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Complete List of Authors:	Sun, Qi Li, Jinyu Chen, Jiang Zheng, Chenying Liu, Chuyin Jia, Yusong; Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital, Orthopedics
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Comparison of the different routes of tranexamic acid administration in patients undergoing total knee and hip arthroplasty: A PRISMA-compliant meta-analysis of randomized controlled trials

Qi Sun[1¶], Jinyu Li[1¶], Jiang Chen[1], Chenying Zheng[1], Chuyin Liu[1], Yusong Jia[1]*

[1]Department of Orthopedics, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing , China.

*Corresponding author E-mail: spioneer2001@sina.com

Qi Sun: sunqi2001@sina.com

Jinyu Li: lijinyu84@126.com

Jiang Chen: 964402173@qq.com

Chenying Zheng: zhengchenying99@sina.com

Chuyin Liu: 1827193473@qq.com

[¶]These authors contributed equally to this work.

Running title: TXA in treatment of TKA or THA

Abbreviations, Nomenclature and Symbols

TXA: tranexamic acid; TKA: total knee arthroplasty; THA: total hip arthroplasty; RCT: randomized controlled trials; RR: relative risk; WMD: weighted mean difference; CI: confidence interval; IV: intravenous; Hb: hemoglobin; LOS: length of stay; VTE: venous thromboembolism; TJA: total joint arthroplasty; PE: pulmonary embolism; DVT: deep vein thrombosis; LMWH: low molecular weight heparin.

Abstract

Objective: This study aimed to investigate the effects of tranexamic acid (TXA) on blood loss and transfusion requirements in patients undergoing total knee and hip arthroplasty (TKA and THA).

Design: This was a meta-analysis of randomized controlled trials (RCTs) in which the weighted mean difference (WMD) and the relative risk (RR) were used for data synthesis employed the random-effects model.

Setting: We searched the PubMed, Embase, and Cochrane CENTRAL databases for randomized controlled trials (RCTs) that compared different routes of TXA administration.

Participants: patients undergoing TKA or THA

Interventions: intravenous or topical TXA.

Results: Twenty-six RCTs were selected, and the IV route did not differ substantially from the topical route with regard to total blood loss (WMD = 30.92, P = 0.31), drain blood loss (WMD = –34.53, P = 0.50), postoperative hemoglobin (Hb) levels (WMD = –0.01, P = 0.96), Hb decline (WMD = –0.39, P = 0.08), length of hospital stay (WMD = 0.15, P = 0.38), transfusion rate (RR = 1.08, P = 0.75), and venous thromboembolism (VTE) occurrence (RR = 1.89, P = 0.15). Compared to the combined-delivery group, the single route group had significantly increased total blood loss (WMD = 198.07, P < 0.05), greater Hb decline (WMD = 0.56, P < 0.05), and higher transfusion rates (RR = 2.51, P < 0.05). However, the two groups did not differ significantly with regard to drain blood loss, postoperative Hb levels, and VTE events. The IV and topical routes had comparable efficacy and safety profiles.

Conclusions: The combined use of IV and topical TXA appeared to be relatively more effective at controlling bleeding without increasing the risk of VTE.

Strengths and limitations of this study

1. All of included studies with randomized controlled designed, and the uncontrolled biases could avoide.

2. The combination of topical and systemic administration of TXA was also calculated.

3. The heterogeneity was explored by sensitivity, subgroup, and meta-regression analyses.

4. The number of participants in most of the included studies was small, and the prevalence of VTE was low following joint replacement.

5. Only a small number of trials evaluated the combined-delivery group, which precluded sufficient exploration of heterogeneity through subgroup or meta-regression analysis

Keywords: tranexamic acid; total knee arthroplasty; total hip arthroplasty; IV; topical; meta-analysis

Introduction

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine, which inhibits the process of fibrinolysis by blocking the lysine binding site on plasminogen.[1] Currently, it is one of the most commonly used hemostatic drugs. TXA is capable of reducing blood loss in surgical patients by approximately 34%.[2,3] TXA has effectively reduced blood loss and the transfusion rate in various surgical settings, including in traumatic hemorrhage,[4] cesarean section,[5] endoscopic sinus surgery,[6] cardiac surgery,[7] and arthroplasty.[8]

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are reliable surgical procedures for patients suffering from moderate to severe degenerative joint diseases. Total joint arthroplasty (TJA) has proved effective in relieving pain, restoring physical function, and in improving health-related quality of life.[9] By 2030, the demand for primary THA is estimated to increase to 572,000, and that for primary TKA is estimated to grow to 3.48 million procedures.[10] Despite substantial advances in surgical and anesthetic techniques, TKA and THA are still associated with a large amount of perioperative blood loss.[11] Specifically, intraoperative blood loss during either of these procedures is generally between 500 mL to 1,500 mL. Additionally, patients may experience a postoperative drop in hemoglobin between 1 and 3 g/dL.[12] Up to 50% patients undergoing TJA inevitably experience postoperative anemia.[11]

The role of TXA during arthroplasty has been a hot but controversial issue for the past two decades. Abundant previous trials or meta-analyses have mainly focused on comparing TXA and normal saline, proving that both intravenous (IV) and topical TXA were associated with significantly reduced perioperative blood loss and blood transfusion requirements.[13-16] In contrast, few studies have directly compared different TXA administration routes.[17] In most clinical scenarios, TXA is

well-tolerated. However, the potential for thromboembolic events (deep vein thromboembolism or pulmonary embolism) after its use represents TXA's Achilles' heel.[1] Compared with the systemic method, topical application of TXA during arthroplasty may be a safer route that may reduce postoperative hemorrhage without contributing to hypercoagulation. Notably, the topical route has been shown to be a cost-effective and convenient route for TXA administration during dental, cardiac, and spinal surgeries.[18] Several relevant trials have been published recently. Thus, we compiled this systematic review and meta-analysis to compare the efficacy and safety of topical and IV TXA use during TKA and TXA. In addition, the combination of topical and systemic administration of TXA was also evaluated.

Methods

Search strategy

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009.[19] Ethics approval was not necessary for this study, as only de-identified pooled data from individual studies was analyzed. We searched PubMed, Embase, and Cochrane CENTRAL for relevant studies from the time of these databases' inception to April, 2018. The following groups of keywords and medical terms were used for the literature search: "tranexamic acid" AND ("total knee arthroplasty" OR "total knee replacement" OR "total hip arthroplasty" OR "total hip replacement" OR arthroplasty) AND (random* OR prospective* OR trial*). The language was restricted to English. We also conducted an additional search by screening the references of eligible studies.

Selection of studies

Studies were pooled for meta-analysis if they met the following criteria: (1) randomized controlled trials (RCTs); (2) comparing IV TXA with topical TXA, or considering their combination, in total knee/hip arthroplasty; (3) presenting the relevant outcomes, including intraoperative blood loss, total blood loss, transfusion rate, low postoperative hemoglobin (Hb) level, postoperative Hb decline, significant length of hospital stay (LOS), and/or the occurrence of venous thromboembolism (VTE). VTE may present as pulmonary embolism (PE) or deep vein thrombosis (DVT).

Data collection and quality assessment

Two reviewers independently evaluated the eligibility of the collected studies and extracted their data. Any discrepancy was resolved via a consensus meeting. The full text of the eligible studies was reviewed, and information was extracted into an electronic database, including author, year of publication, design, region, patient characteristics (e.g., age, gender, surgery type), TXA regimen, transfusion criteria, tourniquet use, thromboembolism prophylaxis, and the outcomes. For the quality assessment of RCTs, the Jadad score was employed,[20] which assigned a score of 0 to 5 according to the items of randomization, blinding, and withdrawals reported during the study period.

Statistical analysis

All meta-analyses were conducted using Stata 12.0 (StataCorp LLC, College Station, TX, USA). For dichotomous outcomes, we employed relative risk (RR) and 95% confidence intervals (CI) as estimates. For continuous data, we used weighted mean differences (WMD) and 95% CIs as estimates. We converted median to mean following Hozo's method.[21] The random-effects model was used for data processing. Statistical heterogeneity among the studies was assessed by using the Cochrane Q statistic, and was quantified according to I^2 statistics. We considered low, moderate, and high heterogeneity as I^2 values of ≤ 25%, 25–75%, and ≥75%, respectively.[22] Sensitivity analysis was performed by removing one trial at a time to determine its influence on the overall result. Subgroup analysis was further performed according to the following variables: surgery (THA or TKA), region (Asia, North America, or Europe), IV dose (≥2 g or <2 g), topical dose (≥2 g or <2 g), and transfusion protocol (strict or loose). We categorized the TXA dose of 30 mg/kg into the subgroup of ≥2 g. We considered a strict transfusion protocol for the threshold of Hb < 8 g/dL. When more than 10 studies were available for certain outcomes, meta-regression was performed to examine the impact of sample size. A funnel plot was constructed to visually evaluate the publication bias. Egger's and Begg's tests were used for quantitative assessment of publication bias.[23,24] $P < 0.05$ was considered statistically significant.

Results

Fig. 1 shows the flow diagram of the study selection process. After step-by-step exclusion, 26 RCTs were finally included. One trial had three comparison arms of IV TXA, topical TXA, and their combination.[25] Tables 1 and 2 show the main features of the trials. We identified 20 RCTs comparing IV TXA with topical TXA, totaling 1,912 participants (Table 1).[25-44] Fifteen trials used TXA in TKA procedures, and five trials used TXA in THA procedures. For TKA studies, only one did not use a tourniquet during surgery.[42] Ten trials were conducted in Asia, seven in Europe, and

three in the United States. The mean patient age ranged from 44 to 73 years. Seventeen trials presented a thromboprophylaxis protocol, with low molecular weight heparin used most frequently. Seven RCTs compared single-route administration (IV or intra-articular) with a combination of IV and topical routes[25,45-50] (Table 2), with a total of 877 patients. Most of them (5/7) were conducted in the Chinese population. Four studies were on TKA, and three studies were on THA. For the arm of single route, five trials used the IV route, one used the topical route, and one used both. All the studies implemented a thromboprophylaxis protocol. With regard to TKA studies, only Nielsen et al. did not use an intraoperative tourniquet.[48] The quality assessment of the selected trials using the Jadad score is shown in Supplemental Table 1, and the total score of the included trials is presented in Tables 1 and 2. The total score ranged from 1 to 5, with a mean score of 3.7. The items related to blinding was least satisfied.

IV versus topical route

Blood loss

Fourteen studies were available. Compared with the topical route, IV administration of TXA did not lead to significantly increased total blood loss (WMD = 30.92, 95% CI –28.40-90.25, P = 0.31; I^2 = 87.0%, P< 0.05). This effect was not substantially different for either TKA (WMD = 52.69, 95% CI –18.58-123.97, P = 0.15) or THA (WMD = –31.03, 95% CI –156.16-94.10, P = 0.63). (Fig. 2).

Subgroup analysis showed that neither region (Asia, Europe, or USA), IV dose (≥2 g or <2 g) nor topical dose (≥2 g or <2 g) markedly affected the overall effect (all P > 0.05). We did not identify any study that significantly changed the overall effect in the sensitivity analysis. Meta-regression demonstrated that sample size did not account for the heterogeneity (P = 0.20). The funnel plot appeared to be symmetrical. No publication bias was revealed on using Egger's test (P = 0.37) or Begg's test (P = 0.27).

Eight studies presented the outcome of drain blood loss. No significant difference was shown for the IV route versus the topical route (WMD = –34.53, 95% CI –135.39-66.34, P = 0.50; I^2 = 97.2%, P< 0.05). No significant change in the overall effect was displayed for TKA (WMD = –38.28, 95% CI –146.29-69.73, P = 0.49) or THA (WMD = –7.50, 95% CI –95.00-80.00, P = 0.87).

Postoperative Hb

By pooling data from 14 relevant studies, no significant difference was found between the IV and topical routes of TXA administration with respect to the postoperative Hb level (WMD = –0.01, 95% CI –0.23-0.22, P = 0.96; I^2 = 80.5%, P< 0.05). The result remained insignificant for TKA

(WMD = –0.00, 95% CI –0.25-0.25, P = 0.99) and THA (WMD = –0.03, 95% CI –0.76-0.70, P = 0.94) (Fig. 3). When stratified according to region, IV dose, and topical dose, no significant data was displayed for any subgroup (all P > 0.05). Sensitivity analysis performed by excluding studies one by one did not detect any significant change. Meta-regression analysis did not reveal a significant role for sample size in explaining the heterogeneity (P = 0.27). The funnel plot was symmetrical, and no bias was shown on using Egger's test (P = 0.38) or Begg's test (P = 0.91).

Seven studies reported a decline in Hb levels after arthroplasty. The pooled data did not reveal a significant difference for the IV route versus the topical route (WMD = –0.39, 95% CI –0.82-0.04, P = 0.08; I^2 = 89.4%, P< 0.05). In subgroup analysis, two studies on THA showed that the IV route had a significantly lesser amount of Hb decline than the topical route (WMD = –0.49, 95% CI –0.70-–0.28, P < 0.05). However, no statistical significance was revealed for the TKA procedure (WMD = –0.35, 95% CI –1.02-0.32, P = 0.31). When excluding the studies by Soni et al. or by Tzatzairis et al.;[31,42] however, the overall effect turned out to be significant (P < 0.05).

Transfusion rate

Seventeen studies were available with regard to having information on transfusion rate. The pooled results demonstrated that no significant difference regarding the transfusion rate for IV route versus topical route was present (RR = 1.08, 95% CI 0.78-1.50, P = 0.75). No heterogeneity was detected (I^2 = 0%, P = 0.63). In a separate analysis completed according to different arthroplasty procedures, the result was not substantially altered (TKA: RR = 1.25, 95% CI 0.80-1.96, P = 0.32; THA: RR = 0.80, 95% CI 0.46-1.37, P = 0.41) (Fig. 4). When stratified according to transfusion threshold (i.e., loose or strict), no significant result was shown for any subgroup (loose: RR = 1.13, P = 0.65; strict: RR = 1.00, P = 1.00). Similarly, we did not detect any substantially significant results for subgroups based on region, IV dose, or topical dose (all P > 0.05). Sensitivity analysis did not show that the inclusion of any individual study significantly changed the overall effect. The sample size was not the source of heterogeneity in meta-regression analysis (P = 0.36). The funnel plot was symmetrical. No publication bias was shown on using Egger's test (P = 0.69) or Begg's test (P = 1.00).

Length of stay

The length of stay (LOS) in the hospital was reported in seven studies. One study was excluded due to zero standard deviation.[42] The pooled results showed that the IV route and the topical route had similar LOS (WMD = 0.15, 95% CI –0.18-–0.47, P = 0.38; I^2 = 90.1%, P < 0.05). No marked change was revealed for TKA (WMD = 0.27, 95% CI –0.01-–0.54, P = 0.06) or THA (WMD = –0.05, 95% CI –0.42-0.32, P = 0.80).

VTE events

A total of 20 studies reported VTE events. However, 11 trials showed no VTE occurrence in any study group[29-33,35-39,42] and were thus excluded from meta-analysis. For the remaining nine trials, except for one study,[27] low molecular weight heparin was unanimously used for thromboprophylaxis. The aggregated data showed no significant difference for the IV versus topical route (RR = 1.89, 95% CI 0.79-4.55, P = 0.15). No heterogeneity was detected (I^2 = 0, P = 0.90). The pooled results remained non-significant for TKA (RR = 2.14, 95% CI 0.74-6.18, P = 0.16) and THA (RR = 1.45, 95% CI 0.30-6.93, P = 0.64) (Fig. 5). No single study played a substantial role in sensitivity analysis. Sample size was not the source of heterogeneity in meta-regression (P = 0.74).

Combined routes versus single route

Blood loss

The pooled data showed that compared with the combined regimen, the single route had significant increased total blood loss (WMD = 198.07, 95% CI 88.46-307.67, P < 0.05; I^2 = 92.3%). When stratified according to different procedures, the results remained significant for TKA (WMD = 168.34, 95% CI 85.44-251.25, P < 0.05; I^2 = 59.4%) and THA (WMD = 210.36, 95% CI 13.34-407.39, P < 0.05; I^2 = 96.3%) (Fig. 6). When stratified according to different routes, either IV route (WMD = 228.93, P < 0.05) or topical route (WMD = 108.80, P < 0.05) showed significantly increased total blood loss. Only two studies had data on drain blood loss,[45,49] and their pooled results showed no significant difference between single route and combined regimen (WMD = 109.51, 95% CI −34.73-253.74, P = 0.14; I^2 = 98.1%, P < 0.05).

Hb level

Three studies presented the postoperative Hb levels, including two on TKA[46,48] and one on THA.[50] No significant difference was revealed for single route in comparison with combined routes (WMD = −0.28, 95% CI −1.30-0.74, P = 0.59; I^2 = 89.6%, P < 0.05). Six studies presented the outcome of Hb decline following surgery. The pooled results revealed that the single route had a significantly greater magnitude of Hb decline than the combined method (WMD = 0.56, 95% CI 0.30-0.81, P < 0.05; I^2 = 85.2%, P < 0.05). The result remained significant for both studies on TKA (WMD = 0.44, P < 0.05), and for those on THA (WMD = 0.67, P < 0.05).

Transfusion rate

Seven studies were eligible, including four studies on TKA,[45-48] and three studies on THA.[25,49,50]

Xie et al. reported both the use of IV and topical during TXA.[25] The single route had a significantly higher rate of blood transfusion than the combined group (RR = 2.51, 95% CI 1.48-4.25, P < 0.05). No heterogeneity was shown (I^2 = 0). This trend remained significant for studies on TKA (RR = 0.09, P < 0.05) and THA (RR = 2.66, P < 0.05) (Fig. 7). When stratified according to the routes, IV route still showed a markedly higher transfusion rate than did the combination group (RR = 2.39, 95% CI 1.38-4.11, P < 0.05). However, two studies that used the topical route did not show a significantly higher rate (RR = 5.45, 95% CI 0.64-46.42, P = 0.12).

Length of stay

Four studies were relevant in terms of for evaluating the length of hospital stay,[25,45,48,49] and Xie et al. presented on both IV and topical routes.[25] The length of stay did not differ significantly between the single route and combination regimen (WMD = 0.09, 95% CI −0.10-0.28, P = 0.36; I^2 = 45.8%, P = 0.12). No significant change was detected for TKA or THA (both P > 0.05). For four studies on the IV route, the result remained non-significant (WMD = 0.14, P = 0.22).

VTE events

Six studies were eligible for consideration of VTE events.[25,45-47,49,50] One study showed zero events for both arms,[46] and one study presented both IV and topical routes.[25] The pooled data suggested that the risk of VTE events did not differ substantially between the single and combination routes (RR = 0.80, 95% CI 0.27-2.35, P = 0.68; I^2 = 0). No statistical significance was shown between the different types of arthroplasty (TKA: RR = 2.98, P = 0.34; and THA: RR = 0.54, P = 0.32) (Fig. 8), or for different single-delivery routes (IV: RR = 0.98, P = 0.97; topical: RR = 0.20, P = 0.30).

Discussion

TXA use represents one of the most tremendous advances in recent history for reducing blood loss during total joint replacement and for ensuring a fast postoperative recovery. To our knowledge, this is the most comprehensive meta-analysis of updated randomized trials investigating the efficacy and safety of IV versus topical TXA in total knee and hip arthroplasty. The role of a combined regimen using IV plus topical routes was firstly assessed by using the meta-analytic approach. We found that the IV and topical routes did not differ substantially for the outcomes of total blood loss, drain blood loss, postoperative Hb level, postoperative Hb fall, transfusion rate, and/or length of hospitalization. The incidence of VTE was low for both studied arms. The two routes appeared to be of comparable safety profiles for patients receiving arthroplasty. Except for two THA studies

showing the IV route resulted in a lesser magnitude of Hb decline, the overall effect remained insignificant for the majority of subgroups stratified based on THA or TKA. When comparing the combination regimen with the single route, our meta-analysis demonstrated that the combination of IV and topical routes could significantly decrease the total blood loss and reduce transfusion requirements. A relatively lesser degree of Hb decline was revealed the combined-delivery regimen. The length of hospitalization was similar for both arms. Overall, VTE events occurred rarely for both routes, and no marked difference was revealed in the comparison between the combination and single route groups.

In terms of mechanisms, following IV administration, TXA widely distributes among the extracellular and intracellular compartments. It rapidly diffuses into the synovial fluid until its concentration in the synovial fluid reaches to that of the serum. The biological half-life is three hours in the joint fluid, and 90% of TXA is eliminated within 24 hours after administration.[51] For the intra-articular route, administration of TXA in this manner could provide a maximum local dose at the site where needed. Local administration of TXA inhibits fibrin dissolution and induces partial microvascular hemostasis.[52] Especially, the release of the tourniquet always causes increased fibrinolysis, which can be attenuated by topical TXA.[53] Compared with the IV route, the systemic absorption for local use is at a substantially lower level.[54] Additionally, the use of topical TXA could be safer than IV TXA in patients with renal impairment.[34]

Several meta-analyses have been published on TXA use during arthroplasty. Both IV and intra-articular administration of TXA have been demonstrated to reduce blood loss without increased risk of thromboembolic complications, and the use of IV TXA is considerably more common.[13,14,16,55-60] However, most of these compared TXA with a placebo. We only identified two meta-analyses that did a head-to-head comparison between the topical and IV routes, including one on TKA,[17] and the other on THA.[61] Both of these analyses included only a very small number of studies. In addition, they had a methodological flaw, in that they included non-randomized or retrospective studies.

Our meta-analysis has several apparent strengths: first and foremost, all of the included studies were RCTs. The number of included trials was also much larger in our meta-analysis than the numbers of included trials in other meta-analyses, which increased the statistical power. All relevant trials published during the past two years were analyzed. In addition, we first investigated the efficacy of the combination of topical and IV routes. Given the similar mechanism of TXA administration in both TKA and THA, both procedures were considered for this meta-analysis.

Several clinical variables may influence the efficacy of TXA. The optimal dose of TXA remained

controversial. When topically used, there was no difference in the efficacy of 1.5 g versus 3 g of TXA wash in reducing perioperative blood loss.[62] However, a meta-analysis of seven trials suggested that a higher dose (> 2 g), but not a low dose, was correlated with significantly reduced transfusion requirements[15] In our subgroups stratified according to high dose (≥2 g) and low dose (< 2 g), no marked difference was shown between them regarding most of the outcomes. In fact, the effect on blood loss reduction between the low-dose and high-dose TXA may be explained by the "tissue contact time"—namely, the time at which TXA is applied on the joint bed.[63] At least five minutes of contact time was allowed before TXA was suctioned from the wound to allow for the repair of the retinaculum.[37] Sa-Ngasoongsong et al. suggested that prolonging the contact time could enhance the effects of low-dose TXA.[63]

We were aware of several limitations with respect to this meta-analysis. The number of participants in most of the included studies was small. As the prevalence of VTE was low following joint replacement, trials with a larger sample size were further needed to increase the statistical power. Only a small number of trials evaluated the combined-delivery group, which precluded sufficient exploration of heterogeneity through subgroup or meta-regression analysis. Many included trials also had methodological deficits, such as the description of the randomization process, the blinded assessment, and/or the explanation of withdrawal and dropouts. Several studied outcomes have been criticized for their inaccuracy. For example, drains may not be suitable for the measurement of blood loss, as the hematocrit in the drain output declined over time, and drains may increase the blood loss. The existing literature provided variable and heterogeneous information with respect to the clinical features. For instance, the estimation of blood loss, the timing of Hb measurement, and the indications for blood transfusion were not standardized among the various trials. Several studies used tourniquet to facilitate the arthroplasty procedure, which may adversely impact the efficacy of intraoperative IV TXA.[37] A meta-analysis showed that the use of a tourniquet was associated with increased risk for vein thrombosis.[64] Intraoperative hypotension or hypertension may affect the amount of blood loss, whereas related information was unclear in most included trials. Additionally, the length of hospitalization may be further affected by the patients' age, surgical experience, and/or infection complications. We speculated that these confounding factors were balanced between different comparison groups due to the randomized design. Not searching grey literature and articles in other languages might also have skewed the results. Finally, high heterogeneity was observed in places, which might limit the ability to make strong inferences.

Conclusions

Our meta-analysis showed that IV and topical TXA had comparable efficacy and safety profiles. The combined delivery method using IV and topical TXA may be the most efficacious strategy that can be used while remaining safe.

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Conflicts of interest statement

Not declared.

Author contributions

SQ and LJ contributed to conception and design. SQ, LJ, CJ, ZC, LC, and JY contributed to data acquisition or analysis and interpretation of data. SQ and LJ were involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published.

Data sharing statement

No additional data are available.

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Figure legends:

Figure 1. The flowdiagram showing the study selection process.

Figure 2. Forest plot comparing the efficacy of intravenous versus topical TXA on total blood loss.

Figure 3. Forest plot comparing the efficacy of intravenous versus topical TXA on postoperative hemoglobin levels.

Figure 4. Forest plot comparing the efficacy of intravenous versus topical TXA on postoperative transfusion rate.

Figure 5. Forest plot comparing the safety of intravenous versus topical TXA on postoperative venous thromboembolism.

Figure 6. Forest plot comparing theefficacy of intravenous versus combination of intravenous and topical TXA on total blood loss.

Figure 7. Forest plot comparing the efficacy of intravenous versus combination of intravenous and topical TXA on blood transfusion rate.

Figure 8. Forest plot comparing the safety of intravenous versus combination of intravenous and topical TXA on postoperative venous thromboembolism.

Table 1. Characteristics of prospective studies comparing topical with intravenous tranexamic acid in patients receiving total knee or hip anthroplasty.

Author (year)	Sample size	Region	Mean age	Female, %	Surgery	IV regimen	Topical regimen	Transfusion threshold	Tourniquet use	TP	Jadad score
Maniar et al. (2012)	80	India	67	80	Unilateral TKA	10mg/kg	3g	Hb< 8.5 g/dL without CHD, Hb< 10 g/dL with CHD, anemic symptoms, organ dysfunction	Yes	LMWH	5
Seo et al. (2013)	100	Korea	67	89	Unilateral TKA	1.5g	1.5g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	NA	2
Patel et al. (2014)	89	USA	65	74	Unilateral TKA	10mg/kg	2g	Hb< 8 g/dL with anemic symptoms	Yes	LMWH	5
Sarzaeem et al. (2014)	100	Iran	68	86	Unilateral TKA	0.5g	3g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	NA	3
Gomez-Barrena et al. (2014)	78	Spain	71	65	Unilateral THA	15mg/kg*2	3g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	Enoxaparin	5
Soni et al. (2014)	40	India	69	73	Unspecified TKA	10mg/kg*3	3g	Hb< 8 g/dL	Yes	LMWH	2
Wei et al. (2014)	203	China	62	64	THA	3g	3g	Hb< 9 g/dL	-	LMWH	5
Aguilera et al. (2015)	100	Spain	73	70	Primary TKA	2g	1g	Hb< 8 g/dL, Hb< 8.5 g/dL with CHD or over 70 years, Hb< 9 g/dL with anemic symptoms or organ dysfunction	Yes	LMWH	3

Digas et al. (2015)	60	Greece	71	85	Unilateral TKA	15mg/kg	2g	Hb< 8.5 g/dL without CHD, Hb< 9.5 g/dL with CHD, anemic symptoms, organ dysfunction	Yes	Tinzaparin	3
Oztas et al. (2015)	60	Turkey	68	85	Unilateral TKA	15mg/kg +10mg/kg	2g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	Enoxaparin	3
Tzatzairis et al. (2016)	80	Greece	69	80	Unilateral TKA	1g	1g	Hb< 10 g/dL, anemic symptoms/ organ dysfunction	No	LMWH	3
North et al. (2016)	139	USA	65	23	Unilateral THA	2g	2g	Hb<7 g/dL, symptomatic anemia and Hb<8 g/dL	-	Enoxaparin, rivaroxaban, or aspirin	5
Ugurlu et al. (2016)	82	Turkey	70	76	Unilateral TKA	20mg/kg	3g	Hb<8 g/dL	Yes	enoxaparin	3
Zhang et al. (2016)	50	China	44	46	Unilateral THA	1g	1g	Hb<8 g/dL, symptomatic anemia and Hb< 10 g/dL	-	LMWH	3
May et al. (2016)	131	USA	64	78	Unilateral TKA	2g	2g	Hb<7 g/dL, symptomatic anemia and Hb<10 g/dL	Yes	LMWH or oral Xa inhibitor	5
Keyhani et al. (2016)	80	Iran	68	39	Unilateral TKA	0.5g	3g	Hb<8 g/dL	Yes	LMWH	2
Drosos et al. (2016)	60	Greece	70	80	Unilateral TKA	1g	1g	Hb< 10 g/dL, anemic symptoms/ organ dysfunction	Yes	NA	2

Chen et al. (2016)	100	Singapore	65	75	Unilateral TKA	1.5g	1.5g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	LMWH	5
Aggarwal et al. (2016)	70	India	57	36	Bilateral TKA	15mg/kg	15mg/kg	Hb< 8 g/dL, Hct< 25%	Yes	Aspirin	4
Xie et al. (2016)	210	China	61	68	THA	1.5g	3g	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	NA	Enoxaparin	5

* Hb, hemoglobin; Hct, hematocrit; IV, intravenous; LMWH, low molecular weight heparin; LOS, length of stay; MT, mechanical thromboprophylaxis; NA, not available; THA, total hip anthroplasty; TKA, total knee anthroplasty; TP, thromboembolism prophylaxis; TXA, tranexamic acid; VTE, venous thromboembolism.

Table 2. Characteristics of prospective studies comparing combination of topical and intravenous tranexamic acid with placebo in patients receiving total knee or hip anthroplasty.

Author (year)	Sample size	Region	Mean age	Female, %	Surgery	Combination regimen	Single regimen	Transfusion threshold	Tourniquet use	TP	Jadad score
Huang et al. (2014)	184	China	65	64	Unilateral TKA	IV: 1.5g + topical: 1.5g	IV: 3g	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 10 g/dL	Yes	LMWH	5
Lin et al. (2015)	120	China	71	79	Unilateral TKA	IV: 1g + topical: 1g	topical: 1g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 9 g/dL	Yes	Rivaroxaban	3
Nielsen et al. (2016)	60	Denmark	64	53	Unilateral TKA	IV: 1g + topical: 3g	IV: 1g	Hb< 7.5 g/dL, Hb< 10 g/dL with CHD, anemic symptoms with Hb drop > 25%	No	Rvaroxaban	5
Jain et al. (2016)	119	India	69	63	Unilateral TKA	IV: (15 mg/kg preoperative + 10mg/kg postoperative) + topical: 2 g	IV: 15 mg/kg preoperative + 10mg/kg postoperative	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 8 g/dL	Yes	Aspirin	3
Zeng et al. (2016)	100	China	534	47	THA	IV: 15 mg/kg + topical: 1 g	IV: 15 mg/kg	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	NA	Enoxaparin	5

Xie et al. (2016)	210	China	61	68	THA	IV: 1g + topical: 2g.	IV: 1.5g, topical 3g	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	NA	Enoxaparin	5
Wu et al. (2016)	84	China	60	48	THA	IV: 15 mg/kg + topical: 3 g	IV: 15 mg/kg	Hb< 8 g/dL, anemic symptoms	NA	LMWH	3

*Hb, hemoglobin; Hct, hematocrit; IV, intravenous; LMWH, low molecular weight heparin; LOS, length of stay; MT, mechanical thromboprophylaxis; NA, not available; THA, total hip anthroplasty; TKA, total knee anthroplasty; TP, thromboembolism prophylaxis; TXA, tranexamic acid; VTE, venous thromboembolism.

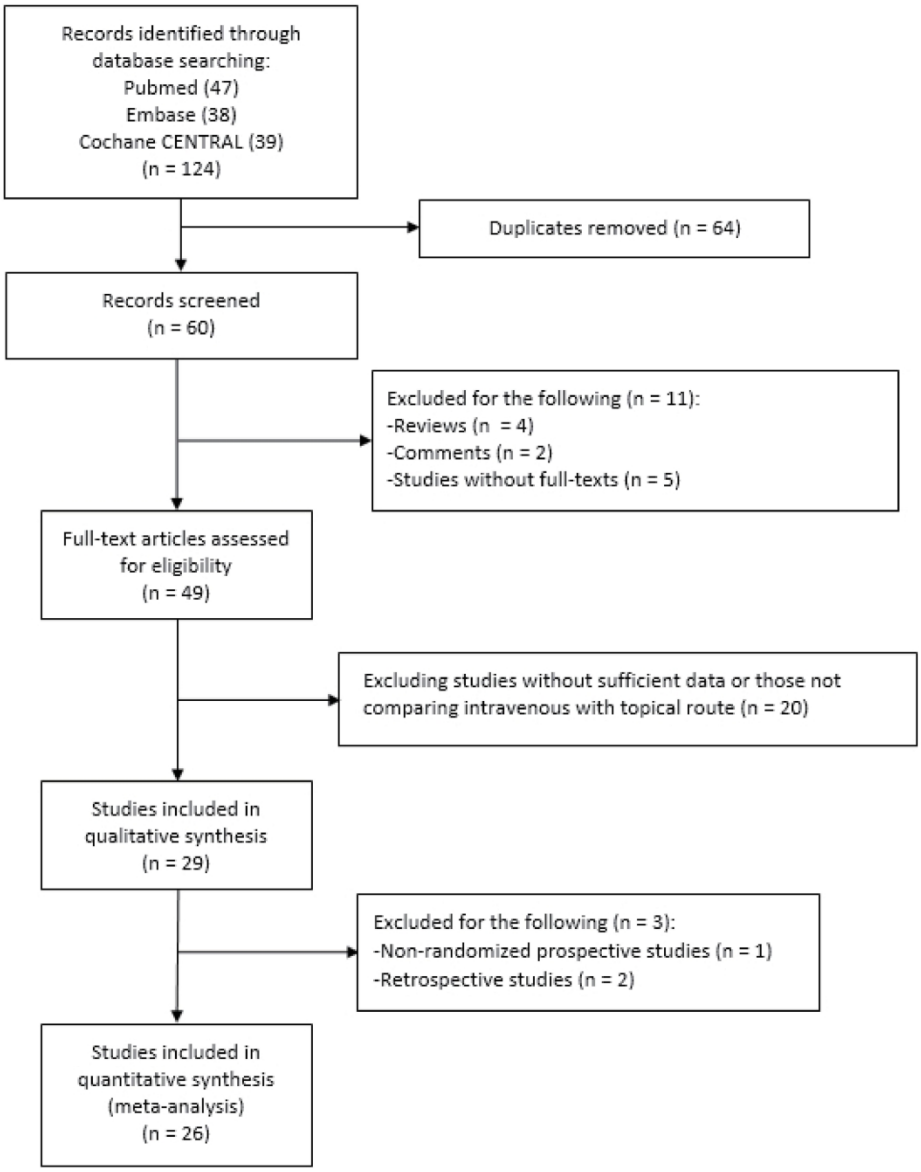

Figure 1. The flowdiagram showing the study selection process.

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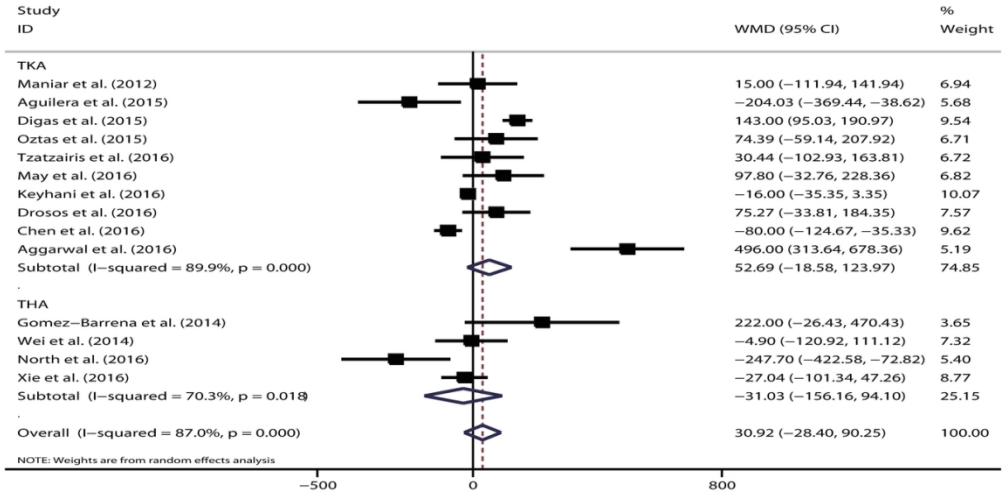

Figure 2. Forest plot comparing the efficacy of intravenous versus topical TXA on total blood loss.

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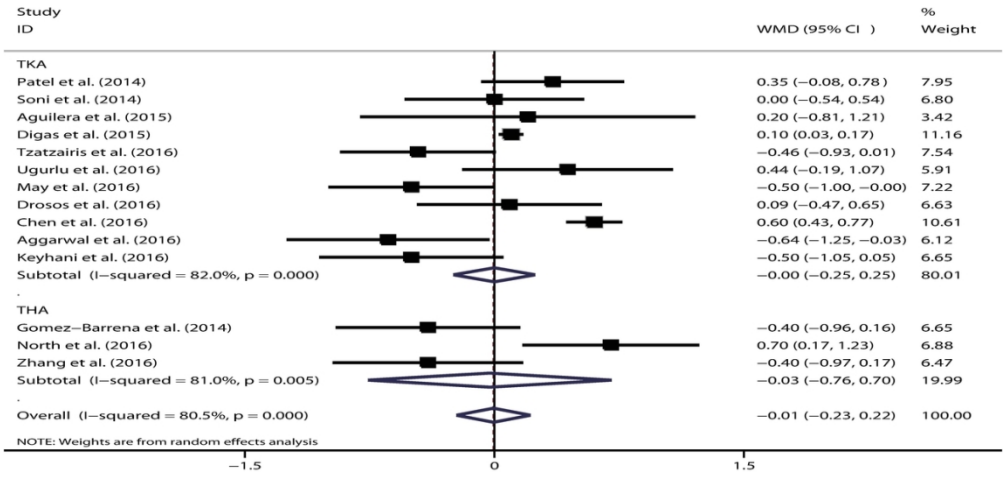

Figure 3. Forest plot comparing the efficacy of intravenous versus topical TXA on postoperative hemoglobin levels.

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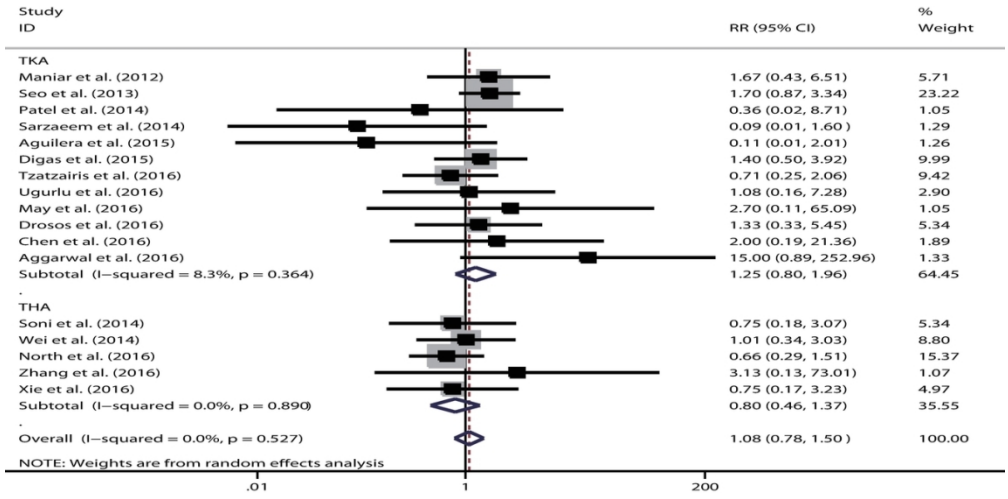

Figure 4. Forest plot comparing the efficacy of intravenous versus topical TXA on postoperative transfusion rate.

113x55mm (300 x 300 DPI)

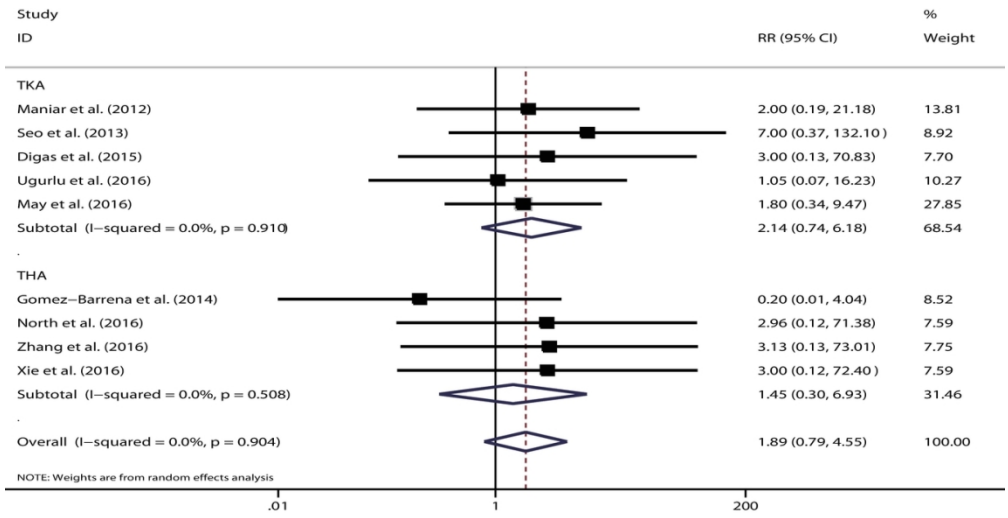

Figure 5. Forest plot comparing the safety of intravenous versus topical TXA on postoperative venous thromboembolism.

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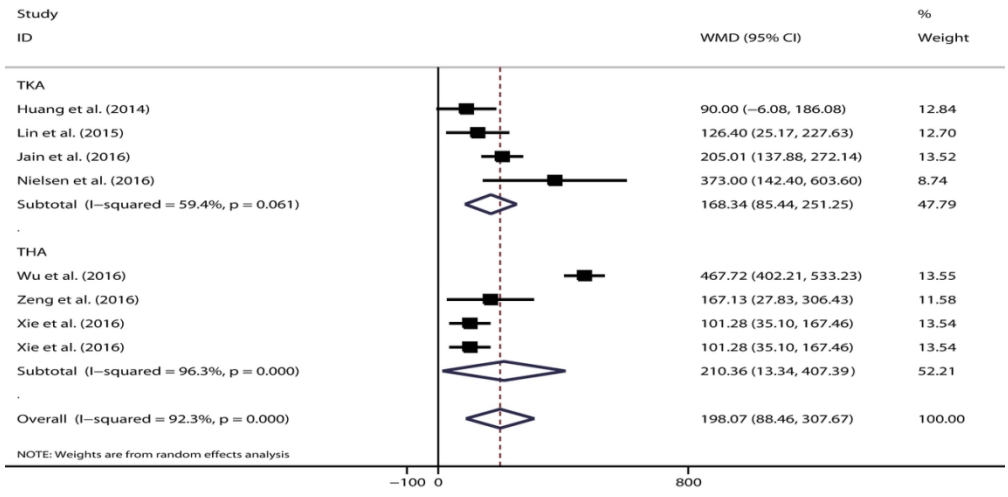

Figure 6. Forest plot comparing theefficacy of intravenous versus combination of intravenous and topical TXA on total blood loss.

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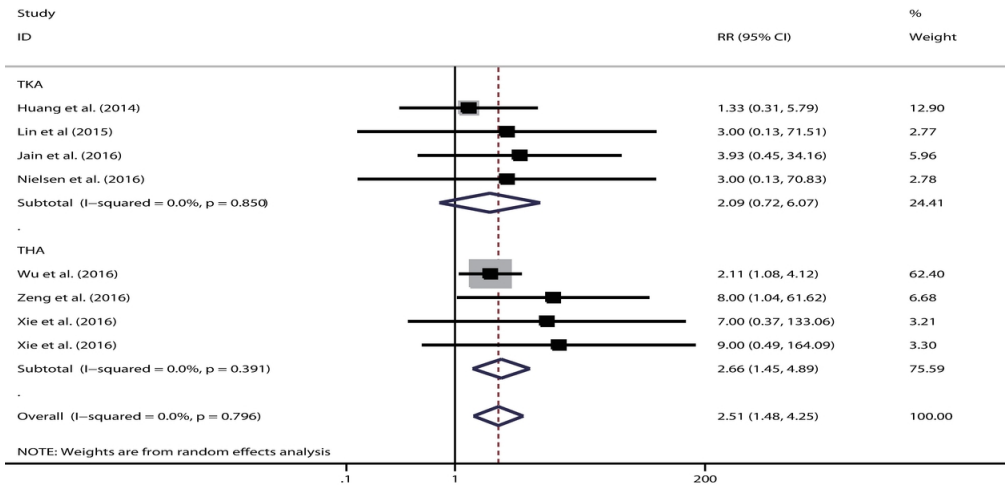

Figure 7. Forest plot comparing the efficacy of intravenous versus combination of intravenous and topical TXA on blood transfusion rate.

105x50mm (300 x 300 DPI)

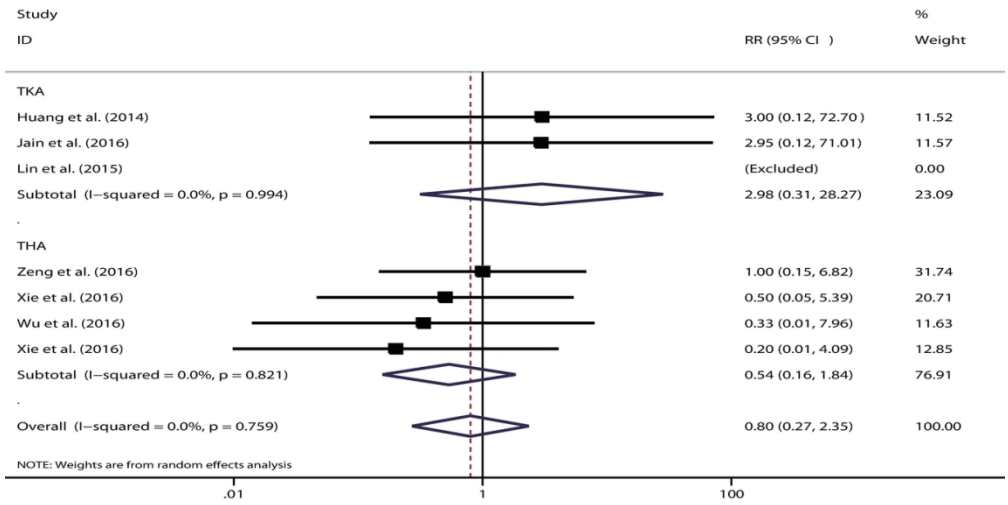

Figure 8. Forest plot comparing the safety of intravenous versus combination of intravenous and topical TXA on postoperative venous thromboembolism.

115x56mm (300 x 300 DPI)

Supplemental Table 1. Quality assessment of studies by the Jadad scale.

Author (year)	Randomization		Blinding		Description of withdrawal and dropouts	Total score
	Mentioned	Appropriate	Mentioned	Appropriate		
Maniar et al. (2012)	1	1	1	1	1	5
Seo et al. (2013)	1	1	0	0	0	2
Lin et al. (2015)	1	1	0	0	1	3
Huang et al. (2014)	1	1	1	1	1	5
Patel et al. (2014)	1	1	1	1	1	5
Sarzaeem et al. (2014)	1	1	1	0	0	3
Gomez-Barrena et al. (2014)	1	1	1	1	1	5
Soni et al. (2014)	1	1	0	0	0	2

Wei et al. (2014)	1	1	1	1	1	5
Aguilera et al. (2015)	1	1	0	0	1	3
Digas et al. (2015)	1	1	1	0	0	3
Oztas et al. (2015)	1	0	0	0	0	1
Tzatzairis et al. (2016)	1	1	0	0	1	3
North et al. (2016)	1	1	1	1	1	5
Ugurlu et al. (2016)	1	1	0	0	1	3
Zhang et al. (2016)	1	1	0	0	1	3
May et al. (2016)	1	1	1	1	1	5
Keyhani et al.(2016)	1	0	0	0	1	2
Drosos et al. (2016)	1	1	0	0	0	2
Chen et al. (2016)	1	1	1	1	1	5

Aggarwal et al. (2016)	1	1	1	1	0	4
Xie et al. (2016)	1	1	1	1	1	5
Zeng et al. (2016)	1	1	1	1	1	5
Jain et al. (2016)	1	1	0	0	1	3
Nielsen et al. (2016)	1	1	1	1	1	5
Wu et al. (2016)	1	1	0	0	1	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5,6,7,8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5,6,7,8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5,6,7,8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5,6,7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

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COMPARISON OF INTRAVENOUS, TOPICAL, OR COMBINED ROUTES OF TRANEXAMIC ACID ADMINISTRATION IN PATIENTS UNDERGOING TOTAL KNEE AND HIP ARTHROPLASTY: A META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

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COMPARISON OF INTRAVENOUS, TOPICAL, OR COMBINED ROUTES OF TRANEXAMIC ACID ADMINISTRATION IN PATIENTS UNDERGOING TOTAL KNEE AND HIP ARTHROPLASTY: A META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

Qi Sun[1¶], Jinyu Li[1¶], Jiang Chen[1], Chenying Zheng[1], Chuyin Liu[1], Yusong Jia[1*]

[1]Department of Orthopedics, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing , China.

*Corresponding author: E-mail: spioneer2001@sina.com

Qi Sun: sunqi2001@sina.com

Jinyu Li: lijinyu84@126.com

Jiang Chen: 964402173@qq.com

Chenying Zheng: zhengchenying99@sina.com

Chuyin Liu: 1827193473@qq.com

¶These authors contributed equally to this work.

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Abbreviations, Nomenclature and Symbols

TXA: tranexamic acid; TKA: total knee arthroplasty; THA: total hip arthroplasty; RCT: randomized controlled trials; RR: relative risk; WMD: weighted mean difference; CI: confidence interval; IV: intravenous; Hb: hemoglobin; LOS: length of stay; VTE: venous thromboembolism; TJA: total joint arthroplasty; PE: pulmonary embolism; DVT: deep vein thrombosis; LMWH: low molecular weight heparin.

ABSTRACT

Objective: This study aimed to compare the effects of intravenous (IV), topical, and combined routes of tranexamic acid (TXA) administration on blood loss and transfusion requirements in patients undergoing total knee and hip arthroplasty (TKA and THA).

Design: This was a meta-analysis of randomised controlled trials (RCTs) wherein the weighted mean difference (WMD) and relative risk (RR) were used for data synthesis applied in the random effects model. Stratified analyses based on the surgery type, region, IV and topical TXA dose and transfusion protocol were also conducted. The main outcomes included intraoperative and total blood loss volume, transfusion rate, low postoperative haemoglobin (Hb) level, and postoperative Hb decline. However, the secondary outcomes included length of hospital stay (LOS) and/or occurrence of venous thromboembolism (VTE).

Setting: We searched the PubMed, Embase and Cochrane CENTRAL databases for RCTs that compared different routes of TXA administration.

Participants: Patients undergoing TKA or THA

Interventions: IV, topical or combined IV, and topical TXA

Results: Twenty-six RCTs were selected, and the IV route did not differ substantially from the topical route with respect to the total blood loss volume (WMD=30.92, P=0.31), drain blood loss (WMD=-34.53, P=0.50), postoperative Hb levels (WMD=-0.01, P=0.96), Hb decline (WMD=-0.39, P=0.08), LOS (WMD=0.15, P=0.38), transfusion rate (RR=1.08, P=0.75) and VTE occurrence (RR=1.89, P=0.15). Compared to the combined-delivery group, the single route group had significantly increased total blood loss volume (WMD=198.07, P<0.05), greater Hb decline (WMD=0.56, P<0.05) and higher transfusion rates (RR=2.51, P<0.05). However, no significant difference was noted in the drain blood loss, postoperative Hb levels, and VTE events between the two groups. The IV and topical routes had comparable efficacy and safety profiles.

Conclusions: The combination of IV and topical TXA was relatively more effective in controlling bleeding without increased risk of VTE.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. All included studies used the randomised controlled design to avoid uncontrolled biases.

2. The combination of topical and systemic TXA administration was also studied.

3. The heterogeneity was assessed using sensitivity, subgroup and meta-regression analyses.

4. The number of participants in most of the included studies was small, and the prevalence of VTE following joint replacement was low.

5. Only a small number of trials evaluated the combined-delivery group, which precluded sufficient exploration of heterogeneity through subgroup or meta-regression analysis.

Keywords: tranexamic acid; total knee arthroplasty; total hip arthroplasty; IV; topical; meta-analysis

INTRODUCTION

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine, which inhibits fibrinolysis by blocking the lysine-binding site of plasminogen.[1] Currently, it is one of the most commonly used haemostatic drugs and is capable of reducing blood loss volume in surgical patients by approximately 34%.[2,3] Moreover, this drug has effectively reduced the blood loss volume and transfusion rate in various surgical settings, including in traumatic haemorrhage,[4] caesarean section,[5] endoscopic sinus[6] and cardiac[7] surgeries and arthroplasty.[8]

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are reliable surgical procedures for patients suffering from moderate to severe degenerative joint diseases. Total joint arthroplasty (TJA) is effective in relieving pain, restoring physical function, and improving health-related quality of life.[9] By 2030, the demand for primary THA is estimated to increase to 572,000 and that for primary TKA is estimated to reach 3.48 million procedures.[10] Despite substantial advances in surgical and anaesthetic techniques, TKA and THA are still associated with a large amount of perioperative blood loss.[11] The intraoperative blood loss volume in either procedure is generally between 500 and 1,500 mL. Additionally, patients may experience a postoperative drop in haemoglobin level between 1 and 3 g/dL.[12] Up to 50% of the patients undergoing TJA inevitably experience postoperative anaemia.[11]

The role of TXA during arthroplasty has been an issue of concern for the past two decades. Several

previous trials or meta-analyses have mainly focused on comparing TXA and non-TXA, proving that oral, intravenous (IV) and topical TXA were associated with significantly reduced perioperative blood loss volume and blood transfusion requirements.[13-19] Furthermore, two important meta-analysis showed comparable haemostatic effects between oral and IV TXA.[20-21] Moreover, another two studies showed that patients who received combined IV and topical TXA experienced more benefit than those with single-route TXA administration.[22-23] However, few studies have directly compared the different TXA administration routes, and they were limited due to combination of various study design types and relatively small number of included studies.[24] In addition, the potential for thromboembolic events [deep vein thromboembolism (DVT) or pulmonary embolism (PE)] after TXA use represents TXA's Achilles' heel.[1] Topical TXA application during arthroplasty may be a safer route than the systemic method, which may reduce postoperative haemorrhage without causing hypercoagulation. Notably, the topical route has been shown to be a cost-effective and convenient route for TXA administration during dental, cardiac and spinal surgeries.[25] Several relevant trials have been published recently. Thus, we compiled this systematic review and meta-analysis to compare the efficacy and safety of topical and IV TXA use in patients undergoing TKA and TXA. In addition, the combination of topical and systemic administration of TXA was evaluated.

METHODS

Patient and public involvement

No patients were involved in the study design or conduct of the study.

Search strategy

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement issued in 2009.[26] Ethical approval was not necessary for this study, as only de-identified pooled data from individual studies were analysed. We searched the PubMed, Embase and Cochrane CENTRAL databases for relevant studies from the time of these databases' inception to April 2018. The following groups of keywords and medical terms were used for the literature search: 'tranexamic acid' and 'total knee arthroplasty', 'total knee replacement', 'total hip arthroplasty', 'total hip replacement' or 'arthroplasty' and random*, prospective* or trial*. The details of the search

strategy in PubMed are shown in supplementary file 1. This study was restricted to the English language. Furthermore, an additional search was conducted by screening the references of eligible studies.

Selection of studies

Studies were pooled for meta-analysis if they met the following criteria: (1) Study design: randomised controlled trials (RCTs), (2) Patients: those with TKA or THA, (3) Intervention and control: comparing IV TXA with topical TXA or considering their combination with single TXA regimen and (4) Outcomes: the main outcomes included intraoperative and total blood loss, transfusion rate, low postoperative haemoglobin (Hb) level and postoperative Hb decline. However, the secondary outcomes included length of hospital stay (LOS) and/or the occurrence of venous thromboembolism (VTE) which may present as PE or DVT.

Data collection and quality assessment

Two reviewers independently evaluated the eligibility of the collected studies and extracted their data. Any discrepancy was resolved via a consensus meeting. The full text of the eligible studies was reviewed, and information were entered into an electronic database, including author, year of publication, region, sample size, patient characteristics (e.g. age, gender, surgery type), IV and topical regimen, transfusion threshold, tourniquet use, thromboembolism prophylaxis and outcomes. The Jadad scale was used for the quality assessment of RCTs,[27] which assigned a score of 0 to 5 according to the items of randomisation, blinding, and withdrawals reported during the study period.

Statistical analysis

All meta-analyses were conducted using Stata 12.0 (StataCorp LLC, College Station, TX, USA). The relative risk (RR) and 95% confidence interval (CI) were used as estimates to analyse dichotomous outcomes. The weighted mean differences (WMD) were used for continuous data and 95% CI was used for estimates. We converted the median to mean following Hozo's method.[28] The random effects model was used for data processing. In addition, statistical heterogeneity among the studies was assessed by using the Cochran's Q statistic and was quantified according to the I^2 statistics. We considered the low, moderate, and high heterogeneity as I^2 values of $\leq$ 25%, 25–75% and $\geq$75%, respectively.[29] Sensitivity analysis was performed by removing one trial at a time to determine its

influence on the overall result. Subgroup analysis was further performed according to the following variables: surgery (THA or TKA), region (Asia, North America or Europe), IV dose (≥2 g or <2 g), topical dose (≥2 g or <2 g) and transfusion protocol (strict or loose). The TXA dose of 30 mg/kg was categorised into the subgroup ≥2 g. A strict transfusion protocol was implemented for the threshold of Hb <8 g/dL. When more than ten studies were available for certain outcomes, meta-regression analysis was performed to examine the impact of the sample size. A funnel plot was constructed to visually evaluate the publication bias. The Egger's and Begg's tests were used for quantitative assessment of publication bias.[30,31] A P-value <0.05 was considered statistically significant.

RESULTS

Fig. 1 shows the flow diagram of the study selection process. After step-by-step exclusion, 26 RCTs were finally included. One trial had three comparison arms of IV and topical TXA and their combination.[32] Tables 1 and 2 show the main features of the trials. We identified 20 RCTs comparing IV TXA with topical TXA, with a total of 1,912 participants (Table 1).[32-51] About 15 trials used TXA in TKA procedures and five trials used TXA in THA procedures. Only one TKA study did not use a tourniquet during surgery.[49] Ten trials were conducted in Asia, seven in Europe and three in the United States. The patients' mean age ranged from 44 to 73 years. Seventeen trials presented a thromboprophylaxis protocol, with low-molecular-weight heparin used most frequently. Seven RCTs compared single-route administration (IV or intra-articular) with a combination of IV and topical routes[32,52-57] (Table 2), with a total of 877 patients. Most of the studies (5/7) were conducted in the Chinese population. Four studies were conducted on patients who underwent TKA, whereas three studies were performed among those with THA. For the arm of single route, five trials used the IV route, one used the topical route, and one used both. All studies implemented a thromboprophylaxis protocol. With regards to the TKA studies, only Nielsen et al. did not use an intraoperative tourniquet.[55] The quality assessment of the selected trials using the Jadad scale is shown in Supplemental Table 1, and the total score of the included trials is presented in Tables 1 and 2. The total score ranged from 1 to 5, with a mean score of 3.7. The items related to blinding were least satisfied.

IV versus topical route

Blood loss

About 14 studies reported on blood loss. No significant difference was observed in the total blood loss volume (WMD=30.92, 95% CI –28.40-90.25, P=0.31; I2=87.0%, P<0.05) between IV TXA administration and topical administration. This effect was not substantially different for either TKA (WMD=52.69, 95% CI=-18.58–123.97, P=0.15) or THA (WMD=-31.03, 95% CI=-156.16–94.10, P=0.63) (Fig. 2).

Subgroup analysis showed that region (Asia, Europe or USA), IV dose (≥2 g or <2 g), or topical dose (≥2 g or <2 g) did not markedly affected the overall effect of the analysis (all P>0.05). None of the studies that significantly changed the overall effect in the sensitivity analysis was identified. Meta-regression demonstrated that the sample size did not account for the heterogeneity of the study (P=0.20). The funnel plot appeared to be symmetrical. No publication bias was revealed based on the Egger's (P=0.37) or Begg's test (P=0.27).

Eight studies presented the outcome of drain blood loss. No significant difference was demonstrated in the IV route (WMD=-34.53, 95% CI=-135.39–66.34, P=0.50; I^2=97.2%, P<0.05) and overall effect on TKA (WMD=-38.28, 95% CI=-146.29–69.73, P=0.49) or THA (WMD=-7.50, 95% CI=-95.00–80.00, P=0.87).

Postoperative Hb

By pooling data from 14 relevant studies, no significant difference was found between the IV and topical routes of TXA administration with respect to the postoperative Hb level (WMD=-0.01, 95% CI=-0.23-0.22, P=0.96; I^2=80.5%, P<0.05). The result remained insignificant for TKA (WMD=-0.00, 95% CI=-0.25–0.25, P=0.99) and THA (WMD=-0.03, 95% CI=-0.76–0.70, P=0.94) (Fig. 3). When stratified according to the region and IV and topical dose, no significant data were noted in any subgroup (all P>0.05). Sensitivity analysis was performed by excluding studies one at a time; however, no significant difference was noted. The significant role of the sample size in explaining the heterogeneity (P=0.27) was not revealed in the meta-regression analysis. The funnel plot was symmetrical, and no bias was shown based on the Egger's (P=0.38) or Begg's test (P=0.91).

Seven studies reported a decline in Hb levels after arthroplasty. The pooled data revealed no significant difference in the IV route compared to the topical route (WMD=-0.39, 95% CI=-0.82–0.04, P=0.08;

I^2=89.4%, P<0.05). In the subgroup analysis, two studies on THA showed that the IV route had a significantly lesser amount of Hb decline than the topical route (WMD=-0.49, 95% CI=-0.70–0.28, P<0.05). However, no statistical significance was noted on the TKA procedure (WMD=-0.35, 95% CI=-1.02–0.32, P=0.31). When excluding the studies by Soni et al. or Tzatzairis et al., [38,49] the overall effect was significant (P<0.05).

Transfusion rate

Information on the transfusion rate was reported in 17 studies. The pooled results demonstrated that no significant difference was observed in the transfusion rate of the IV route (RR=1.08, 95% CI=0.78–1.50, P=0.75). No heterogeneity was detected (I^2=0%, P=0.63). In a separate analysis completed according to different arthroplasty procedures, the result was not substantially altered (TKA: RR=1.25, 95% CI=0.80–1.96, P=0.32; THA: RR=0.80, 95% CI=0.46–1.37, P=0.41) (Fig. 4). When stratified according to the transfusion threshold (i.e. loose or strict), no significant result was shown in any subgroup (loose: RR=1.13, P=0.65; strict: RR=1.00, P=1.00). Similarly, no substantially significant results were noted in the subgroups based on the region and IV or topical dose (all P>0.05). The sensitivity analysis did not show that the inclusion of any individual study significantly changed the overall effect. The sample size was not the source of heterogeneity in meta-regression analysis (P=0.36). The funnel plot was symmetrical. No publication bias was shown based on the Egger's (P=0.69) or Begg's test (P=1.00).

LOS

The LOS was reported in seven studies. One study was excluded due to zero standard deviation.[49] The pooled results showed that patients with the IV and topical routes had similar LOS (WMD=0.15, 95% CI=-0.18–0.47, P=0.38; I^2=90.1%, P<0.05). No marked change was revealed for TKA (WMD=0.27, 95% CI=-0.01–0.54, P=0.06) or THA (WMD=-0.05, 95% CI=-0.42–0.32, P=0.80).

VTE events

A total of 20 studies reported VTE events. However, 11 trials showed no VTE occurrence in any study group[36-40,42-46,49] and thus, were excluded from meta-analysis. For the remaining nine trials, except for one study,[34] low molecular weight heparin was unanimously used for thromboprophylaxis. The aggregated data showed no significant difference for the IV versus topical

route (RR=1.89, 95% CI=0.79–4.55, P=0.15). No heterogeneity was detected (I^2=0%, P=0.90). The pooled results remained non-significant for TKA (RR=2.14, 95% CI=0.74–6.18, P=0.16) and THA (RR=1.45, 95% CI=0.30–6.93, P=0.64) (Fig. 5). No single study played a substantial role in sensitivity analysis. Sample size was not the source of heterogeneity in meta-regression analysis (P=0.74).

Combined routes versus single route

Blood loss

The pooled data showed that the single route had significant increased total blood loss volume (WMD=198.07, 95% CI=88.46–307.67, P<0.05; I^2=92.3%) compared with the combined regimen. When stratified according to different procedures, the results remained significant for TKA (WMD=168.34, 95% CI=85.44–251.25, P<0.05; I^2=59.4%) and THA (WMD=210.36, 95% CI=13.34–407.39, P<0.05; I^2=96.3%) (Fig. 6). Either the IV (WMD=228.93, P<0.05) or topical route (WMD=108.80, P<0.05) showed significantly increased total blood loss volume. Only two studies reported data on drain blood loss,[52,56] and their pooled results showed no significant difference between single-route and combined regimen (WMD=109.51, 95% CI=-34.73–253.74, P=0.14; I^2=98.1%, P<0.05).

Hb level

Three studies presented the postoperative Hb levels, including two on TKA[53,55] and one on THA.[57] No significant difference was noted on the single route compared with the combined routes (WMD=-0.28, 95% CI=-1.30–0.74, P=0.59; I^2=89.6%, P<0.05). Six studies presented the outcome of Hb decline following surgery. The single route had a significantly greater magnitude of Hb decline than the combined method (WMD=0.56, 95% CI=0.30–0.81, P<0.05; I^2=85.2%, P<0.05). The result remained significant for studies on both TKA (WMD=0.44, P<0.05) and THA (WMD=0.67, P<0.05).

Transfusion rate

Seven studies were eligible, including four studies on TKA[52-55] and three studies on THA.[32,56,57] Xie et al. reported the use of both IV and topical TXA administration.[32] The single route had a significantly higher transfusion rate than the combined group (RR=2.51, 95% CI=1.48–4.25, P<0.05). No heterogeneity was shown (I^2=0%). This trend remained significant for studies on TKA (RR=0.09, P<0.05) and THA (RR=2.66, P<0.05) (Fig. 7). The IV route still showed a markedly

higher transfusion rate than the combination group (RR=2.39, 95% CI=1.38–4.11, P<0.05). However, a significantly higher transfusion rate (RR=5.45, 95% CI=0.64–46.42, P=0.12) was not observed in two studies that used the topical route.

LOS

Four studies were relevant in terms of evaluating the LOS,[32,52,55,56] and Xie et al. presented on both IV and topical routes.[32] The LOS did not differ significantly between the single route and combination regimen (WMD=0.09, 95% CI=-0.10–0.28, P=0.36; I^2=45.8%, P=0.12). No significant difference was noted in the LOS of patients who underwent TKA or THA (both P>0.05). The result remained non-significant (WMD=0.14, P=0.22) as reported in four studies conducting IV TXA administration.

VTE events

Six studies were eligible for consideration of VTE events.[32,52-54,56,57] One study showed zero events for both arms,[53] and one study presented both IV and topical routes.[32] The pooled data suggested that the risk of VTE events did not differ substantially between the single and combination routes (RR=0.80, 95% CI=0.27–2.35, P=0.68; I^2=0%). No statistical significance was shown between the different types of arthroplasty (TKA: RR=2.98, P=0.34; and THA: RR=0.54, P=0.32) (Fig. 8) or different single-delivery routes (IV: RR=0.98, P=0.97; topical: RR=0.20, P=0.30).

DISCUSSION

In recent history, TXA is one of the most commonly used haemostatic drug for reducing blood loss during total joint replacement and ensuring fast postoperative recovery. To our knowledge, this is the most comprehensive meta-analysis of updated randomised trials investigating the efficacy and safety of IV versus topical TXA in patients undergoing TKA and THA. We found that the IV and topical routes did not differ substantially for the outcomes of total blood loss, drain blood loss, postoperative Hb level, postoperative Hb decline, transfusion rate, and/or LOS. The incidence of VTE was low for both studied arms. The two routes appeared to be of comparable safety profiles for patients undergoing arthroplasty. Except for two THA studies showing that the IV route resulted in a lesser magnitude of Hb decline, the overall effect remained insignificant for the majority of subgroups stratified based on

THA or TKA. When comparing the combination regimen with the single route, our meta-analysis demonstrated that the combination of IV and topical routes could significantly decrease the total blood loss volume and reduce transfusion requirements. A relatively lesser degree of Hb decline was revealed in the combined-delivery regimen. LOS was similar for both arms. Overall, VTE events occurred rarely for both routes, and no marked difference was revealed when comparing the combination and single route groups.

Following IV administration, TXA is spread in the extracellular and intracellular compartments. It rapidly diffuses into the synovial fluid until its concentration reaches to that of the serum. The biological half-life is three hours in the joint fluid, and 90% of TXA is eliminated within 24 hours after administration.[58] For the intra-articular route, TXA administration could provide a maximum local dose at the site where needed. Local administration of TXA inhibits fibrin dissolution and induces partial microvascular haemostasis.[59] Particularly, the release of the tourniquet always causes increased fibrinolysis, which can be attenuated by topical TXA.[60] Compared with the IV route, the systemic absorption for local use is at a substantially lower level.[61] Additionally, topical TXA could be safer than IV TXA in patients with renal impairment.[41] Moreover, the antifibrinolytic effect of topical TXA is limited to postoperative bleeding. Preoperatively, IV TXA was associated with lower blood loss volume during arthroplasty, which explains the greater benefit of combined regimen of using IV along with topical routes.[62]

Several meta-analyses have been published on TXA use during arthroplasty. Both IV and intra-articular administration of TXA have been demonstrated to reduce the blood loss volume without increased risk of thromboembolic complications, and the use of IV TXA is considerably more common.[13,14,16,21-24,63-68] However, most of these meta-analyses compared TXA with a placebo. We only identified two meta-analyses that performed a head-to-head comparison between the topical and IV routes, including one on TKA[24] and the other on THA.[61] Both analyses included only a very small number of studies. In addition, a methodological flaw was observed because they included non-randomised or retrospective studies.

Our meta-analysis has several apparent strengths. First, all included studies were RCTs. The number of included trials was also larger in our meta-analysis than that in other meta-analyses, which increased the statistical power. All relevant trials published during the past two years were analysed. In addition, we investigated the efficacy of the combination of topical and IV routes. Given the similar mechanism

of TXA administration in both TKA and THA, both procedures were considered for this meta-analysis.

Several clinical variables may influence the efficacy of TXA. The optimal dose of TXA remained controversial. When topically applied, there was no difference in the efficacy of 1.5 g versus 3 g of TXA wash in reducing perioperative blood loss.[69] However, a meta-analysis of seven trials suggested that a higher dose of TXA (>2 g), but not a low dose, was correlated with significantly reduced transfusion requirements.[15] In our subgroups stratified based on the high (≥2 g) and low doses (<2 g), no significant difference was observed between the doses and most outcomes. In fact, the effect on blood loss reduction between low- and high-dose TXA may be explained by the 'tissue contact time'— the time when TXA is applied on the joint bed.[70] At least five minutes of contact time was allowed before TXA was suctioned from the wound to allow for the repair of the retinaculum.[44] Sa-Ngasoongsong et al. suggested that prolonging the contact time could enhance the effects of low-dose TXA.[70]

We were aware of several limitations with respect to this meta-analysis. The number of participants in most of the included studies was small. As the prevalence of VTE was low following joint replacement, trials with a larger sample size were further needed to increase the statistical power. Only a small number of trials evaluated the combined-delivery group, which precluded sufficient exploration of heterogeneity through subgroup or meta-regression analysis. Additionally, many included trials had methodological deficits, such as the description of the randomisation process, blinded assessment and/or explanation of withdrawal and dropouts. Several studied outcomes have been criticised for their inaccuracy. For example, drains may not be suitable for the measurement of blood loss volume, as the haematocrit in the drain output declined over time and drains may increase the blood loss. The existing literature provided variable and heterogeneous information with respect to the clinical features. For instance, the estimated blood loss, timing of Hb measurement and indications for blood transfusion were not standardised among various trials. Several studies used tourniquet to facilitate the arthroplasty procedure, which may adversely impact the efficacy of intraoperative IV TXA.[44] A meta-analysis showed that the use of a tourniquet was associated with increased risk for vein thrombosis.[71] Intraoperative hypotension or hypertension may affect the blood loss volume, whereas related information was unclear in most included trials. Additionally, LOS may be further affected by the patients' age, surgical experience, and/or infection complications. We speculated that these confounding factors were balanced between different comparison groups due to the randomised design.

Not searching grey literature and articles in other languages might have also skewed the results. Finally, high heterogeneity was observed in places that might limit the ability to make strong inferences.

CONCLUSIONS

Our meta-analysis showed that IV and topical TXA had comparable efficacy and safety profiles. The combined delivery method using IV and topical TXA may be the most effective strategy that can be used while maintaining patient safety.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

SQ and LJ contributed to the conception and design of the study. SQ, LJ, CJ, ZC, LC, and JY contributed to data acquisition or analysis and interpretation. SQ and LJ were involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published.

DATA SHARING STATEMENT

No additional data are available.

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Figure legends:

Figure 1. The flowdiagram showing the study selection process.

Figure 2. Forest plot comparing the efficacy of intravenous versus topical TXA on total blood loss.

Figure 3. Forest plot comparing the efficacy of intravenous versus topical TXA on postoperative hemoglobin levels.

Figure 4. Forest plot comparing the efficacy of intravenous versus topical TXA on postoperative transfusion rate.

Figure 5. Forest plot comparing the safety of intravenous versus topical TXA on postoperative venous thromboembolism.

Figure 6. Forest plot comparing the efficacy of single versus combined routes of TXA on total blood loss.

Figure 7. Forest plot comparing the efficacy of single versus combined routes of TXA on blood transfusion rate.

Figure 8. Forest plot comparing the safety of single versus combined routes of on postoperative venous thromboembolism.

Table 1. Characteristics of prospective studies comparing topical with intravenous tranexamic acid in patients receiving total knee or hip anthroplasty.

Author (year)	Sample size	Region	Mean age (years)	Female, %	Surgery	IV regimen	Topical regimen	Transfusion threshold	Tourniquet use	TP	Jad sco
Maniar et al. (2012)	80	India	67	80	Unilateral TKA	10mg/kg	3g	Hb< 8.5 g/dL without CHD, Hb< 10 g/dL with CHD, anemic symptoms, organ dysfunction	Yes	LMWH	5
eo et al. (2013)	100	Korea	67	89	Unilateral TKA	1.5g	1.5g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	NA	2
ate et al. (2014)	89	USA	65	74	Unilateral TKA	10mg/kg	2g	Hb< 8 g/dL with anemic symptoms	Yes	LMWH	5
Sarzaeem et al. (2014)	100	Iran	68	86	Unilateral TKA	0.5g	3g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	NA	3
omez-Barrena et al. (2014)	78	Spain	71	65	Unilateral THA	15mg/kg*2	3g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	Enoxaparin	5
oni et al. (2014)	40	India	69	73	Unspecified TKA	10mg/kg*3	3g	Hb< 8 g/dL	Yes	LMWH	2
Ver et al. (2014)	203	China	62	64	THA	3g	3g	Hb< 9 g/dL	-	LMWH	5
Aguilera et al. (2015)	100	Spain	73	70	Primary TKA	2g	1g	Hb< 8 g/dL, Hb< 8.5 g/dL with CHD or over 70 years, Hb< 9 g/dL with anemic symptoms or organ dysfunction	Yes	LMWH	3
gas et al. (2015)	60	Greece	71	85	Unilateral TKA	15mg/kg	2g	Hb< 8.5 g/dL without CHD, Hb< 9.5 g/dL with CHD, anemic symptoms, organ dysfunction	Yes	Tinzaparin	3

ztas et al. (2015)	60	Turkey	68	85	Unilateral TKA	15mg/kg +10mg/kg	2g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	Enoxaparin	3
Tzatzairis et al. (2016)	80	Greece	69	80	Unilateral TKA	1g	1g	Hb< 10 g/dL, anemic symptoms/ organ dysfunction	No	LMWH	3
orth et al. (2016)	139	USA	65	23	Unilateral THA	2g	2g	Hb<7 g/dL, symptomatic anemia and Hb<8 g/dL	-	Enoxaparin, rivaroxaban, or aspirin	5
Ugurlu et al. (2016)	82	Turkey	70	76	Unilateral TKA	20mg/kg	3g	Hb<8 g/dL	Yes	enoxaparin	3
ang et al. (2016)	50	China	44	46	Unilateral THA	1g	1g	Hb<8 g/dL, symptomatic anemia and Hb< 10 g/dL	-	LMWH	3
lay et al. (2016)	131	USA	64	78	Unilateral TKA	2g	2g	Hb<7 g/dL, symptomatic anemia and Hb<10 g/dL	Yes	LMWH or oral Xa inhibitor	5
Keyhani et al. (2016)	80	Iran	68	39	Unilateral TKA	0.5g	3g	Hb<8 g/dL	Yes	LMWH	2
Dosos et al. (2016)	60	Greece	70	80	Unilateral TKA	1g	1g	Hb< 10 g/dL, anemic symptoms/ organ dysfunction	Yes	NA	2
hen et al. (2016)	100	Singapore	65	75	Unilateral TKA	1.5g	1.5g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	Yes	LMWH	5
Aggarwal et al. (2016)	70	India	57	36	Bilateral TKA	15mg/kg	15mg/kg	Hb< 8 g/dL, Hct< 25%	Yes	Aspirin	4

Xie et al. (2016)	210	China	61	68	THA	1.5g	3g	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	NA	Enoxaparin	5

* Hb, hemoglobin; Hct, hematocrit; IV, intravenous; LMWH, low molecular weight heparin; LOS, length of stay; MT, mechanical thromboprophylaxis; NA, not available; THA, total hip anthroplasty; TKA, total knee anthroplasty; TP, thromboembolism prophylaxis; TXA, tranexamic acid; VTE, venous thromboembolism.

Table 2. Characteristics of prospective studies comparing combination of topical and intravenous tranexamic acid with single tranexamic acid in patients receiving total knee or hip anthroplasty.

Author (year)	Sample size	Region	Mean age	Female, %	Surgery	Combination regimen	Single regimen	Transfusion threshold	Tourniquet use	TP	Jada score
Huang et al. (2014)	184	China	65	64	Unilateral TKA	IV: 1.5g + topical: 1.5g	IV: 3g	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 10 g/dL	Yes	LMWH	5
Lin et al. (2015)	120	China	71	79	Unilateral TKA	IV: 1g + topical: 1g	topical: 1g	Hb< 8 g/dL, anemic symptoms/ organ dysfunction when Hb< 9 g/dL	Yes	Rivaroxaban	3
Nielsen et al. (2016)	60	Denmark	64	53	Unilateral TKA	IV: 1g + topical: 3g	IV: 1g	Hb< 7.5 g/dL, Hb< 10 g/dL with CHD, anemic symptoms with Hb drop > 25%	No	Rvaroxaban	5
Jain et al. (2016)	119	India	69	63	Unilateral TKA	IV: (15 mg/kg preoperative + 10mg/kg postoperative) + topical: 2 g	IV: 15 mg/kg preoperative + 10mg/kg postoperative	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 8 g/dL	Yes	Aspirin	3
Zeng et al. (2016)	100	China	534	47	THA	IV: 15 mg/kg + topical: 1 g	IV: 15 mg/kg	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	NA	Enoxaparin	5
Xie et al. (2016)	210	China	61	68	THA	IV: 1g + topical: 2g.	IV: 1.5g, topical 3g	Hb< 7 g/dL, anemic symptoms/ organ dysfunction when Hb< 10g/dL	NA	Enoxaparin	5
Wu et al. (2016)	84	China	60	48	THA	IV: 15 mg/kg + topical: 3 g	IV: 15 mg/kg	Hb< 8 g/dL, anemic symptoms	NA	LMWH	3

*Hb, hemoglobin; Hct, hematocrit; IV, intravenous; LMWH, low molecular weight heparin; LOS, length of stay; MT, mechanical thromboprophylaxis; NA, not

available; THA, total hip anthroplasty; TKA, total knee anthroplasty; TP, thromboembolism prophylaxis; TXA, tranexamic acid; VTE, venous thromboembolism.

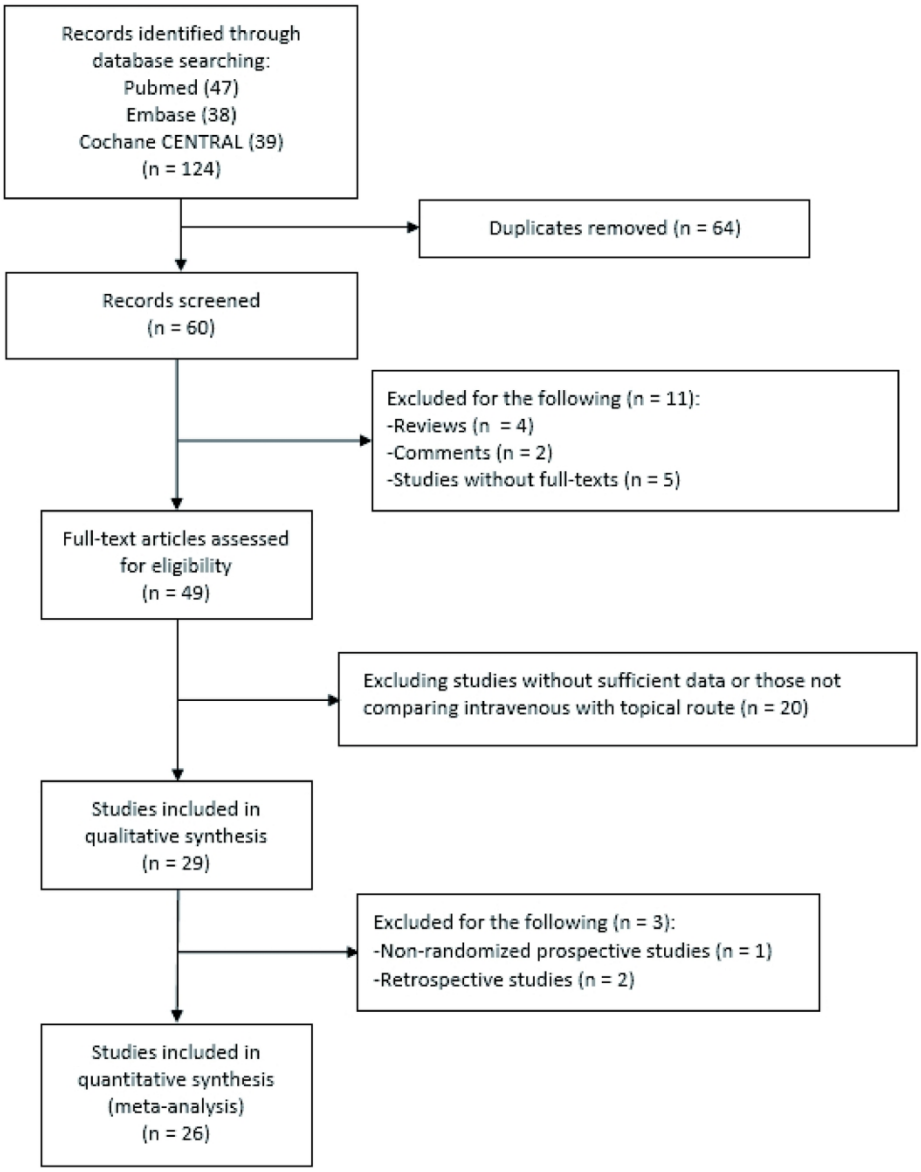

Figure 1. The flowdiagram showing the study selection process.

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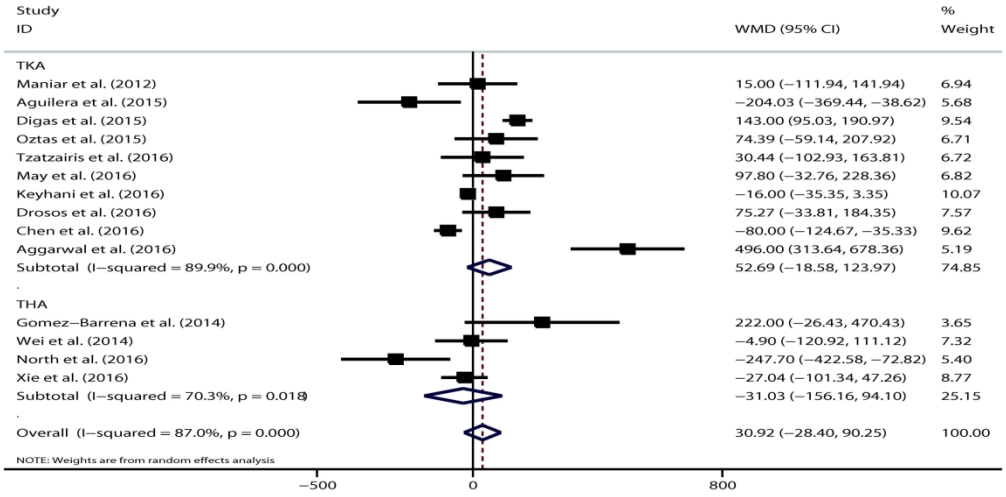

Figure 2. Forest plot comparing the efficacy of intravenous versus topical TXA on total blood loss.

228x114mm (300 x 300 DPI)

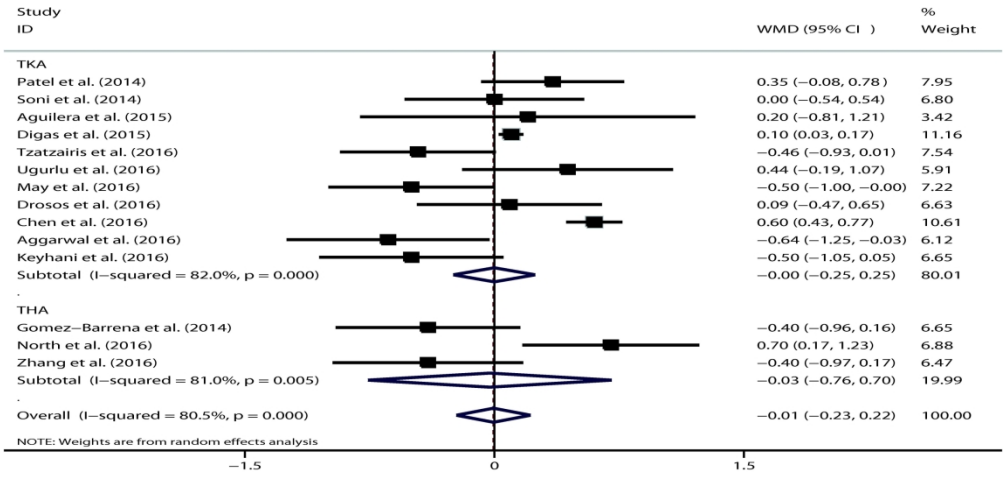

Figure 3. Forest plot comparing the efficacy of intravenous versus topical TXA on postoperative hemoglobin levels.

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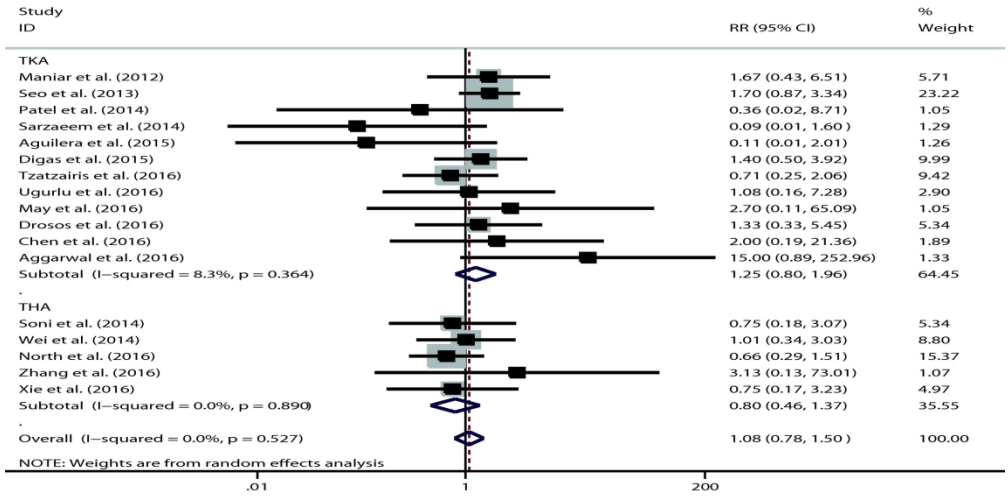

Figure 4. Forest plot comparing the efficacy of intravenous versus topical TXA on postoperative transfusion rate.

233x113mm (300 x 300 DPI)

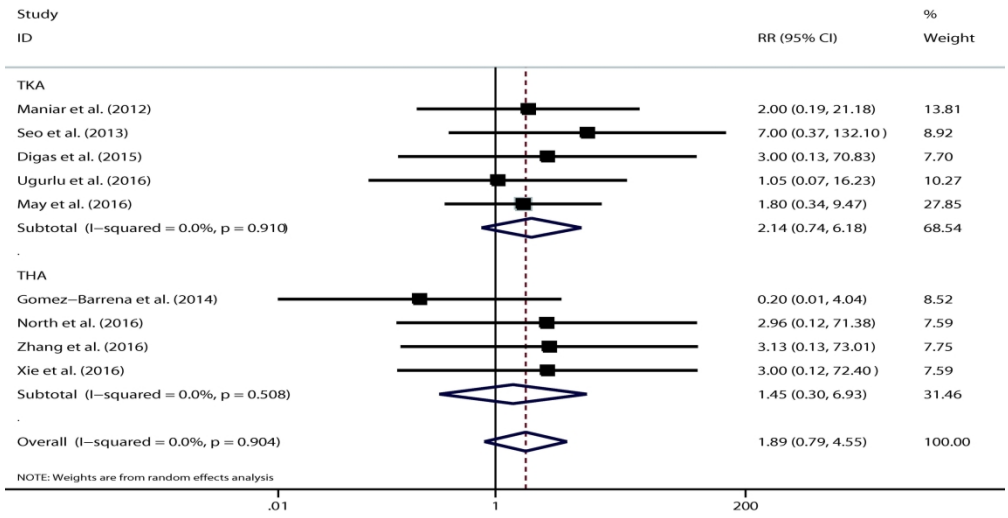

Figure 5. Forest plot comparing the safety of intravenous versus topical TXA on postoperative venous thromboembolism.

229x115mm (300 x 300 DPI)

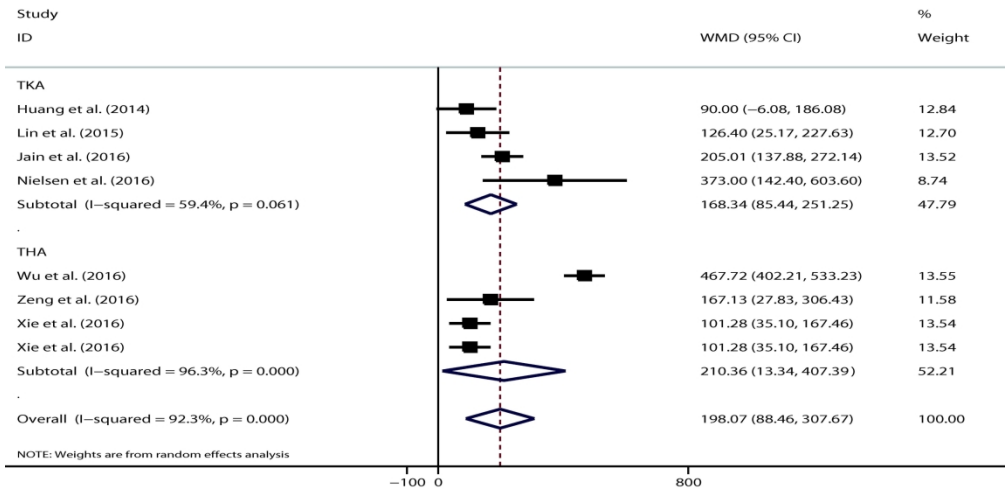

Figure 6. Forest plot comparing the efficacy of single versus combined routes of TXA on total blood loss.

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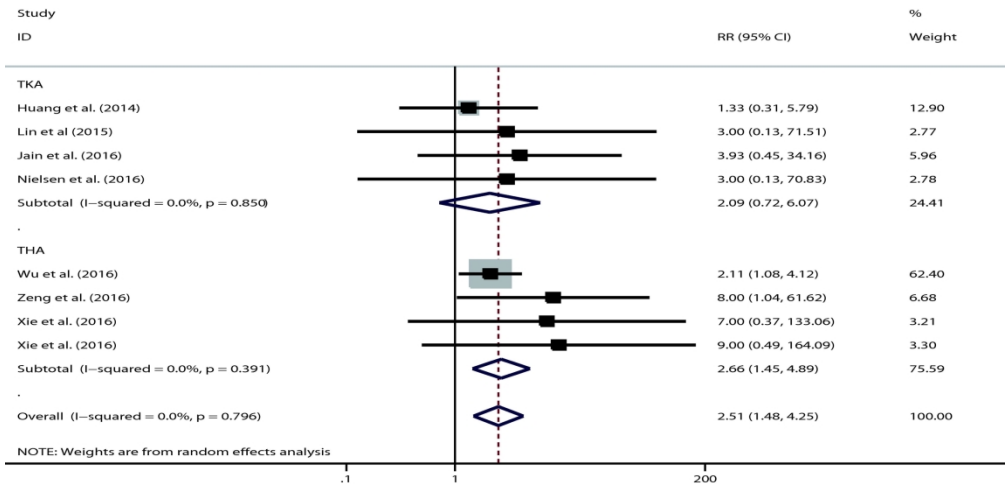

Figure 7. Forest plot comparing the efficacy of single versus combined routes of TXA on blood transfusion rate.

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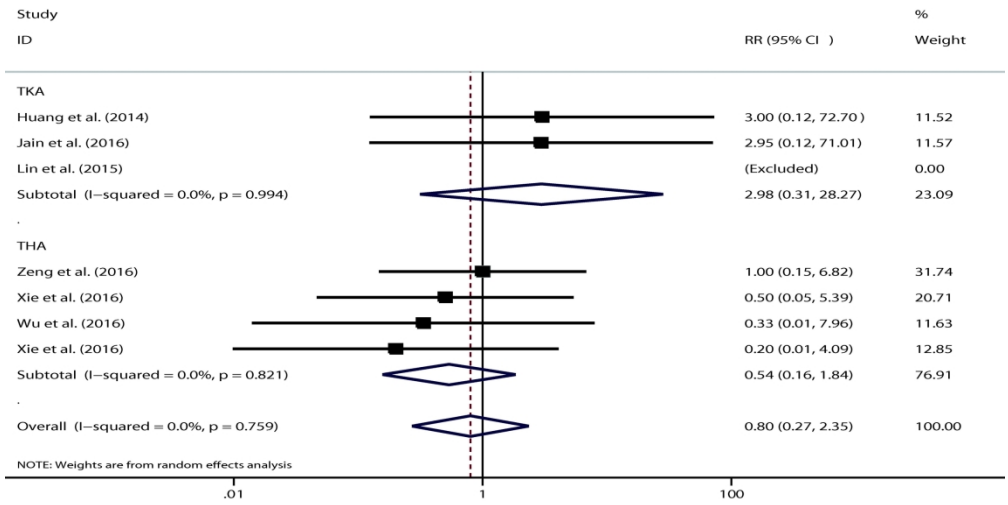

Figure 8. Forest plot comparing the safety of single versus combined routes of on postoperative venous thromboembolism.

234x115mm (300 x 300 DPI)

Supplemental Table 1. Quality assessment of studies by the Jadad scale.

Author (year)	Randomization		Blinding		Description of withdrawal and dropouts	Total score
	Mentioned	Appropriate	Mentioned	Appropriate		
Maniar et al. (2012)	1	1	1	1	1	5
Seo et al. (2013)	1	1	0	0	0	2
Lin et al. (2015)	1	1	0	0	1	3
Huang et al. (2014)	1	1	1	1	1	5
Patel et al. (2014)	1	1	1	1	1	5
Sarzaeem et al. (2014)	1	1	1	0	0	3
Gomez-Barrena et al. (2014)	1	1	1	1	1	5
Soni et al. (2014)	1	1	0	0	0	2
Wei et al. (2014)	1	1	1	1	1	5
Aguilera et al. (2015)	1	1	0	0	1	3
Digas et al. (2015)	1	1	1	0	0	3
Oztas et al. (2015)	1	0	0	0	0	1
Tzatzairis et al. (2016)	1	1	0	0	1	3

North et al. (2016)	1	1	1	1	1	5
Ugurlu et al. (2016)	1	1	0	0	1	3
Zhang et al. (2016)	1	1	0	0	1	3
May et al. (2016)	1	1	1	1	1	5
Keyhani et al.(2016)	1	0	0	0	1	2
Drosos et al. (2016)	1	1	0	0	0	2
Chen et al. (2016)	1	1	1	1	1	5
Aggarwal et al. (2016)	1	1	1	1	0	4
Xie et al. (2016)	1	1	1	1	1	5
Zeng et al. (2016)	1	1	1	1	1	5
Jain et al. (2016)	1	1	0	0	1	3
Nielsen et al. (2016)	1	1	1	1	1	5
Wu et al. (2016)	1	1	0	0	1	3

Search strategy in PubMed

#1. “Arthroplasty, Replacement, Knee”[Mesh]
#2. TKR
#3. TKA
#4. Total knee replacement
#5. Total knee arthroplasty
#6. #1-5/or
#7. “Arthroplasty, Replacement, Hip”[Mesh]
#8. THR
#9. THA
#10. Total hip replacement
#11. Total hip arthroplasty
#12. #7-11/or
#13. Tranexamic acid
#14. Randomized controlled trials
#15. #6 and #12 and #13 and #14

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5,6,7,8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5,6,7,8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5,6,7,8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5,6,7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

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