplasty. Considering that only 5 studies were included in our study. More RCTs with large sample size were needed for future research.

Surgical site infection remains a devastating complication that is a deep concern for patients and surgeons alike. It may lead to periprosthetic joint infection which prolonged hospital stays, delayed recoveries, and subsequent revision surgeries which are a financial burden.[28] It has been reported that the infection rate of total knee arthroplasty (TKA) is 1% to 3% and 0.7% to 2.5% for total hip arthroplasty (THA).[29] The present meta-analysis showed no significant difference in the incidence of infection. Larger RCTs with more patients are required to confirm whether the combined treatment strategy is safe without increasing the risk of infection.

There would be a high risk of thrombotic complications when utilizing the TXA for the antifibrinolytic effect.[30] The most common thrombotic events were DVT and PE which could induce severe results and even death after arthroplasty surgery. Previous articles have indicated that no increased risk of DVT or PE were observed when topical or intravenous administration of TXA.[31] All the included studies in our studies also showed no significant difference in the incidence rate of DVT or PE in the combined groups which was in accordance with the previous studies. However, due to the small amount of the included studies, more RCTs with longer follow up are required to confirm our conclusion.

Several potential limitations of this study should be noted. Only 5 RCTs were included, and the sample size was relatively small. Some important outcome parameters such as range of motion were not fully described and could not be included in the meta-analysis. The methods of random sequence generation, allocation concealment, and blinding were unclear or not described in some included studies which may influence our result. Short-term follow-up may lead to the underestimation of complications. Publication bias is an inherent weakness that exists in all meta-analyses.

Despite the limitations above, this is the first meta-analysis from RCTs to compare the efficiency and safety of the combined and single application of TXA in patients with total joint arthroplasty. There is a need for an adequately sized, placebo-controlled trial with a well-defined protocol for blood transfusion and a protocol for evaluating tranexamic acid-related adverse events to shed more light on the effectiveness of TXA given perioperatively to reduce blood loss. Future research should also focus on optimal dose, appropriate application with TXA.

4.1. Implications for practice and research

We assessed the quality of the evidence as high; therefore, we highly recommended the combined use of TXA for reducing blood loss in patients with TKA and THA. Further studies should focus on multimodal hemostasis strategies that may deliver significant clinical benefits through reduced blood loss, potential side effects also should be detected by long-term follow-up.

5. Conclusions

Combined administration of TXA in TKA and THA was associated with significantly reduced total blood loss, postoperative hemoglobin decline, drainage volume, and transfusion requirements. Well-designed, high-quality RCTs with long-term follow-up are still required.

References

[1] Sculco TP. Global blood management in orthopaedic surgery. Clin Orthop Relat Res 1998;357:43–9.

[2] Mannucci PM, Levi M. Prevention and treatment of major blood loss. New Engl J Med 2007;356:2301–11.

[3] Conteduca F, Massai F, Iorio R, et al. Blood loss in computer-assisted mobile bearing total knee arthroplasty. A comparison of computer-assisted surgery with a conventional technique. Int Orthop 2009;33:1609–13.

[4] Bilgili MG, Ercin E, Peker G, et al. Efficiency and cost analysis of cell saver auto transfusion system in total knee arthroplasty. Balkan Med J 2014;31:149–53.

[5] Benoni G, Lethagen S, Fredin H. The effect of tranexamic acid on local and plasma fibrinolysis during total knee arthroplasty. Thromb Res 1997;85:195–206.

[6] Cid J, Lozano M. Tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a meta-analysis of randomized controlled trials. Transfusion 2005;45:1302–7.

[7] Xu X, Xiong S, Wang Z, et al. Topical administration of tranexamic acid in total hip arthroplasty: a meta-analysis of randomized controlled trials. Drug Discov Therap 2015;9:173–7.

[8] Huang Z, Ma J, Shen B, et al. Combination of intravenous and topical application of tranexamic acid in primary total knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty 2014;29:2342–6.

[9] Lin SY, Chen CH, Fu YC, et al. The efficacy of combined use of intraarticular and intravenous tranexamic acid on reducing blood loss and transfusion rate in total knee arthroplasty. J Arthroplasty 2015;30:776–80.

[10] Xie J, Ma J, Yue C, et al. Combined use of intravenous and topical tranexamic acid following cementless total hip arthroplasty: a randomised clinical trial. Hip Int 2015;26:36–42.

[11] Karaaslan F, Karaoglu S, Mermerkaya MU, et al. Reducing blood loss in simultaneous bilateral total knee arthroplasty: combined intravenous-intra-articular tranexamic acid administration. A prospective randomized controlled trial. Knee 2015;22:131–5.

[12] Jain NP, Nisthane PP, Shah NA. Combined administration of systemic and topical tranexamic acid for total knee arthroplasty: Can it be a better regimen and yet safe? A randomized controlled trial. J Arthroplasty 2015;31:542–7.

[13] Alshryda S, Sukeik M, Sarda P, et al. A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. Bone Joint J 2014;96-B:1005–15.

[14] Wang H, Shen B, Zeng Y. Comparison of topical versus intravenous tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled and prospective cohort trials. Knee 2014;21:987–93.

[15] Wei Z, Liu M. The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: a meta-analysis of 2720 cases. Transfus Med 2015;25:151–62.

[16] Zeng Y, Si HB, Shen B, et al. Intravenous combined with topical administration of tranexamic acid in primary total hip arthroplasty: a randomized controlled trial. Orthop Surg 2017;9:174–9.

[17] Ronday HK, Te Koppele JM, Greenwald RA, et al. Tranexamic acid, an inhibitor of plasminogen activation, reduces urinary collagen cross-link excretion in both experimental and rheumatoid arthritis. Br J Rheumatol 1998;37:34–8.

[18] Benoni G, Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. J Bone Joint Surg Br 1996;78:434–40.

[19] Camarasa MA, Olle G, Serra-Prat M, et al. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. Br J Anaesth 2006;96:576–82.

[20] Hiippala S, Strid L, Wennerstrand M, et al. Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. Br J Anaesth 1995;74:534–7.

[21] Veien M, Sorensen JV, Madsen F, et al. Tranexamic acid given intraoperatively reduces blood loss after total knee replacement: a randomized, controlled study. Acta Anaesthesiol Scand 2002;46:1206–11.

[22] Danninger T, Rasul R, Poeran J, et al. Blood transfusions in total hip and knee arthroplasty: an analysis of outcomes. TheScientificWorldJournal 2014;2014:623460.

[23] Frisch NB, Wessell NM, Charters MA, et al. Predictors and complications of blood transfusion in total hip and knee arthroplasty. J Arthroplasty 2014;29(Suppl):189–92.

[24] Klika AK, Small TJ, Saleh A, et al. Primary total knee arthroplasty allogenic transfusion trends, length of stay, and complications: nationwide inpatient sample 2000–2009. J Arthroplasty 2014;29:2070–7.

[25] Yoshihara H, Yoneoka D. National trends in the utilization of blood transfusions in total hip and knee arthroplasty. J Arthroplasty 2014;29:1932–7.

[26] Digas G, Koutsogiannis I, Meletiadis G, et al. Intra-articular injection of tranexamic acid reduce blood loss in cemented total knee arthroplasty. Eur J Orthop Surg Traumatol 2015;25:1181–8.

[27] Pitta M, Zawadsky M, Verstraete R, et al. Intravenous administration of tranexamic acid effectively reduces blood loss in primary total knee arthroplasty in a 610-patient consecutive case series. Transfusion 2016;56:466–71.

[28] de Dios M, Cordero-Ampuero J. [Risk factors for infection in total knee artrhoplasty, including previously unreported intraoperative fracture and deep venous thrombosis]. Revista espanola de cirugia ortopedica y traumatologia 2015;59:36–43.

[29] Soriano A, Bori G, Garcia-Ramiro S, et al. Timing of antibiotic prophylaxis for primary total knee arthroplasty performed during ischemia. Clin Infect Dis 2008;46:1009–14.

[30] Wang C, Han Z, Zhang T, et al. The efficacy of a thrombin-based hemostatic agent in primary total knee arthroplasty: a meta-analysis. J Orthop Surg Res 2014;9:90.

[31] Raveendran R, Wong J. Tranexamic acid: more evidence for its use in joint replacement surgery. Transfusion 2014;54:2–3.