Systematic Review and Meta-Analysis

Medicine

OPEN

Is the combined application of both drain-clamping and tranexamic acid superior to the single use of either application in patients with total-knee arthroplasty?

A meta-analysis of randomized controlled trials

Yan-hong Han, MD[a], He-tao Huang, PhD[a], Jian-ke Pan, PhD[b], Ling-feng Zeng, PhD[b,c], Gui-hong Liang, MD[b,c], Hao-dong Liang, MD[a], Wei-yi Yang, PhD[b], Da Guo, PhD[b], Jun Liu, PhD[b,c,*]

Abstract

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

Methods: Databases (EMBASE, PubMed, Cochrane Library, Web of Sciences, the Google database, and the Ovid database) were searched from their inception through April 2018 for randomized controlled trials (RCTs) comparing the combined application of both drain-clamping and TXA versus single use of either application in patients with TKA. The Cochrane risk of bias (ROB) tool was used to assess the methodologic quality. The primary outcomes were blood loss in drainage, total blood loss, transfusion rate, and hemoglobin decline. The secondary outcomes were postoperative complications, the Knee Society Score (KSS), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. The statistical analysis was performed with RevMan 5.3.5 software.

Results: A total of five RCTs (479 participants) were included in our meta-analysis. The present meta-analysis indicated that significant differences existed in the total blood loss (mean difference [MD] = −145.86, 95% confidence interval [CI]: −228.64 to −63.08, P = .0006), blood loss in drainage (MD = −169.06, 95% CI: −248.56 to −89.57, P < .0001), hemoglobin decline (MD = −0.66, 95% CI: −1.00 to −0.33, P = .0001), and transfusion rate (MD = 0.44, 95% CI: 0.26–0.75, P = .002) between the groups. However, regarding postoperative complications, no significant differences were found between the 2 groups in the KSS and the WOMAC score (P > .05).

Conclusion: Combined application of both drain-clamping and TXA was associated with significant reductions in blood loss in drainage, total blood loss, hemoglobin decline, and the need for transfusion. However, high-quality, well-designed RCTs with long-term follow-up are still required.

Abbreviations: CIs = confidence intervals, HRB = high risk of bias, KSS = the Knee Society Score, LRB = low risk of bias, MD = mean difference, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, RCTs = randomized controlled trials, ROB = risk of bias, TJA = total-joint arthroplasty, TKA = total-knee arthroplasty, TXA = tranexamic acid, WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index score.

Keywords: drain-clamping, meta-analysis, randomized control trials, total-knee arthroplasty, tranexamic acid

Editor: Saeed Alzghari.

YHH, HTH, and JKP authors contributed equally to this work.

This study was supported by the National Ministry of Industry and the State Health Planning Commission "orthopedic surgery robot application center" construction projects (no: 2017MHDOSR1008), the Project of Guangdong Provincial Department of Finance (nos: [2014]157 and [2018]8), the Science and Technology Research Project of Guangdong Provincial Hospital of Chinese Medicine (no: YKYN2015MS15).

The authors have no conflicts of interest to disclose.

[a] Second School of Clinical Medicine, Guangzhou University of Chinese Medicine, [b] Department of Orthopaedics, Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangdong Provincial Hospital of Chinese Medicine), [c] Bone and Joint Research Team of Degeneration and Injury, Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, China.

[*] Correspondence: Jun Liu, Bone and Joint Research Team of Degeneration and Injury, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou 510120, China (e-mail: liujun.gdtcm@hotmail.com)

Medicine (2018) 97:36(e11573)

Received: 16 October 2017 / Accepted: 28 June 2018

http://dx.doi.org/10.1097/MD.0000000000011573

1. Introduction

The rate of total-joint arthroplasty (TJA) has increased considerably over the past decade with the aging population and improvements in medical technology. Total-knee arthroplasty (TKA) is a popular, well-known surgical procedure for the treatment of degenerative disorders and traumatic diseases.[1] However, TKA surgeries are usually complicated by postoperative bleeding, which can lead to significant postoperative anemia and transfusion requirements.[2–4] Allogenic blood transfusion is associated with adverse events, such as hemolytic reactions, immunologic reactions, disease transmission, transfusion-related acute renal failure, and cardiovascular dysfunction, resulting in financial burdens and potentially life-threatening effects on patients.[5–7] To date, various strategies have been attempted to minimize blood loss, including drug intervention, autologous donation, and allogenic blood transfusion.[8] In addition, several methods for bleeding control have been successfully employed in an effort to reduce postoperative blood loss and transfusion, including drain-clamping, tranexamic acid (TXA) administration, and tourniquets, among others.[4,6,9]

Recent studies have focused on TXA to reduce perioperative blood loss in patients following TKA.[10] TXA 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.[11] Previous studies have indicated that topical or intravenous TXA was effective and safe.[12–14] Drain-clamping is one method proposed to reduce blood loss in the early postoperative period of TKA. The routine clamping of drains used in TKA has been advocated by some but remains a controversial topic even among surgeons who still use postoperative drains.[9–15] Several methods have been reported to reduce blood loss and the need for blood transfusion after TKA; however, the best method remains unknown. We are interested in both drain-clamping[16–18] and TXA administration[19,20] as simple methods of bleeding control. The combined effect of these 2 methods remains unknown. Recently, the combined application of both drain-clamping and TXA administration in TKA have become increasingly popular among orthopedic surgeons.

Although previous studies have compared the efficacy of the combined use of drain-clamping and TXA in knee arthroplasty, it is still unclear whether the combined use of drain-clamping and TXA is superior to the use of either strategy alone due to limitations in the number of studies and small sample sizes. Therefore, we conducted a meta-analysis of clinical randomized controlled trials (RCTs) of the combined use of drain-clamping and TXA to evaluate the efficacy and safety of the combination.

2. Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria, we created a prospective protocol including objectives, literature-search strategies, inclusion and exclusion criteria, outcome measurements, and methods of statistical analysis before commencing the study. The study was approved by the ethics committee of Guangdong Provincial Hospital of Chinese Medicine. This review is registered in Research Registry: reviewregistry313 (http://www.researchregistry.com/).

2.1. Search strategy

A comprehensive search was performed in the PubMed, EMBASE, Cochrane Library, Web of Sciences, the Google database, and the Ovid database up to April 2018. Only English-language articles were selected. The search terms included "tranexamic acid," "arthroplasty, replacement, knee," "total-knee arthroplasty," "total-knee replacement," "total-knee prosthes," "drainage," "drain," "clamping," and "delayed releasing." The related references in the identified studies were manually searched.

2.2. Inclusion criteria and study selection

2.2.1. Participants. Only published articles with adult participants with a diagnosis of end-stage osteoarthritis undergoing TKA were included.

2.2.2. Interventions. The intervention group received intravenous or intra-articularly TXA plus drain-clamping for perioperative blood management, and no restriction on the dose of TXA or the duration of clamping was applied.

2.2.3. Comparisons. The control groups received only TXA or only drain-clamping.

2.2.4. Outcomes. The outcomes assessed were total blood loss, blood loss in drainage, hemoglobin decline, transfusion rate, postoperative complications, the Knee Society Score (KSS), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.

2.2.5. Study design. The RCTs were regarded as eligible in our study. Articles were excluded from the current meta-analysis, if they were duplicate articles, case reports, cohort studies, reviews, editorials, letters, conference abstracts, or animal experimental studies. Two reviewers independently scanned the titles and abstracts of the potential articles identified by the above searches. Subsequently, the full text of the studies that met the inclusion criteria were screened, and a final decision was made. Any disagreements were resolved by discussion or were arbitrated by the corresponding author (JL).

2.3. Data extraction

Two reviewers (Han and Pan) independently extracted the key data from the included studies: first authors' names, date of publication, sample size, patients' age and gender, surgical procedures, dose of TXA, clamping time, and follow-up periods. The primary outcomes were transfusion rate, blood loss in drainage, total blood loss, and hemoglobin decline. The secondary outcomes were postoperative complications, the KSS, and the WOMAC score. In the event of missing data, we attempted to contact the corresponding authors for details.

2.4. Assessment of methodologic quality

Two independent reviewers (Han and Luo) evaluated the methodologic quality of the included studies using the risk of bias (ROB) tool provided by the Cochrane collaboration. The following 7 items were assessed in all included studies: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other bias. Each item was assigned a judgment of "a high risk of bias (HRB)," "an unclear risk," or "a low risk of bias (LRB)" based on the data presented in the article.[21] Namely, the judgment was "high risk," if the item was reported incorrectly. The judgment was "low risk" if the item possessed sufficient and correct information. If the item possessed insufficient or unmentioned information, the judgment was "an unclear risk." An "unclear risk" judgment was also assigned if the item was reported, but the ROB was unknown. Disagreements were addressed by obtaining a consensus between experienced reviewers (Han and Liu).

2.5. Data analysis and statistical methods

The statistical analysis was performed with RevMan 5.3.5 (The Cochrane Collaboration, Oxford, UK) software by 2 reviewers (Han and Zeng). The mean difference (MD) and odds ratio (OR), both of which are reported with 95% confidence intervals (CIs), were adopted to analyze continuous variables and dichotomous data, respectively. The I^2 value was used to estimate statistical heterogeneity. When $I^2 > 50\%$, heterogeneity was accepted, and the randomized-effects model was adopted. Otherwise, the fixed-effects model was adopted. A sensitivity analysis was performed to identify the source of the heterogeneity. For all analyses, $P < .05$ was considered statistically significant.

3. Results

3.1. Search results

A total of 282 records were identified from the electronic databases (EMBASE=68, PubMed=75, Cochrane Library=98, Web of Science=9, Google database=6, and Ovid database=26). No gray literature was included. After a thorough screening of titles and abstracts, 126 records were excluded. The remaining 19 articles were assessed by full-text review. Ultimately, 5 clinical studies[10,22–25] met the inclusion criteria and were included in the meta-analysis (Fig. 1).

3.2. Study characteristics

The characteristics of the included studies are presented in Table 1. All of the studies performed TKA. The data set consisted of 479 participants. In these studies, the experimental groups received combined drain-clamping and TXA and the control groups received either TXA or drain-clamping alone. The gender ratios, average ages, types of surgery, follow-up times, and outcomes were also noted. In each study, the demographic characteristics of the 2 groups were similar.

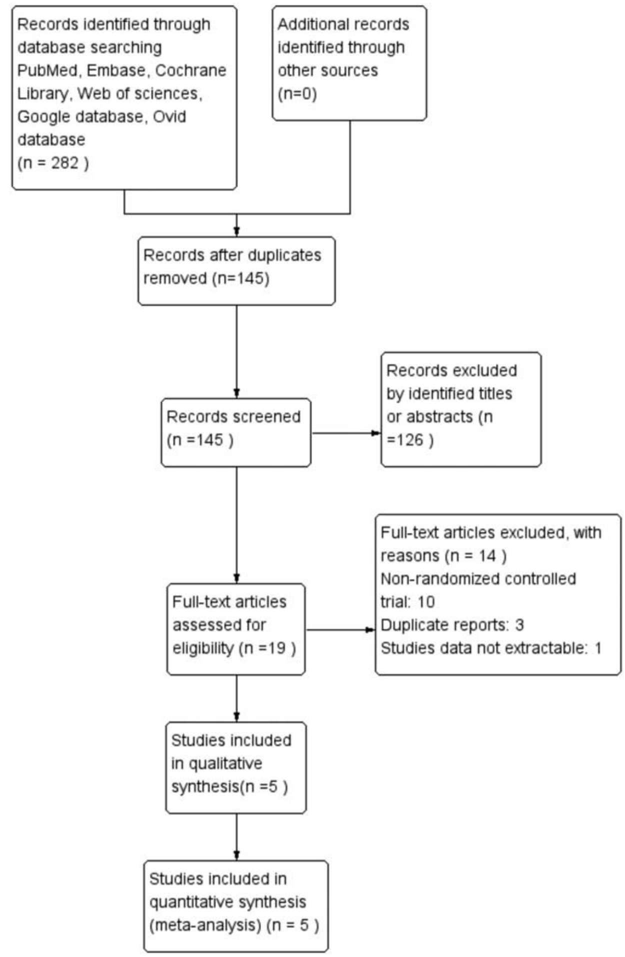

Figure 1. Flow diagram of the identified, included, and excluded studies.

3.3. Assessment of the ROB

We evaluated the methodologic quality of all studies using the Cochrane ROB criteria. The assessment of ROB is shown in Figures 2 and 3. Randomly generated sequences were judged as

Table 1

Characteristics of the studies.

Author	Date	Patient: Cases (E/C)	Patient: Mean age (E/C)	Patient: Gender (F/M)	Type of surgery	Intervention: E	Intervention: C	Outcomes	Follow-up
Chareancholvanich et al[23]	2012	60/60	70.1/69.4	103/17	TKA	Preop 10 mg/kg TXA iv, postop 10 mg/kg TXA iv, and 3-h clamping	Preop 10 mg/kg TXA iv and postop 10 mg/kg TXA iv	2,3,4,5	6 mo
Sa-Ngasoongsong et al[25]	2011	24/24	69.0/69.2	40/8	TKA	250 mg TXA topical injection and 2-h clamping	2-h clamping	1,2,3,4,5,6	6 mo
Onodera et al[24]	2012	50/50	70.4/70.5	83/17	TKA	1 g TXA topical injection and 1-h clamping	1-h clamping	1,3,4,5	2 y
Sa-Ngasoongsong et al[22]	2013	45/45	67.6/66.2	85/5	TKA	250 mg TXA topical injection and 2-h clamping	2-h clamping	1,2,3,4,5,6,7	1 y
Wu et al[10]	2017	60/61	65.2/64.9	77/44	TKA	10 mg/kg TXA iv and 4-h clamping	10 mg/kg TXA iv	1,3,4,5	6 mo

Outcomes: 1=total blood loss, 2=blood loss in drainage, 3=hemoglobin decline, 4=transfusion rate, 5=complications, 6=Knee Society Score, 7=Western Ontario and McMaster Universities Osteoarthritis Index score.
C=control group, E=experiment group, F=female, iv=intravenous injection, M=male, TKA=total-knee arthroplasty, TXA = tranexamic acid.

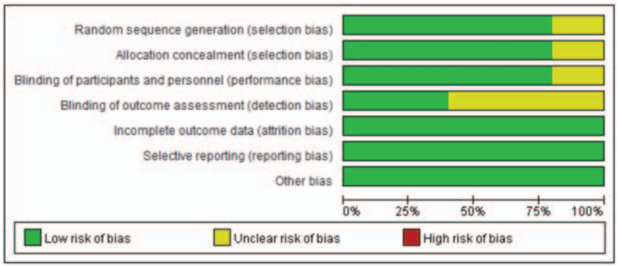

Figure 2. Risk of bias summary.

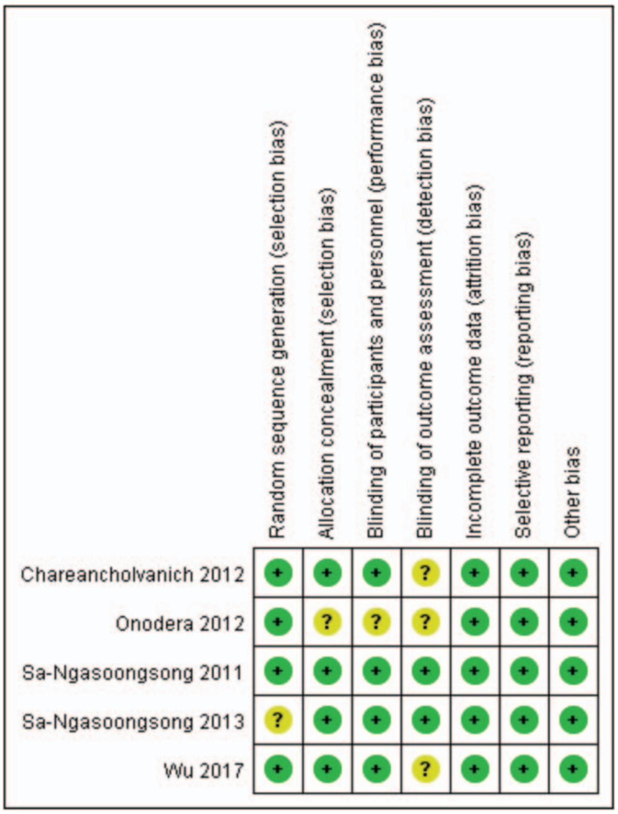

Figure 3. Risk of bias assessment.

an LRB in 4 studies.[10,23–25] However, 1 study[22] mentioned that the clinical trial was randomized, but did not report further details. Blinding of the treating doctors, the subjects, and the outcome assessors was judged as an LRB in 4 studies,[10,22,23,25] 4 studies,[10,22,23,25] and 2 studies,[22,25] respectively. None of the studies had a high risk of incomplete outcome data due to a lack of details in some adverse events. In addition, we did not identify selective reporting or other obvious sources of bias in these studies.

3.4. Outcomes of the meta-analysis

3.4.1. Total blood loss. Total blood loss following the operation was reported in 4 studies[10,22,24,25] including 359 knees. Significant heterogeneity was found among these studies (χ^2 = 16.07, df = 3, I^2 = 81%, P = .001); therefore, a random-effects model was used. The pooled results demonstrated that compared with the control groups, the total blood loss was significantly reduced in the experimental groups (MD = −145.86, 95% CI: −228.64 to −63.08, P = .0006; Fig. 4).

3.4.2. Blood loss in drainage. Blood loss in drainage following the operation was reported in 3 studies[22,23,25] including 258 knees. Significant heterogeneity was found among these studies (χ^2 = 4.68, df = 2, I^2 = 57%, P = .10); therefore, a random-effects model was used. The pooled results demonstrated that compared with the control groups, blood loss in drainage was significantly reduced in the experimental groups (MD = −169.06, 95% CI: −248.56 to −89.57, P < .0001; Fig. 5).

3.4.3. Hemoglobin decline. Hemoglobin decline was reported in 4 studies,[22–25] including 358 knees. Significant heterogeneity was found among these studies (χ^2 = 9.48, df = 3, I^2 = 68%, P = .02); therefore, a random-effects model was used. The pooled results demonstrated that compared with the control groups, hemoglobin decline was significantly mitigated in the experimental groups (MD = −0.66, 95% CI: −1.00 to −0.33, P = .0001; Fig. 6).

3.4.4. Transfusion rate. The transfusion rate following the operation was reported in 5 studies,[10,22–25] including 479 knees. No significant heterogeneity was found among these studies (χ^2 = 3.85, df = 4, I^2 = 0%, P = .43); therefore, a fixed-effects model was used. The pooled results demonstrated that compared with the control groups, the transfusion rate was significantly reduced in the experimental groups (MD = 0.44, 95% CI: 0.26–0.75, P = .002; Fig. 7).

3.4.5. Complications. The outcomes of postoperative complications were reported in 5 studies.[10,22–25] A random-effects model was used because significant heterogeneity was found among these studies (χ^2 = 7.45, df = 2, I^2 = 73%, P = .02). The pooled results demonstrated that no significant difference in the complications was observed between the 2 groups (OR = 0.73, 95% CI: 0.22–2.42, P = .60; Fig. 8).

3.4.6. Knee Society Score. The outcomes of the KSS following the operation were reported in 2 studies.[22,25] All pooled

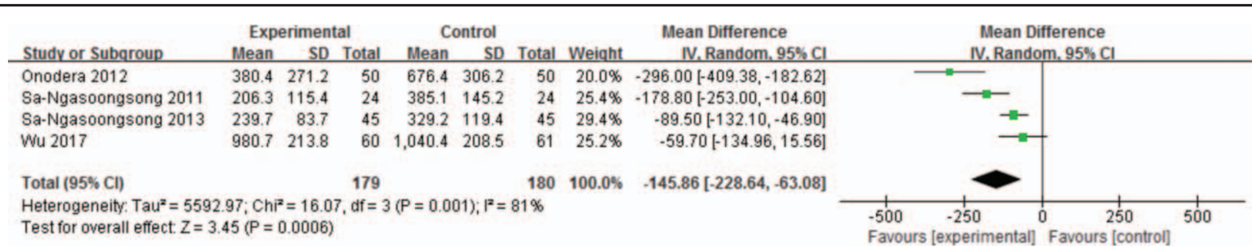

Figure 4. Forest plot comparing total blood loss between the 2 groups.

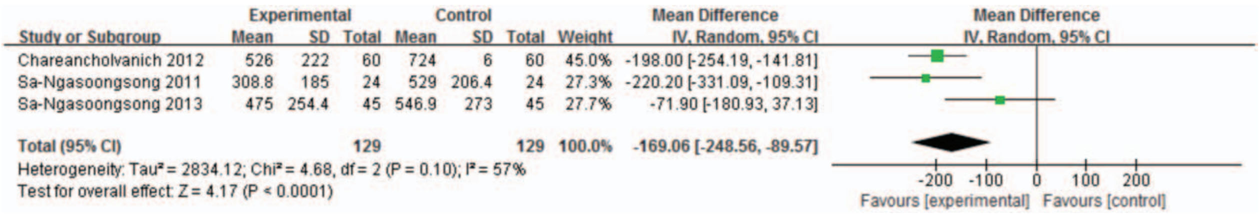

Figure 5. Forest plot comparing blood loss in drainage between the 2 groups.

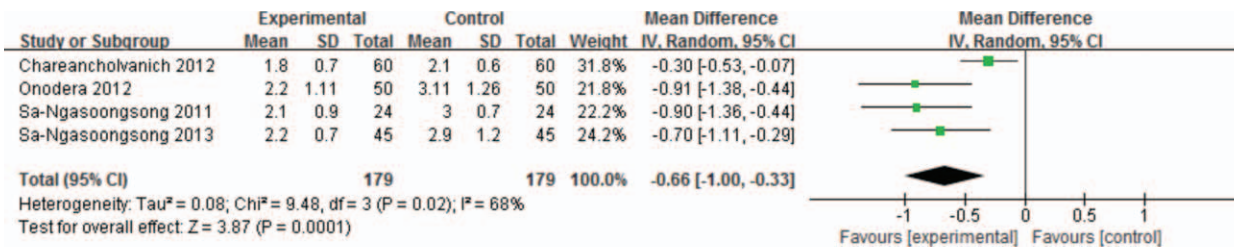

Figure 6. Forest plot comparing hemoglobin decline between the 2 groups.

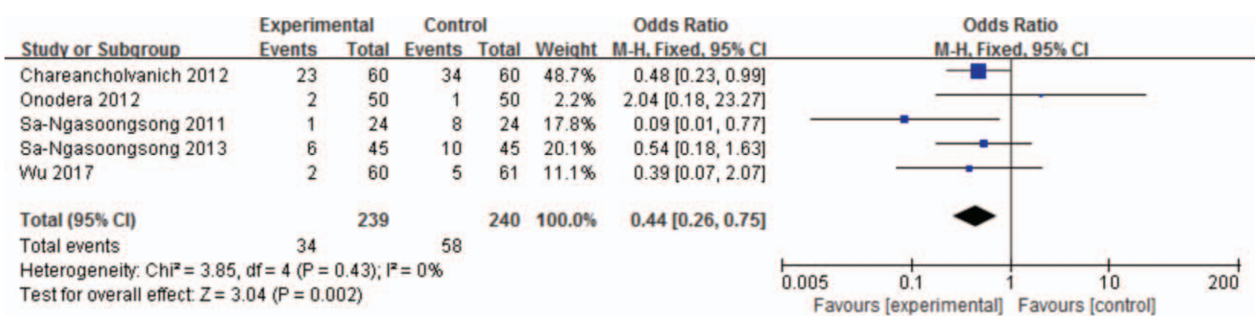

Figure 7. Forest plot comparing transfusion rate between the 2 groups.

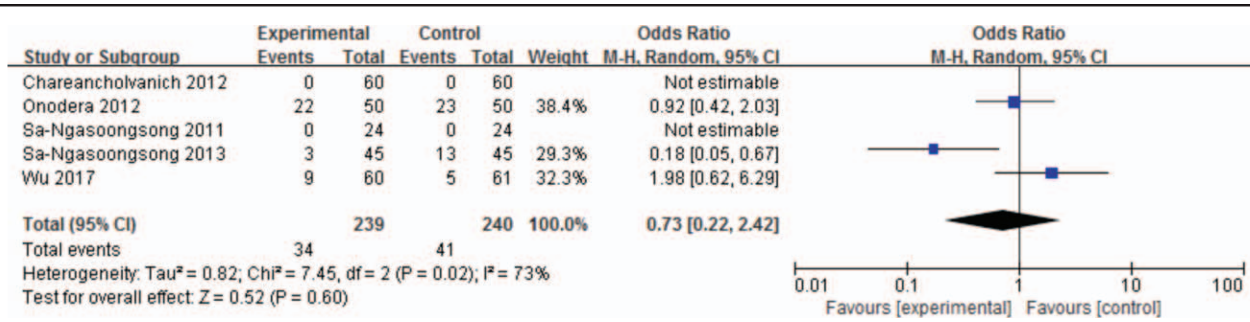

Figure 8. Forest plot comparing complications between the 2 groups.

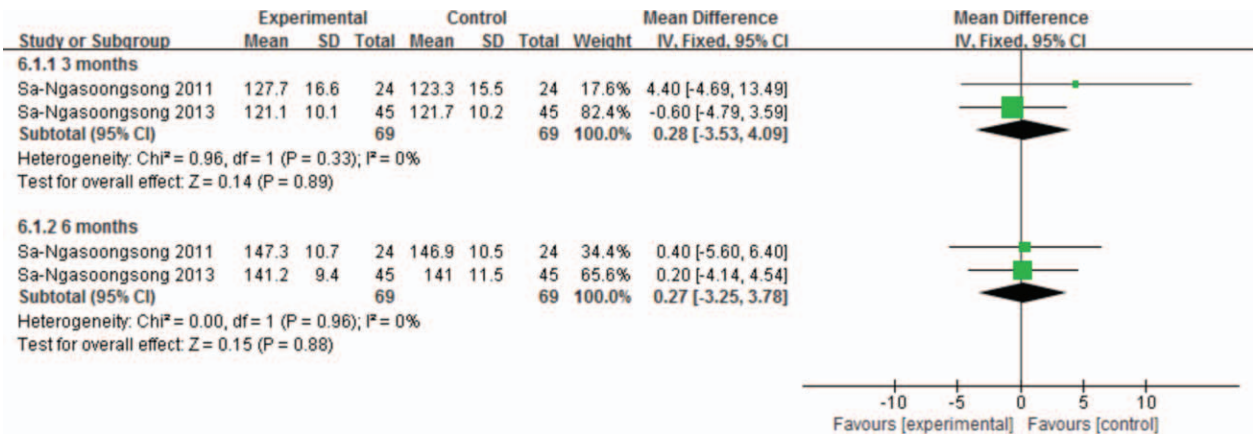

Figure 9. Forest plot comparing the Knee Society Score between the 2 groups.

analyses were conducted with a fixed-effects model because no statistically significant heterogeneity was identified. The results showed that there were no significant differences in the KSS between the 2 groups at 3 months (MD = 0.28, 95% CI: −3.53 to 4.09, P = .89) or 6 months (MD = 0.27, 95% CI: −3.25 to 3.78, P = .88; Fig. 9) postoperation.

3.4.7. WOMAC score. Two studies[22,25] reported the outcomes of the WOMAC score following the operation. All pooled analyses were conducted with a fixed-effects model because of no statistically significant heterogeneity. The results showed no significant differences in the WOMAC score between the 2 groups at 3 months (MD = −1.29, 95% CI: −4.06 to 1.48, P = .36) postoperatively. However, the experimental groups exhibited a better efficacy than the control groups at 6 months (MD = −2.27, 95% CI: −4.44 to −0.10, P = .04; Fig. 10) postoperatively.

4. Discussion

The TXA, a synthetic antifibrinolytic agent for preventing postoperative hemorrhage, has been shown by many studies to play an important role in the prognosis of patients with TJA.[14,26,27] The initial fibrinolysis may be due to surgical trauma and further enhanced by the use of a tourniquet.[28,29] The presence of these causes may lead to increased postoperative bleeding, especially within a few hours after TKA.[30] TXA blocks the interaction of the plasmin heavy chain by acting on the lysine binding site on the fibrinolytic zymogen molecule, thereby preventing plasmin from degrading fibrin and achieving hemostasis.[31]

However, previous studies reported that clamping the drainage is controversial in TKA. Additionally, the method of clamping varies, and the duration of drainage in different studies ranges from 1 to 24 hours postoperatively.[9,18,32] Huang et al[33] have reported that temporary drain-clamping can significantly reduce postoperative drainage at 24 and 48 hours.[34] In addition, compared with patients without drain-clamping, patients with temporary drain-clamping for more than 4 hours had higher levels of hemoglobin at 24 hours postoperation and fewer blood transfusions.[33] Shen et al[32] also found significantly less average blood drainage in the clamped drainage group (514.85 mL) than in the nonclamped drainage group (843.4 mL), without serious wound problems.

Recently, several studies have compared the efficacy of drain-clamping combined with TXA administration for bleeding control following TKA. Chareancholvanich et al[23] found that drain-clamping combined with TXA administration significantly

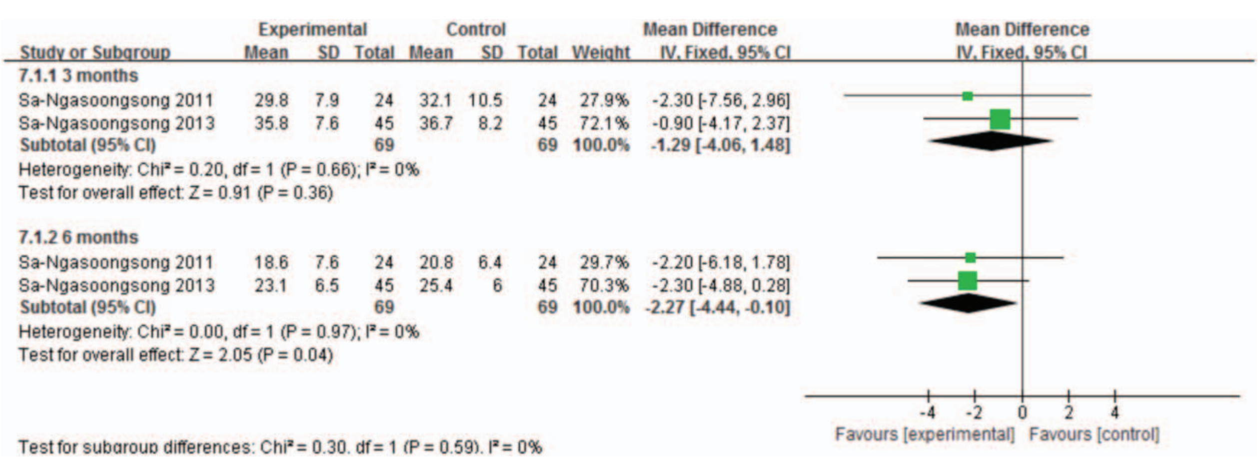

Figure 10. Forest plot comparing the Western Ontario and McMaster Universities Osteoarthritis Index score between the 2 groups.

reduced postoperative blood loss and blood transfusion after TKA compared to using TXA or drain-clamping alone. Theoretically, clamping the drainage system can result in temporary hemostasis by creating a tamponade effect in the joint, which effectively results in less blood loss and a lower transfusion rate.[35] Sa-ngasoongsong et al[22] also found that the combination of low-dose TXA and 2-hour drain-clamping was effective for reducing postoperative blood loss and transfusion requirements in conventional TKA.

As in the previous study,[36,37] our meta-analysis findings showed that compared to the single strategies, the combined application of both drain-clamping and TXA administration was associated with significant reductions in total blood loss, blood loss in drainage, hemoglobin decreases, and transfusion requirements. Zhang et al[36] found that compared to TXA alone, drain-clamping alone, or control treatment, TXA plus drain-clamping achieved a maximal hemostasis effect in patients undergoing primary TKA. Furthermore, the results reported by Liao et al[37] were similar. No increased risk of deep venous thrombosis was identified. However, no studies have focused on the effect of postoperative knee function recovery. Our study showed no significant differences in postoperative knee function between the 2 groups. Since only 2 studies reported KSSs and WOMAC scores, the limited number of included studies may result in insufficient validity of the results. Further verification of the results with more RCTs is required in the future.

Several potential limitations of this study should be noted. Our meta-analysis included only 5 RCTs with a total of 479 patients; thus, the power for all outcomes may be limited by the small sample size. The methods of random sequence generation, allocation concealment, and blinding were unclear or not described in some of the included studies, which may influence our results. Some important clinical outcomes, such as the knee range of motion, have not been fully reported, and thus are difficult to include in meta-analyses. Furthermore, the lack of a long-term follow-up period may lead to the underestimation of complications. All meta-analyses may have inherent weaknesses in publication bias.

Despite the above limitations in our study, this is the first meta-analysis of RCTs comparing whether the combined application of both drain-clamping, and TXA is superior to the use of either alone in patients with TKA. Future research should also focus on the best timing for clamping and the optimal dose of TXA.

5. Conclusion

Combined application of both drain-clamping and TXA was associated with significant reductions in blood loss assessed by drainage, total blood loss, hemoglobin decreases, and the need for transfusion. However, high-quality, well-designed RCTs with long-term follow-up are still required.

Author contributions

Conceived and designed the experiments: JL. Performed the experiments: YHH, JKP, LFZ, and JL. Analyzed the data: YHH, JKP, LFZ, HTH, HDL, WYY, and JL. Contributed reagents/materials/analysis tools: YHH, GHL, HTH, DG, and JL. Wrote the paper: YHH, JKP, and GHL.
Conceptualization: Jun Liu.
Data curation: Yan-hong Han, Jian-ke Pan, Gui-hong Liang.
Formal analysis: Gui-hong Liang.
Funding acquisition: Jun Liu.
Investigation: Ling-feng Zeng, Hao-dong Liang.
Methodology: He-tao Huang, Wei-yi Yang.
Project administration: Jun Liu.
Resources: Jian-ke Pan, Ling-feng Zeng.
Software: Yan-hong Han.
Supervision: Da Guo, Jun Liu.
Validation: He-tao Huang, Hao-dong Liang, Wei-yi Yang.
Visualization: Da Guo.
Writing – original draft: Yan-hong Han, Jian-ke Pan.
Writing – review & editing: Jun Liu.

References

[1] Kim DH, Lee GC, Lee SH, et al. Comparison of blood loss between neutral drainage with tranexamic acid and negative pressure drainage without tranexamic acid following primary total knee arthroplasty. Knee Surg Relat Res 2016;28:194–200.
[2] Mannucci PM, Levi M. Prevention and treatment of major blood loss. N Engl J Med 2007;356:2301–11.
[3] Sculco TP. Global blood management in orthopaedic surgery. Clin Orthop Relat Res 1998;43–9.
[4] Kumar A. Perioperative management of anemia: limits of blood transfusion and alternatives to it. Cleve Clin J Med 2009;76(Suppl 4):S112–8.
[5] 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.
[6] Dennis DA, Kittelson AJ, Yang CC, et al. Does tourniquet use in TKA affect recovery of lower extremity strength and function? A randomized trial. Clin Orthop Relat Res 2016;474:69–77.
[7] Pornrattanamaneewong C, Narkbunnam R, Siriwattanasakul P, et al. Three-hour interval drain clamping reduces postoperative bleeding in total knee arthroplasty: a prospective randomized controlled trial. Arch Orthop Trauma Surg 2012;132:1059–63.
[8] 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.
[9] 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.
[10] Wu Y, Yang T, Zeng Y, et al. Clamping drainage is unnecessary after minimally invasive total knee arthroplasty in patients with tranexamic acid: a randomized, controlled trial. Medicine (Baltimore) 2017;96:e5804.
[11] 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.
[12] Lin C, Qi Y, Jie L, et al. Is combined topical with intravenous tranexamic acid superior than topical, intravenous tranexamic acid alone and control groups for blood loss controlling after total knee arthroplasty: a meta-analysis. Medicine (Baltimore) 2016;95:e5344.
[13] Jiang X, Ma XL, Ma JX. Efficiency and safety of intravenous tranexamic acid in simultaneous bilateral total knee arthroplasty: a systematic review and meta-analysis. Orthop Surg 2016;8:285–93.
[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] Niskanen RO, Korkala OL, Haapala J, et al. Drainage is of no use in primary uncomplicated cemented hip and knee arthroplasty for osteoarthritis: a prospective randomized study. J Arthroplasty 2000;15:567–9.
[16] Ryu J, Sakamoto A, Honda T, et al. The postoperative drain-clamping method for hemostasis in total knee arthroplasty. Reducing postoperative bleeding in total knee arthroplasty. Bull Hosp Jt Dis 1997;56:251–4.
[17] Yamada K, Imaizumi T, Uemura M, et al. Comparison between 1-hour and 24-hour drain clamping using diluted epinephrine solution after total knee arthroplasty. J Arthroplasty 2001;16:458–62.
[18] Raleigh E, Hing CB, Hanusiewicz AS, et al. Drain clamping in knee arthroplasty, a randomized controlled trial. ANZ J Surg 2007;77:333–5.
[19] Hiippala ST, Strid LJ, Wennerstrand MI, et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg 1997;84:839–44.

[20] 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.
[21] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[22] Sa-Ngasoongsong P, Wongsak S, Chanplakorn P, et al. Efficacy of low-dose intra-articular tranexamic acid in total knee replacement; a prospective triple-blinded randomized controlled trial. BMC Musculoskelet Disord 2013;14:340.
[23] Chareancholvanich K, Siriwattanasakul P, Narkbunnam R, et al. Temporary clamping of drain combined with tranexamic acid reduce blood loss after total knee arthroplasty: a prospective randomized controlled trial. BMC Musculoskelet Disord 2012;13:124.
[24] Onodera T, Majima T, Sawaguchi N, et al. Risk of deep venous thrombosis in drain clamping with tranexamic acid and carbazochrome sodium sulfonate hydrate in total knee arthroplasty. J Arthroplasty 2012;27:105–8.
[25] Sa-Ngasoongsong P, Channoom T, Kawinwonggowit V, et al. Postoperative blood loss reduction in computer-assisted surgery total knee replacement by low dose intra-articular tranexamic acid injection together with 2-hour clamp drain: a prospective triple-blinded randomized controlled trial. Orthop Rev (Pavia) 2011;3:e12.
[26] 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.
[27] 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.
[28] Janssens M, Joris J, David JL, et al. High-dose aprotinin reduces blood loss in patients undergoing total hip replacement surgery. Anesthesiology 1994;80:23–9.
[29] Aglietti P, Baldini A, Vena LM, et al. Effect of tourniquet use on activation of coagulation in total knee replacement. Clin Orthop Relat Res 2000;169–77.
[30] Andersson L, Nilsson IM, Nilehn JE, et al. Experimental and clinical studies on AMCA, the antifibrinolytically active isomer of p-aminomethyl cyclohexane carboxylic acid. Scand J Haematol 1965;2:230–47.
[31] Hoylaerts M, Lijnen HR, Collen D. Studies on the mechanism of the antifibrinolytic action of tranexamic acid. Biochim Biophys Acta 1981;673:75–85.
[32] Shen PC, Jou IM, Lin YT, et al. Comparison between 4-hour clamping drainage and nonclamping drainage after total knee arthroplasty. J Arthroplasty 2005;20:909–13.
[33] Huang Z, Ma J, Pei F, et al. Meta-analysis of temporary versus no clamping in TKA. Orthopedics 2013;36:543–50.
[34] Tai TW, Yang CY, Jou IM, et al. Temporary drainage clamping after total knee arthroplasty: a meta-analysis of randomized controlled trials. J Arthroplasty 2010;25:1240–5.
[35] Kiely N, Hockings M, Gambhir A. Does temporary clamping of drains following knee arthroplasty reduce blood loss? A randomised controlled trial. Knee 2001;8:325–7.
[36] Zhang Y, Zhang JW, Wang BH. Efficacy of tranexamic acid plus drain-clamping to reduce blood loss in total knee arthroplasty: a meta-analysis. Medicine (Baltimore) 2017;96:e7363.
[37] Liao L, Chen Y, Tang Q, et al. Tranexamic acid plus drain-clamping can reduce blood loss in total knee arthroplasty: a systematic review and meta-analysis. Int J Surg 2018;52:334–41.