Medicine®

Comparative efficacy and safety of topical hemostatic agents in primary total knee arthroplasty
A network meta-analysis of randomized controlled trials

Shaoshuo Li, PhD[a,c] [ID], Baixing Chen, PhD[b], Zhen Hua, PhD[c], Yang Shao, PhD[c], Heng Yin, PhD[c], Jianwei Wang, PhD[c,*]

Abstract

Background: Topical hemostatic agents are commonly used for reducing perioperative blood loss and transfusion requirement in primary total knee arthroplasty (TKA), although the optimal option has yet to be defined. This study aimed to evaluate the efficacy and safety of topical hemostatic agents and rank the best intervention using the network meta-analysis (NMA) method.

Methods: We searched Web of science, PubMed, and Cochrane Library database up to April 2020, for randomized controlled trials (RCTs) on topical hemostatic agents in primary TKA. The quality of included studies was assessed using the Cochrane "risk of bias" tool. Direct and indirect comparisons were performed for the result of network meta-analysis followed by consistency test.

Results: Thirty seven RCTs with 3792 patients were included in this NMA and the pooled results indicated that tranexamic acid plus diluted epinephrine (TXA+DEP) displayed the highest efficacy in reducing total blood loss, hemoglobin drop and transfusion requirement. None of the included treatments was found to increase risk of thromboembolic events compared to placebo. According to the results of ranking probabilities, TXA+DEP had the highest possibility to be the best topical hemostatic agent with regard to the greatest comparative efficacy and a relatively high safety level.

Conclusion: Current evidence supports that administration of TXA+DEP may be the optimal topical hemostatic agent to decrease blood loss and transfusion requirement in primary TKA. More direct studies that focused on the topical application of TXA+DEP versus other treatments are needed in the future.

Abbreviations: DEP = diluted epinephrine, FS = fibrin sealant, Hb = hemoglobin, MD = mean difference, NMA = network meta-analysis, PRP = platelet-rich plasma, RCTs = randomized controlled trials, SMD = standardized mean difference, SUCRA = surface under the cumulative ranking curve, TKA = total knee arthroplasty, TXA = tranexamic acid.

Keywords: blood loss, network meta-analysis, topical hemostatic agent, total knee arthroplasty

1. Introduction

Total knee arthroplasty (TKA) is a cost-effective procedure in the treatment of end-stage knee osteoarthritis, which can obviously relieve pain and improve functional recovery.[1] However, TKA is also associated with a major risk of blood loss requiring blood transfusion, for the reason of the extensive osteotomy and opening of medullary cavity.[2] Approximately 10 to 40 percent of patients undergoing TKA require blood transfusion because of acute postoperative anemia, which has been linked to increased morbidity and delayed progression in rehabilitation.[3–6] There-

[a] Laboratory for New Techniques of Restoration & Reconstruction of Orthopedics and Traumatology, Nanjing University of Chinese Medicine, Nanjing, China, [b] Department of Development and Regeneration, KU Leuven, University of Leuven, Leuven, Belgium, [c] Department of Traumatology & Orthopedics, Wuxi Affiliated Hospital of Nanjing University of Chinese Medicine, Wuxi, China.

[*] Correspondence: Jianwei Wang, Department of Traumatology & Orthopedics, Wuxi Affiliated Hospital of Nanjing University of Chinese Medicine, No. 8 Zhongnan Xilu Avenue, Wuxi 214071, Jiangsu, China (e-mail: wxwangjianwei1963@126.com).

fore, different kinds of hemostatic agents, such as tranexamic acid (TXA), fibrin sealant (FS), platelet rich plasma (PRP), or combined application have been commonly utilized to reduce blood loss and need for transfusion.[7] A direct retrospective study[8] evaluated the change in ratio of blood transfusion after hip and knee arthroplasty from 2007 to 2015 indicates that, utilization of hemostatic agents has been considered as a key part in the transformation of blood transfusion application.

TXA has been widely executed as the postoperative conventional drug in orthopedic surgery in the past ten years. Recently developed hemostatic agents including diluted-epinephrine, PRP, fibrin sealant and thrombin have become important components in postoperative blood management.[9,10] There are different kinds of administration methods, such as topical, intravenous and oral application of these hemostatic agents. However, consensus on formulation optimization of hemostatic agent have not been reached. Topical administration of hemostatic agent contributes to a higher concentration of drug at the bleeding site, with a minimal systemic distribution, which is believed to reduce adverse effects.[11] Research to date suggests that topical hemostatic agents do perform well efficacy and safety in TKA, but the optimal treatment decision is not clear due to a lack of robust evidence.

In the past few years, a great number of randomized controlled clinical trials (RCTs) and meta-analysis have only compared arbitrary 2 treatments at a time. In the PubMed Database, we found 49 systematic reviews published from 2010 to 2020 dealing with the treatment of hemostatic agent in TKA via different routes, while only 1 study using the method of network meta-analysis (NMA) to compare multiple different administrations of TXA in joint arthroplasty.[12] As a novel synthesis of evidence, NMA can simultaneously draw together evidence of direct and indirect comparisons of more than 2 treatments, which enables a ranking of multiple treatments and helps decision-making of the optimal treatment.

To our knowledge, none of the previous researches was able to pool available data and found conclusive evidence for the optimal treatment of topical hemostatic agent in TKA. Therefore, from a methodological perspective, we present this network meta-analysis comparing various topical formulations of hemostatic agent with the direct and indirect evidence, aim to evaluate the efficacy and safety of these topical hemostatic agents in primary TKA, and assess the most optimal treatment to inform clinical practice.

In this study, randomized controlled trials that focused on topical hemostatic agents in primary TKA were enrolled and selected according to the criteria. Then the quality assessment of included studies and data extraction were performed. Direct and indirect comparisons were performed using network meta-analysis method based on the frequentist approach, and the ranking probability of treatments was estimated. Moreover, publication bias was assessed by the funnel plot analysis. The results of this study may provide a clinical guidance for the use of topical hemostatic agent in TKA.

2. Methods

2.1. Eligibility criteria and exclusion criteria

All randomized controlled trials were considered eligible if they met all of the following criteria:

1. adults (>18 years of age);
2. patients underwent unilateral primary total knee arthroplasty;
3. at least two intraoperative topical therapies for controlling bleeding including placebo/sham treatment;
4. studies evaluated the efficacy or safety of topical formulations using at least one of the following endpoints: (a) amounts of total blood losses, (b) hemoglobin (Hb) drop, (c) blood transfusion requirements, (d) thromboembolic events including deep vein thrombosis, intramuscular venous thrombosis and pulmonary embolism.

The following criteria were used for data exclusion:

1. case reports, letters, comments, review articles, and meeting abstract;
2. retrospective trials or trials of low quality;
3. patients underwent revision TKA or primary arthroplasty of joints other than the knee;
4. data were unavailable on standardized mean difference (SMD) or risk ratios.

2.2. Search strategy and study selection

Electronic literature searches were conducted using Web of science, PubMed, and Cochrane Library database from inception to April 2020. MeSH terms and keywords including "knee arthroplasty," "total knee arthroplasty," "TKA," "total knee replacement," "blood loss," "blood transfusion," "tranexamic acid," "fibrin sealant," "platelet-rich plasma," and "diluted epinephrine" were used in the strategy. Bibliographies lists of all the retrieved studies, and previous meta-analyses were checked manually to identify any initially omitted studies.

Two researchers independently reviewed the title, abstract and the full texts of all the retrieved studies for any potentially eligible trials. Any disagreement about whether included or not was resolved by a discussion or consulted to a third researcher. The recommended PRISMA statement and guidelines[13,14] were followed for the network meta-analysis, and our network meta-analysis was registered in PROSPERO (CRD42018102094).

2.3. Data extraction and quality assessment

We compared the effects of placebo/sham (PLA), platelet-rich plasma (PRP), tranexamic acid plus diluted epinephrine (TXA +DEP), high or low dose of fibrin sealant (FS) and TXA on total blood losses, hemoglobin drop, blood transfusion requirement including allogeneic and autogenous transfusion, and the occurrence of thromboembolic events. High dose of TXA (TXAH group) was defined as bolus dose of any dose greater than 1.5 g, low dose of TXA (TXAL group) was defined as bolus dose of no more than 1.5 g. High dose of FS (FSH group) was defined as bolus dose of any dose greater than 5 ml, low dose of FS (FSL group) was defined as bolus dose of no more than 5 ml. Two same researchers independently used a standardized form to extract data from the included studies, and the extracted data were checked by a third researcher. The information extracted included both study characteristics and measuring outcomes. Study characteristics including year of publication, first author name, sample size, intervention across the groups and dose were extracted. Total blood losses, Hb drop, and transfusion requirements were extracted as the measured outcomes for effectiveness, while the occurrence of thromboembolic events was recorded as the measured outcomes for safety. When relevant data was missing or needed to be identified, attempts were made

to connect with the corresponding author by e-mail. The Cochrane Risk of Bias Tool was adopted to assess the risk of bias in these included randomized trials.[15] A total of 7 domains were assessed and classified as high, unclear, and low risk of bias. Any disagreement on risk of bias ratings was discussed with a third researcher until a consensus was reached.

2.4. Statistical analysis

In order to obtain direct treatment effect estimates for each included comparison, the pairwise meta-analysis was performed first, with risk ratio or SMD and 95% confidence intervals of the endpoints as effect sizes. The random-effects model was used for cases with significant heterogeneity ($P < .1$ and $I^2 > 50\%$); otherwise, the fixed-effects model (Mantel-Haenszel method)

was used. The network meta-analysis method was used to compare different incorporating evidence on both indirect and direct comparisons. Our network meta-analysis was performed by restricted maximum likelihood and framework based on the frequentist approach using STATA 13.0 software (Stata Corp, College Station, TX). The random effect assumption was adopted in our NMA and the consistency model was generated from the STATA network package. Inconsistency, that is, the differences between direct and indirect evidence estimated for the same comparison. The network inconsistency was assessed in 3 ways:

1. a global Wald test for global inconsistency (with P values <.05 favoring inconsistency);
2. a node-splitting method for local inconsistency (with P values <.05 favoring inconsistency);
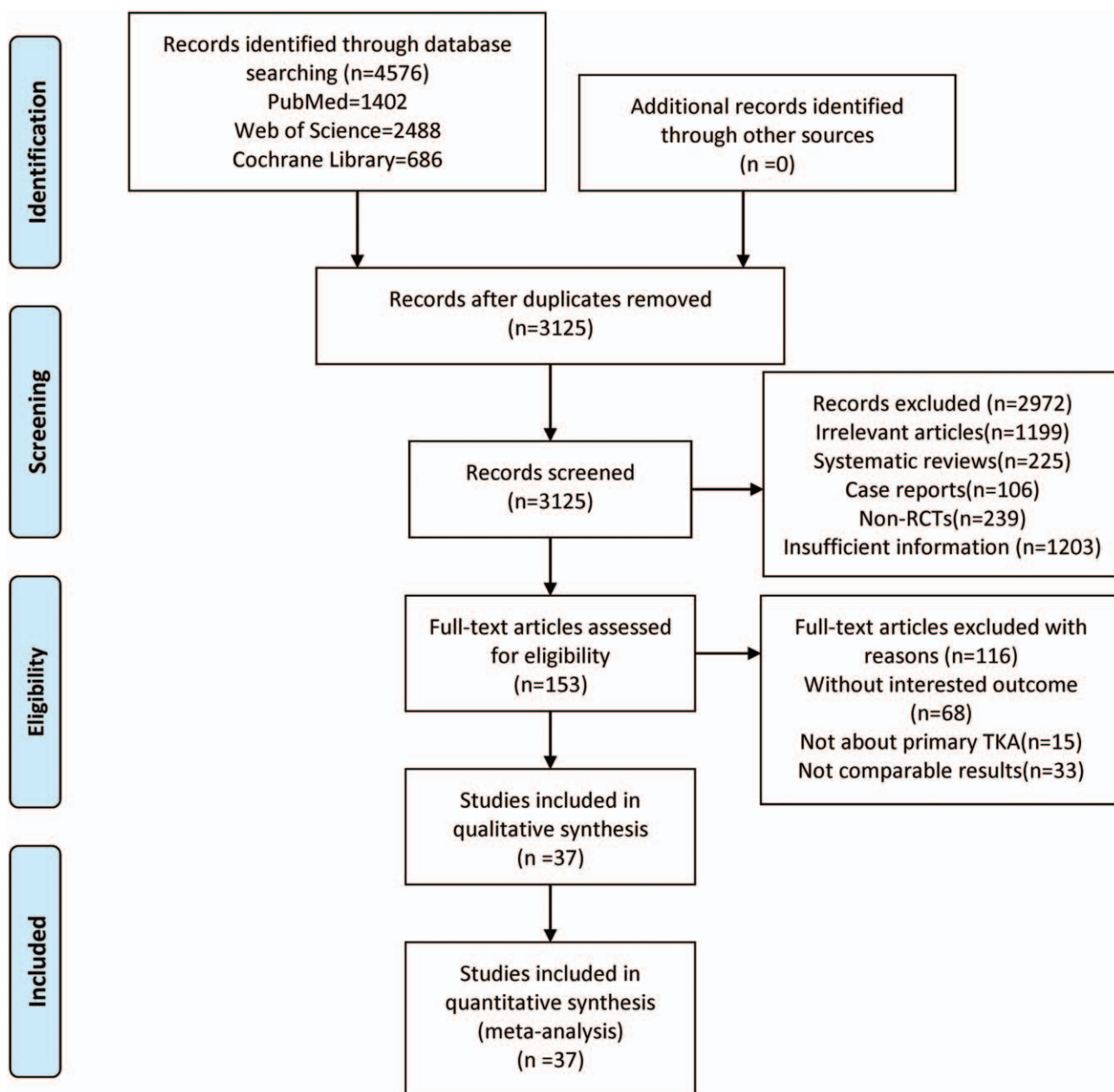

Figure 1. Flow diagram of the study selection procedure.

3. inconsistency factor (IF) among studies in each closed loop was tested for loop inconsistency, the 95% confidence intervals of IF values are truncated at zero indicates that there is no statistically significant inconsistency.[16]

The probability of a treatment being ranked at a specific place according to the outcome was estimated by using surface under the cumulative ranking curve (SUCRA). SUCRA was adjusted by a model of network meta regression accounting for small-study effects, using the variance of the log-odds ratios as covariation.[17] The higher the SUCRA value is, the higher possible ranking of the treatment is. Funnel plot analysis was performed to assess publication bias of pairwise estimates. The funnel plot should be symmetrical near the zero line if there is no publication bias.[18]

3. Results

3.1. Study selection, characteristics and risk of bias assessment

As shown in Figure 1, a total of 4576 citations were initially identified as eligible from electronic databases, no additional record identified from other sources. Following elimination of duplicates, 3125 records were screened for the titles and abstracts. After screened the titles and abstracts carefully, 2972 records were excluded for different reasons. Finally, a total of 37 RCTs involving 3792 patients were included in our network meta-analysis. The study of song[54] compared blood loss between groups with and without topical TXA in 220 patients undergoing cruciate retaining and posterior stabilized TKA, was divided into 2 separate comparisons. The general characteristics of all included studies were presented in Table 1.

All of the included studies were described as randomized-designed. However, 9 of them did not report the randomization details. The allocations were properly concealed in 30 studies. There are 8 studies were unclear risk in the performance bias examination, and 15 studies were unclear risk in the detection bias examination. Only 1 article described that neither patients nor researchers were blinded to the interventions. Most of the studies were placed at low or unclear risk in the attrition bias and reporting bias examination. Furthermore, the overall risk of RCT bias for the included studies is demonstrated in Figure 2A, B (graph and summary).

Table 1

Characteristics of the included studies.

Author	Intervention	Participants, n	Age, years	Male	Dose
Aguilera 2015[19]	PLA/TXAL	50/50	73.68 ± 7.33/72.53 ± 6.60	18/18	Sham/TXA, 1 g
Alshryda 2013[20]	PLA/TXAL	78/79	67.1 ± 10.2/65.5 ± 9.6	44/30	NS/TXA, 1 g
Carvalho 2015[21]	PLA/TXAL/TXAH	40/42	69,3 ± 60/70.8 ± 6.5/70 ± 8.2	10/18/7	NS/TXA, 1.5 g/TXA, 3 g
Digas 2015[22]	PLA/TXAH	30/30	68 ± 5.5/71 ± 7.0	2/7	Sham/TXA,2 g
Drosos 2016[23]	PLA/TXAL	30/30	71.77 ± 6.50/71.10 ± 6.32	6/6	Sham/TXA.1 g
Morishita 2014[24]	PLA/PRP	20/20	74.7 ± 5.7/72 ± 4.1	0/2	Sham/PRP,5 ml
Gao FQ 2015[25]	TXAH/TXA+DEP	50/50	67.4 ± 9.8/68.5 ± 8.1	13/11	TXA, 3 g/TXA, 3 g+DEP, 0.25 mg
Georgiadis 2013[26]	PLA/TXAH	51/50	64.5 ± 8.2/67.0 ± 9.0	12/19	NS/TXA, 2 g
Guerreiro 2015[27]	PLA/PRP	20/20	71.6/66.4	8/6	Sham/PRP,10 ml
Guzel 2016[28]	PLA/TXAL	50/50	67 ± 4.5/66.5 ± 5.1	10/7	Sham/TXA, 1.5 g
Horstmann 2011[29]	PLA/PRP	20/20	66/67	13/14	Sham/PRP,11 ml
Peerbooms 2009[30]	PLA/PRP	52/50	78 ± 5.1/77 ± 4.4	11/13	Sham/PRP,6 ml
Keyhani 2016[31]	PLA/TXAH	40/40	63.9 ± 90/67 ± 11.9	19/23	Sham/TXA,3 g
Levy 1999[32]	PLA/FSH	29/29	70.2 ± 8.2/68.9 ± 6.3	6/6	Sham/FS, 10-20 ml
Lin 2014[33]	PLA/TXAL	40/40	69.7 ± 8.0/71.0 ± 7.2	5/7	NS/TXA, 1 g
Santias 2020[34]	PLA/TXAH	115/115	70.0 ± 8.0/71.1 ± 7.9	74/80	NS/TXA,2g
Molloy 2007[35]	PLA/FSH	50/50	NA	NA	Sham/FS, 10 ml
Notarnicoa 2012[36]	PLA/FSL/FSH	30/30/30	NA	10/9/11	Sham/FS, 5 ml/FS,10 ml
Öztaş 2015[37]	PLA/TXAH	30/30	67.03 ± 6.15/67.06 ± 6.54	5/4	Sham/TXA, 2 g
Roy 2012[38]	PLA/TXAL	25/25	66.56 ± 8.03/66.04 ± 7.15	9/10	NS/TXA, 0.5 g
Sa-ngasoongsong 2011[39]	PLA/TXAL	24/24	69.2 ± 7.6/69.0 ± 8.2	6/3	NS/TXA, 0.25 g
Sa-ngasoongsong 2013[40]	PLA/TXAL/TXAL	45/45/45	66.2 ± 7.3/67.6 ± 8.7/68.1 ± 6.2	2/3/5	NS/TXA, 0.25 g/TXA, 0.5 g
Sarzaeem 2014[41]	PLA/TXAH/TXAL	50/50/50	66.8 ± 8.2/68.1 ± 6.8/67.5 ± 7.6	7/7/6	Sham/TXA,3 g/TXA, 1.5 g
Seo 2012[42]	PLA/TXAL	50/50	67.8 ± 6.1/67.5 ± 6.6	5/5	NS/TXA, 1.5 g
Mochizuki 2016[43]	PLA/PRP	206/109	73.4 ± 8.2/73.0 ± 7.8	43/17	Sham/PRP, 5 ml
Tammachote 2019[44]	TXAL/TXAH	40/40	66 ± 8/67 ± 10	7/7	TXA, 0.5 g/TXA, 3 g
Tzatzairis 2016[45]	PLA/TXAH	40/40	68.58 ± 7.50/69.10 ± 8.68	9/7	Sham/TXA,1g
Wang CG 2015[46]	PLA/TXAL	30/30	64.97 ± 6.75/64.90 ± 6.38	6/9	NS/TXA, 0.5 g
Wang GJ 2001[47]	PLA/FSH	28/25	NA	NA	Sham/FS, 10 ml
Wang GW2015[48]	PA/TXAL	50/50	53.2 ± 10.2/52.6 ± 12.4	22/25	NS/TXA, 1 g
Wang J 2017[49]	PLA/TXAL	50/50	67.66 ± 7.488/67.98 ± 5.971	16/14	NS/TXA, 1 g
Wong 2010[1]	PLA/TXAL/TXAH	35/31/33	68.4 ± 10.4/67 ± 11.9/63.9 ± 10.6	13/6/14	NS/TXA, 1.5 g/TXA, 3 g
Yang Y 2014[50]	PLA/TXAL	40/40	69 ± 5/67 ± 6	10/12	NS/TXA, 0.5 g
Yen 2017[51]	PLA/TXAH	30/32	70.87 ± 6.05/69.66 ± 5.53	6/13	NS/TXA, 3 g
Yuan XW 2017[52]	PLA/TXAH	140/140	64.63 ± 7.58/63.26 ± 6.99	65/63	NS/TXA, 3 g
Randelli, 2014[53]	PLA/FSL	31/31	71 ± 6.5/69 ± 8.0	9/5	Sham/FS, 5 ml
Song 2020 (CR)[54]	PLA/TXAL	55/55	71.3 ± 6.9/71.0 ± 5.4	9/11	Sham/TXA,1 g
Song 2020 (PS)[54]	PLA/TXAL	55/55	68.2 ± 7.4/70.4 ± 7.5	6/8	Sham/TXA, 1 g

CR = Cruciate retaining, FSH = High dose of fibrin sealant, FSL = Low dose of fibrin sealant, NA = Data not available, NS = Normal saline, PLA = Placebo, PRP = Platelet-rich plasma, PS = Posterior stabilized, TXA+DEP = Transexamic acid plus diluted epinephrine, TXAH = High dose of tranexamic acid, TXAL = Low dose of tranexamic acid.
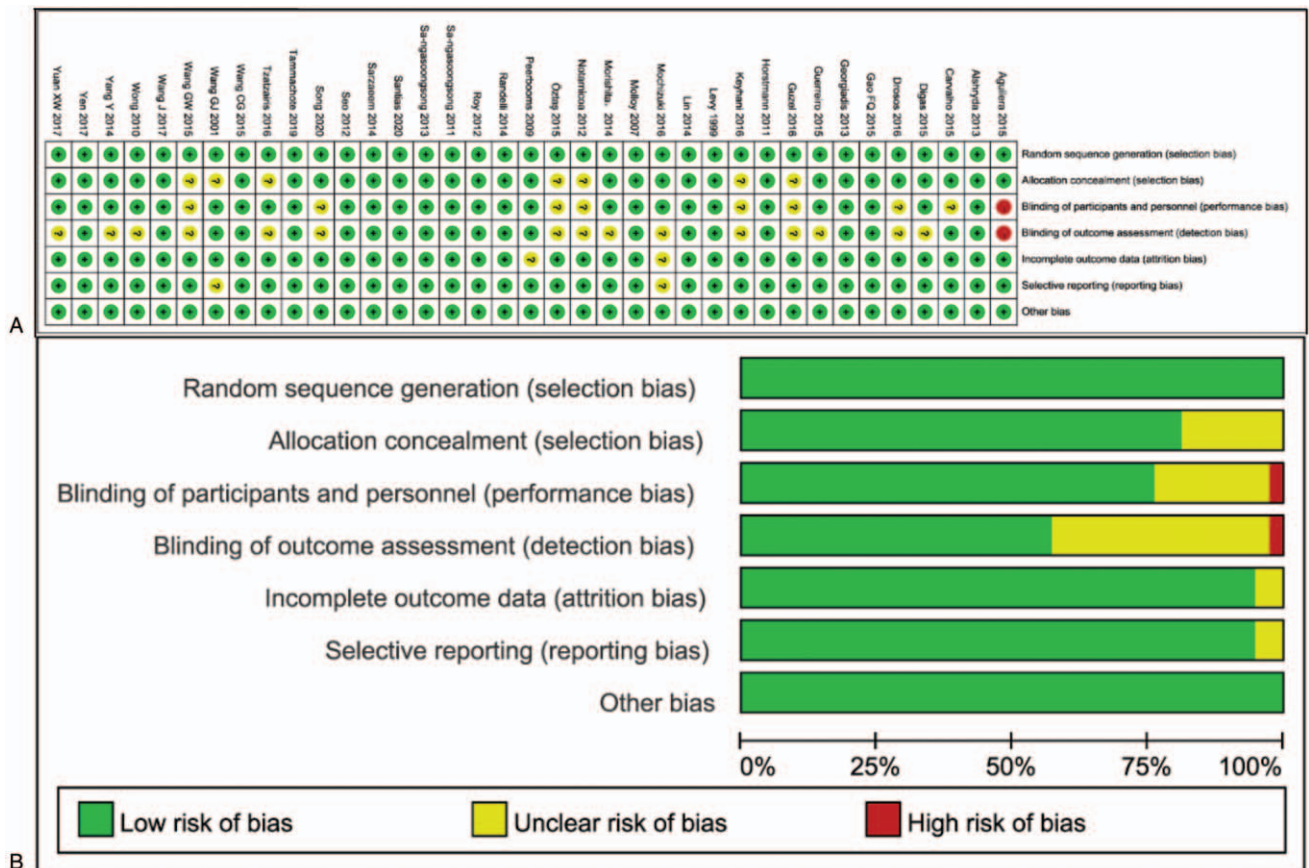
Figure 2. Risk of bias assessment of included studies. (A) The judgements about risk of bias item for included trials; (B) The summary of judgements about risk of bias item presented as percentages.

3.2. Network meta-analysis for the efficacy and safety of topical hemostatic therapies

3.2.1. Total blood loss. Twenty nine studies (n=2822 patients) were included in the NMA for the total blood loss (Fig. 3A). Pooled results of the NMA indicated that injection of tranexamic acid plus diluted epinephrine (mean difference [MD]=−515.70, 95% CI: [−948.95 to −82.45]), FSH (MD=−431.76, 95% CI: [−668.07 to −195.45]), TXAH (MD=−333.98, 95% CI: [−465.42 to −202.54]) and TXAL (MD=−323.23, 95% CI: [−422.84 to −223.62]) were more effective than the placebo/ sham treatment in reducing total blood loss. In the meantime, FSH (MD=−373.81, 95% CI: [−746.12 to −1.51]) showed better reduction of total blood loss than the PRP group. There were no significant differences when comparing FSL, PRP and PLA with each other for decreasing total blood loss (Table 2). With the highest SUCRA values of 84.3, and the best mean ranks of 1.9, TXA+DEP may be more effective than other treatments. Followed by FSH, TXAH and TXAL, ranks 2 to 4, respectively (Figs. 4A and 5A). In contrast, FSL and PRP demonstrated the least comparative effectiveness for total blood loss reduction except for placebo.

3.2.2. Hb drop. In terms of hemoglobin drop, 3162 patients in 32 studies were included in the NMA (Fig. 3B). TXA+DEP (SMD=−1.59, 95% CI: [−2.98 to −0.20]), FSH (SMD=−1.45, 95% CI: [−2.13 to−0.76]), TXAH (−0.97, 95% CI: [−1.43 to −0.51]) and TXAL (SMD=−0.83, 95% CI: [−1.13 to−0.53])

were significantly better than the placebo in reducing Hb drop. Furthermore, the pooled result revealed a significant reduction of Hb drop by FSH topical administration compared with PRP. No significant difference was observed between TXA+DEP, FSH, TXAH, TXAL, and FSL group (Table 2). Based on the SUCRA value and mean ranks, probabilities of rank plot were: TXA +DEP, FSH, TXAH, TXAL, FSL, ranked 1 to 5, respectively (Figs. 4B and 5B).

3.2.3. Need for transfusion. Data on blood transfusion requirement were available in 35 studies with a total of 3343 patients (Fig. 3C). FSH (RR=0.50, 95% CI: [0.33–0.76]), TXAH (RR=0.38, 95% CI: [0.25–0.59]) and TXAL (RR=0.32, 95% CI: [0.24–0.43]) were comparatively better at reducing transfusion requirement than the placebo/sham intervention. Whereas, the transfusion requirement of other 3 topical administrations (TXA+DEP, FSL, and PRP) showed non-statistically significant differences from the placebo/sham group. Besides, TXAL (RR=0.50, 95% CI [0.27–0.92]) was more effective compared with the FSL group (Table 3). General trends from the NMA and direct comparisons for transfusion requirement indicated that TXA+DEP may be the most effective treatment (highest SUCRA value of 89.2 and best mean ranks of 1.7). TXAL, TXAH, FSH, and FSL ranked 2 to 5 in the probabilities of rank plot, respectively. While PRP and placebo appeared least likely to be beneficial for decreasing transfusion requirement (Figs. 4C and 5C).
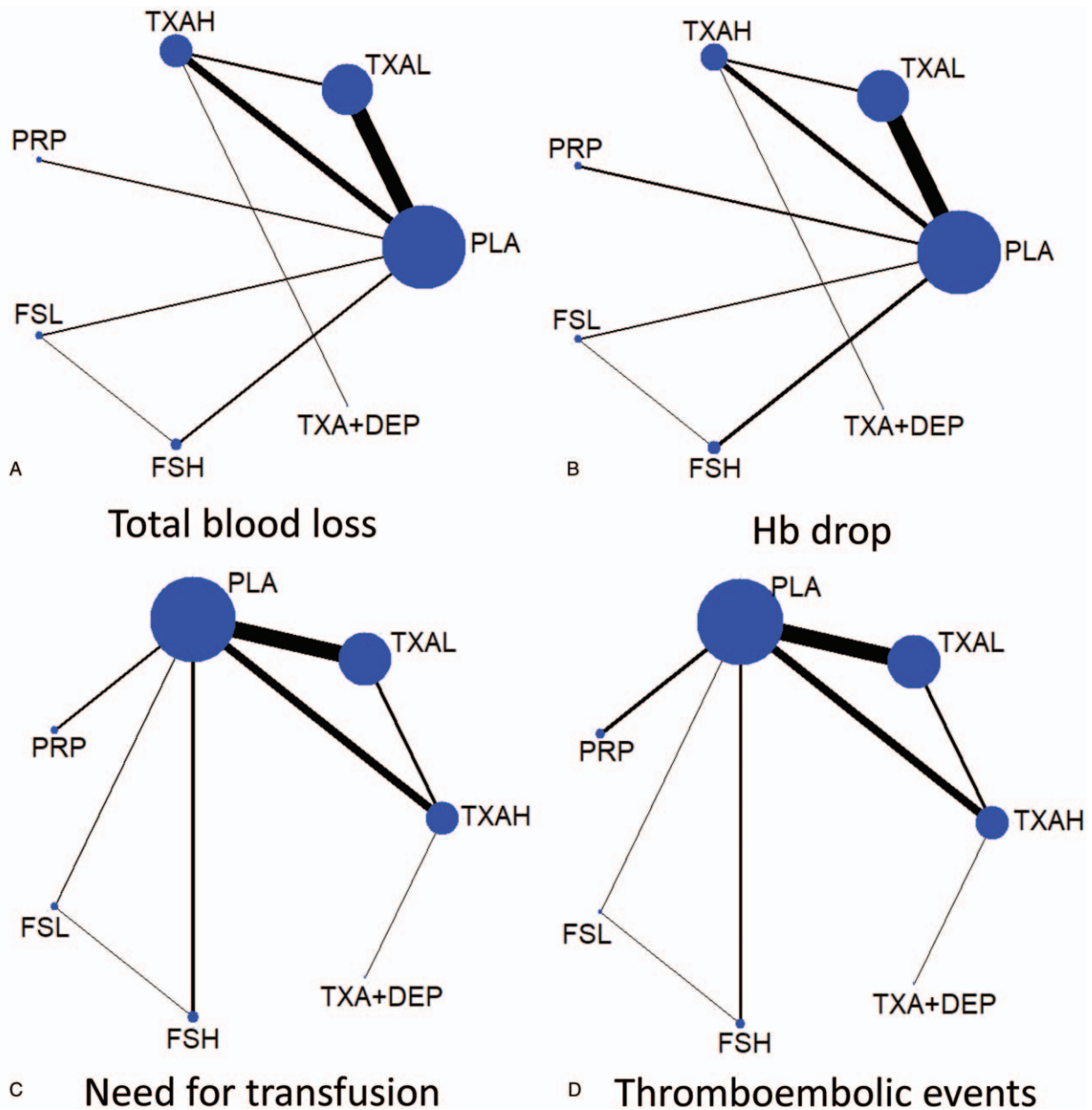
Figure 3. Network plot of included studies for treatment comparisons. As for the outcomes of (A) Total blood loss; (B) Hb drop; (C) Need for transfusion and (D) Thromboembolic events.

3.2.4. Thromboembolic events. The incidence of thromboembolic events was reported in 34 studies including 3330 patients (Fig. 3D). The pooled result of NMA did not show any significantly increased risk of topical administration of hemostatic compared with the placebo in postoperative thrombosis events (Table 3). Most hemostatic administration were not significantly superior to 1 another, with all of these interventions having similar rankings (average SUCRA of 49.99). TXA+DEP, TXAH, TXAL, and PRP ranked 1 to 4 in the rank plot, while FSL and FSH ranked 6 and 7(Figs. 4D and 5D). None of the included treatments was found to increase the risk of postoperative thromboembolic events, while the administration of fibrin sealant may be less safe compared with other hemostatic agents.

3.2.5. Total rank probability. As shown in Figure 5, topical administration of TXA+DEP was ranked as being the most effective treatment for several outcomes evaluated of blood-sparing properties in TKA, including total blood loss, Hb drop as well as blood transfusion requirement. In the meantime, it was also ranked as being the safest treatment for reducing thromboembolic events. The pooled results of total ranking probability of TXA+DEP in all the outcomes demonstrated that, TXA+DEP may be superior that other treatments in this NMA, with the best ranking probability (Fig. 6).

The results of network meta-analysis for efficacy and safety of TXA+DEP compared with other interventions was shown in Figure 7. TXA+DEP demonstrated statistically significant differ-

Table 2

Results of network meta-analysis for the outcomes of total blood loss and Hb drop comparisons should be read from left to right.

TXA+DEP	FSH	TXAH	TXAL	FSL	PRP	PLA
TXA+DEP	−0.14 (−1.70 to 1.41)	−0.62 (−1.94 to 0.70)	−0.76 (−2.17 to 0.65)	−1.02 (−2.68 to 0.65)	−1.43 (−3.03 to 0.17)	**−1.59 (−2.98 to −0.20)**
−83.94 (−577.46 to 409.58)	FSH	−0.48 (−1.30 to 0.34)	**−0.62 (−1.36 to −0.13)**	−0.87 (−1.88 to 0.14)	**−1.29 (−2.33 to −0.24)**	**−1.45 (−2.13 to −0.76)**
−181.72 (−594.56 to 231.12)	−97.78 (−368.21 to 172.64)	TXAH	−0.14 (−0.64 to 0.36)	−0.40 (−1.41 to 0.62)	−0.81 (−1.72 to 0.10)	**−0.97 (−1.43 to −0.51)**
−192.47 (−631.83 to 246.90)	−108.53 (−365.13 to 148.07)	−10.74 (−161.10 to 139.62)	TXAL	−0.26 (−1.21 to 0.70)	−0.67 (−1.52 to 0.17)	**−0.83 (−1.13 to −0.53)**
−266.98 (−789.86 to 255.91)	−183.04 (−502.88 to 136.80)	−85.25 (−406.16 to 235.65)	−74.51 (−384.00 to 234.98)	FSL	−0.41 (−1.61 to 0.79)	−0.57 (−1.48 to 0.33)
−457.75 (−977.85 to 62.34)	**−373.81 (−746.12 to −1.51)**	−276.03 (−592.37 to 40.31)	−265.29 (−569.83 to 39.26)	−190.78 (−601.17 to 219.62)	PRP	−0.16 (−0.95 to 0.63)
−515.70 (−948.95 to −82.45)	**−431.76 (−668.07 to −195.45)**	**−333.98 (−465.42 to −202.54)**	**−323.23 (−422.84 to −223.62)**	−248.72 (−541.44 to 43.99)	−57.95 (−345.68 to 229.78)	PLA

Comparisons should be read from left to right. Mean difference (MD) or standardised mean difference (SMD), with a 95% CI for comparisons are in cells in common between column-row defining treatment. Bold cells are significant. A negative MD/SMD favors column-row defining treatment, and a positive MD/SMD favors row-defining treatment. FSH = high dose of fibrin sealant, FSL = low dose of fibrin sealant, PLA = placebo, PRP = platelet-rich plasma, TXA+DEP = tranexamic acid plus diluted epinephrine, TXAH = high dose of tranexamic acid, TXAL = low dose of tranexamic acid.

ences in the comparisons with PLA separately in the outcomes of total blood loss and Hb drop, while no other significant difference was observed in comparisons in the outcomes of blood transfusion requirement and thromboembolic events. However, TXA+DEP did not show significant advantage over other interventions at all the outcomes.

3.3. Network coherence and publication bias

First, the global Wald tests for inconsistency of the NMA were not significant ($P = .1279$, .6820, .2099, and .7968 for the outcomes of total blood loss, Hb drop, blood transfusion requirement and thromboembolic events, respectively). Second, through a node-splitting method, no significant difference was observed in the direct and indirect comparisons for all the outcomes (all P values were $>.05$). Third, the network was consisted of 2 triangular loops including (PLA)-(TXAL)-(TXAH) and (PLA)-(FSL)-(FSH). The 95% CI of IF values were truncated at zero at the outcomes of Hb drop (IF=0.13, 0.39; 95% CI: [0.00–1.11].[0.00–3.67]), blood transfusion requirement (IF= 0.38, 0.27; 95% CI: [0.00–1.42].[0.00–1.33]) and thromboembolic events (IF=0.26, 2.14, 95% CI: [0.00–1.96].[0.00–6.41]), indicating that there was no evidence of significant loop inconsistency. Whereas, at the outcome of total blood loss, significant inconsistency was observed in the (PLA)-(FSL)-(FSH) loop (IF=195.17, 95% CI: [39.69–350.65]). Funnel plot of the network was presented in Figure 8. All included studies symmetrically distribute around the vertical line ($x = 0$) in terms of the effect size centered at the comparison-specific pooled effect, indicating that there was minimal publication bias.

4. Discussion

4.1. Main Findings

In this network meta-analysis, we included all retrievable RCTs that focused on the blood-sparing properties of different topical hemostatic agents in primary TKA, and analyzed the efficacy and safety of these treatments. The results of the NMA indicated that

1. topical administration of TXA+DEP, FSH, TXAH, and TXAL can significantly reduce total blood loss and Hb drop in TKA when compared with the placebo, the ranking of interventions was TXA+DEP, FSH, TXAH, TXAL, FSL, PRP, and PLA;
2. applications of FSH, TXAL and TXAH had significantly lower risk in terms of postoperative blood transfusion, TXA+DEP, TXAL, TXAH, FSH, FSL, PLA, and PRP ranked 1 to 7 according to the SUCRA value;
3. no significant difference was observed in all the comparisons for the risk of thromboembolic events, the ranking of treatments was TXA+DEP, TXAH, TXAL, PRP, PLA, FSL, and FSH.

From the results of current network meta-analysis, we discovered that treatment TXA+DEP was most likely to be the most preferable topical hemostatic agent in primary TKA based on the test of efficacy and safety.

4.2. Implications for clinical practice and future research

Multiple kinds of hemostatic agent have been widely used in joint arthroplasty for reducing perioperative blood loss and need for blood transfusion. TXA, a synthetic anti-fibrinolytic agent, acts

Table 3

Results of network meta-analysis for the outcomes of need for transfusion and thromboembolic events.

TXA+DEP	0.09 (0.00 to 2.82)	0.20 (0.01 to 4.06)	0.18 (0.01 to 4.04)	0.10 (0.00 to 4.08)	0.14 (0.00 to 5.44)	0.15 (0.01 to 3.13)
0.15 (0.01 to 3.39)	FSH	2.24 (0.41 to 12.16)	2.05 (0.39 to 10.90)	1.11 (0.10 to 12.19)	1.62 (0.13 to 20.02)	1.64 (0.33 to 8.09)
0.20 (0.01 to 4.17)	1.30 (0.72 to 2.37)	TXAH	0.92 (0.45 to 1.87)	0.50 (0.06 to 4.38)	0.72 (0.10 to 5.45)	0.73 (0.42 to 1.28)
0.24 (0.01 to 5.20)	1.57 (0.94 to 2.61)	1.20 (0.74 to 1.96)	TXAL	0.54 (0.06 to 4.70)	0.79 (0.11 to 5.85)	0.80 (0.49 to 1.30)
0.12 (0.01 to 2.69)	0.78 (0.41 to 1.48)	0.60 (0.30 to 1.20)	**0.50 (0.27 to 0.92)**	FSL	1.46 (0.08 to 25.57)	1.47 (0.18 to 12.10)
0.08 (0.00 to 3.43)	0.50 (0.05 to 4.91)	0.38 (0.04 to 3.77)	0.32 (0.03 to 3.07)	0.64 (0.06 to 6.47)	PRP	1.01 (0.15 to 7.03)
0.08 (0.00 to 1.64)	**0.50 (0.33 to 0.76)**	**0.38 (0.25 to 0.59)**	**0.32 (0.24 to 0.43)**	0.64 (0.37 to 1.10)	1.00 (0.11 to 9.46)	PLA

Comparisons should be read from left to right. Relative risk (RR) with a 95% CI for comparisons are in cells in common between column-row defining treatment. Bold cells are significant. RR <1 favors column-defining treatment, RR >1 favors row-defining treatment. FSH = high dose of fibrin sealant, FSL = low dose of fibrin sealant, PLA = placebo, PRP = platelet-rich plasma, TXA+DEP = tranexamic acid plus diluted epinephrine, TXAH = high dose of tranexamic acid, TXAL = low dose of tranexamic acid.

as a reversible blockade of lysine-binding sites of plasminogen molecules.[55] Fibrin sealant, firstly applied in the surgical field in the 1970s, shows great performance on controlling bleeding and improving tissue healing by the complicated contact with fibronectin and factor XIII.[56] Platelet-rich plasma, contains blood coagulation factor V, fibrinogen and thromboxane A2, which is suggested to be beneficial for reducing bleeding.[57,58] Numbers of the publications have attempted to identify the dosage, number of doses, formulation, and timing of administration that provide the optimal blood-sparing properties.
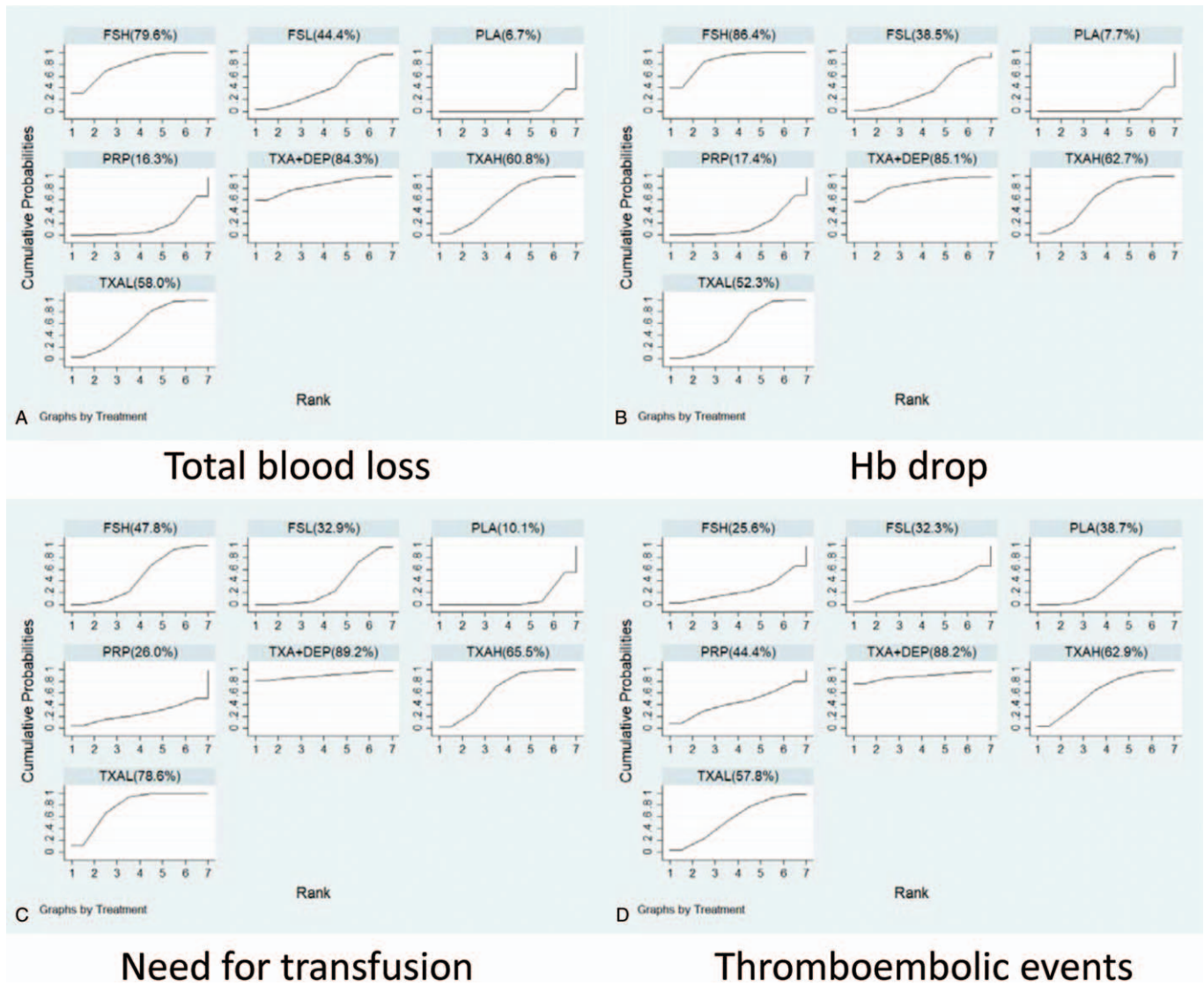
Figure 4. Cumulative ranking plots to show the effectiveness of treatments on the outcomes of (A) Total blood loss; (B) Hb drop; (C) Need for transfusion and (D) Thromboembolic events.
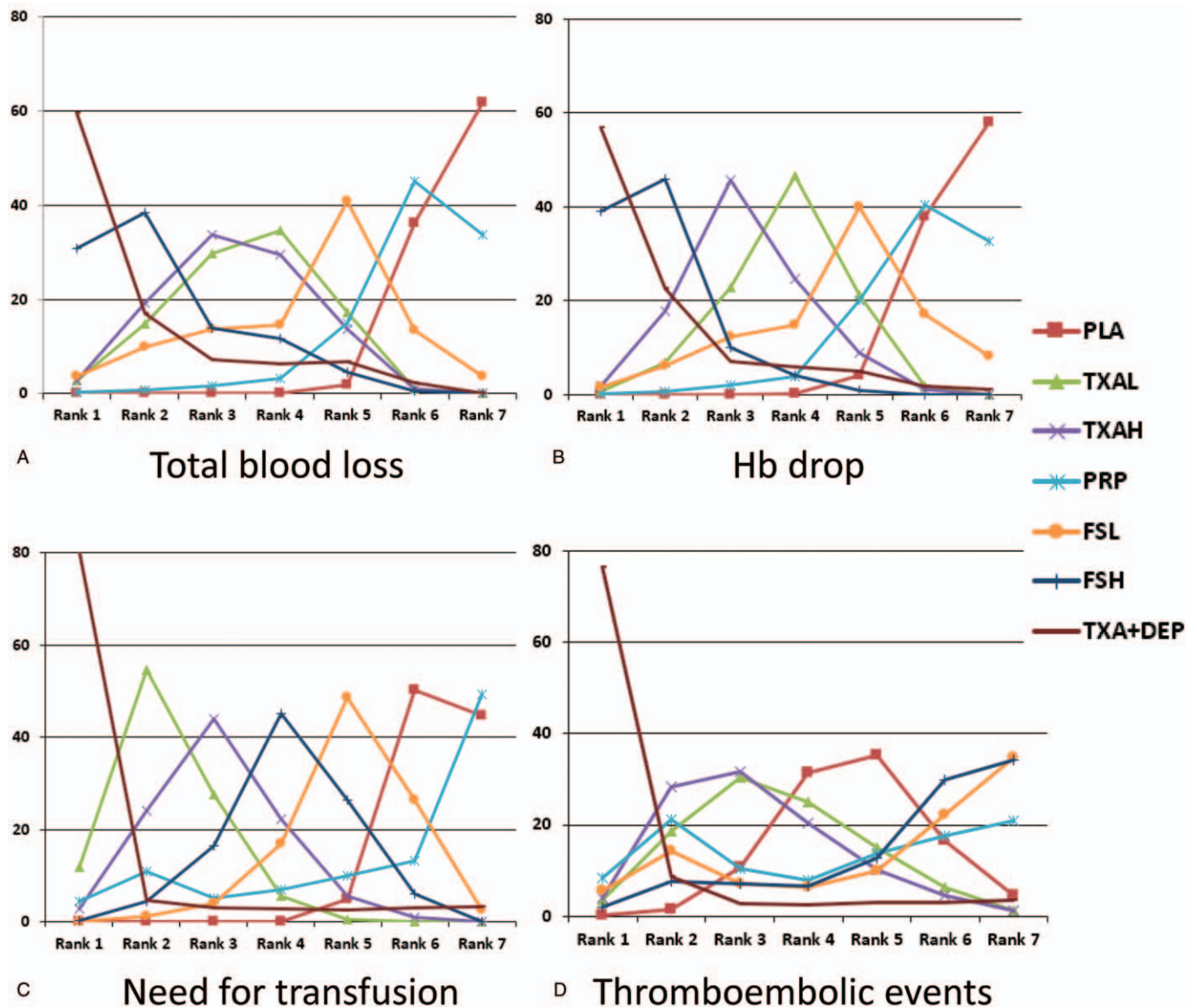
Figure 5. Rankograms to show the ranking probabilities of treatments on the outcomes of (A) Total blood loss; (B) Hb drop; (C) Need for transfusion and (D) Thromboembolic events.

Previously, intravenous administration of TXA was firstly admitted as useful therapy for bleeding control in orthopedic surgery and level I evidence studies have been published.[59] In a previous network meta-analysis, Fillingham et al[12] reported that higher doses and multiple doses of TXA are not necessary, and no route was clearly superior among the administrations of TXA. In another previous meta-analysis,[60] no significant difference was found between the comparison of topical fibrin sealant and intravenous administration of TXA in the outcomes of blood loss and prevalence of complications after TKA. In our NMA, we focused on topical administration of hemostatic agent, which was believed to have higher efficacy and safety in blood-sparing properties, and try to identify the optimal topical hemostatic agent for clinical inform.

To the best of our knowledge, this study is the first comprehensive comparison of different kinds of topical hemostatic agents in primary TKA. Within our NMA, high and low dose of TXA or FS both showed significant effect on decreasing total blood loss and Hb drop compared with the placebo, which is consistent with previous researches.[12,53,60] Furthermore, TXAL, TXAH and FSH all had significantly lower risk in transfusion requirement, but none of the included treatments rose risk of postoperative thromboembolic events compared with the placebo. We believed that all the treatments in this NMA are safe for the patients undergoing TKA. The efficacy of PRP for decreasing perioperative blood loss in TKA is still controversial. The study of Mochizuki enrolled over 300 patients and revealed that topical PRP appears to be effective in reducing postoperative bleeding in TKA.[43] Nevertheless, the mixed estimate results of this NMA indicated that topical administration of PRP do not have better effect on blood-sparing properties than the placebo.

Epinephrine, as another widely-used hemostatic agent, could promote platelet aggregation, enhance thrombocytopoiesis and stimulate the activity of several fibrinolysis molecules and
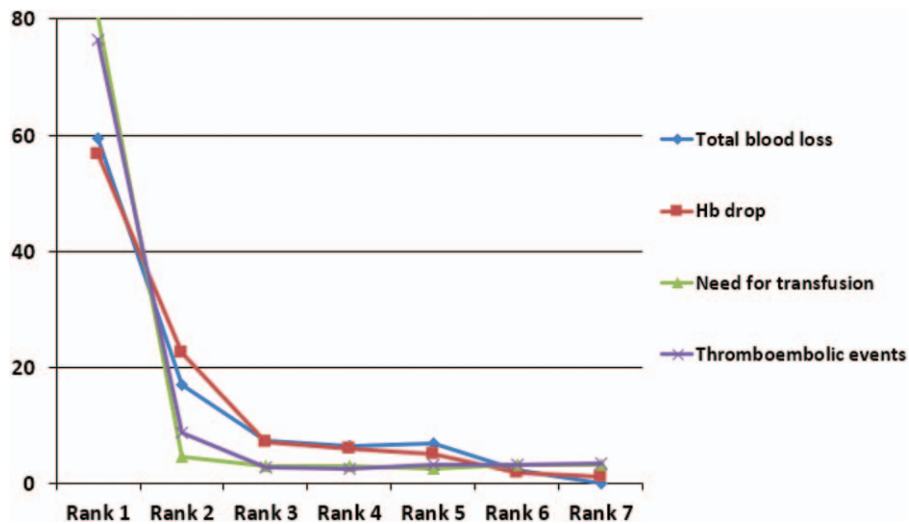
Figure 6. Rankograms of TXA+DEP in the outcomes of total blood loss, Hb drop, need for transfusion and thromboembolic events.

coagulation.[61–63] Several studies have reported the good hemostatic effect of TXA+DEP in decreasing blood loss in TKA.[25,64] The pooled results demonstrated that TXA+DEP has the best efficacy on sparing blood in TKA among all treatments, which is consistent with the previous results of other studies. In the meantime, TXA+DEP do not increase the risk of thromboembolic complications.

Consequently, this NMA suggests that tranexamic acid plus diluted-epinephrine may be the best option for topical hemostatic agent in TKA. Nevertheless, the findings from this NMA must be interpreted with caution, owing to limitations in quality of the evidence. Low quality reporting of study design, variability in outcome measures and small sample sizes should be concerned. High-quality RCTs involving a larger sample size should
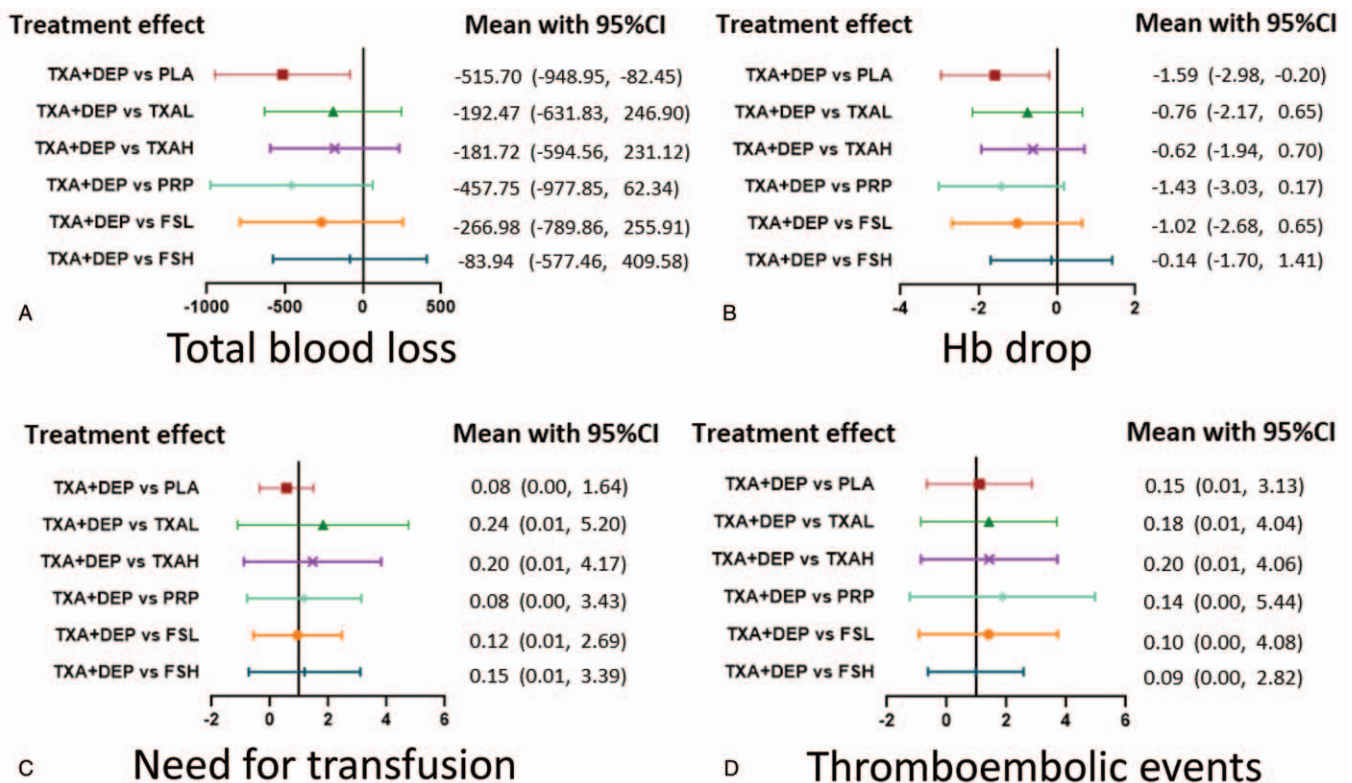

Figure 7. Forest plots for the comparisons between TXA+DEP and other treatments on the outcomes of (A) Total blood loss; (B) Hb drop; (C) Need for transfusion and (D) Thromboembolic events.
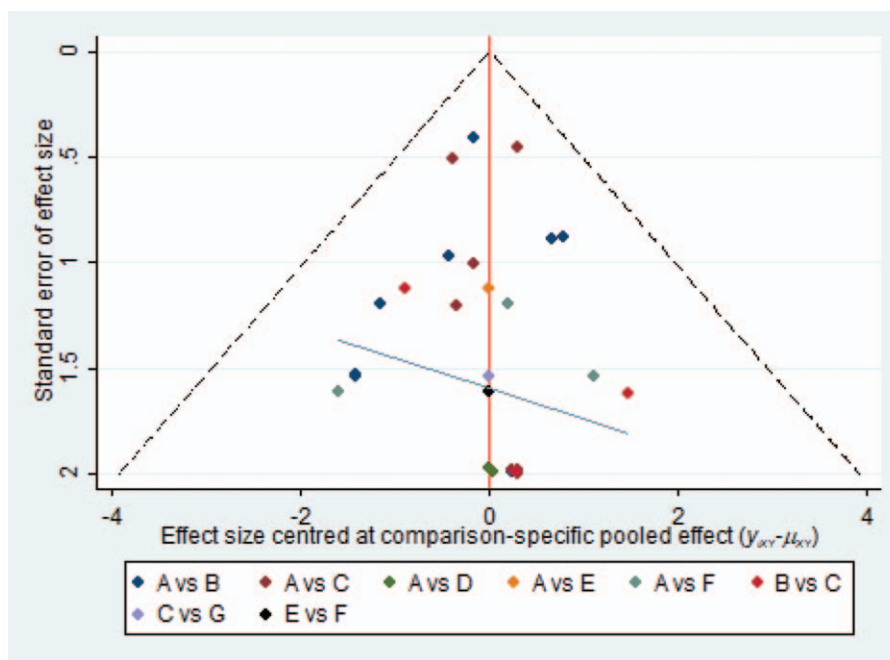
Figure 8. Funnel plot of thromboembolic events.

continue investigating the optimal treatment for reducing perioperative blood loss and adverse events in TKA.

4.3. Strengths and limitations

Within this network meta-analysis, various kinds of topical hemostatic agents were compared by combining direct and indirect evidence, for assessing comparative efficacy and safety in primary TKA. The direct and indirect evidence had reached agreement and achieved consistency for specified treatments. Besides, the large sample size (3928 patients) obtained from 39 RCTs was sufficient for safe conclusions on the research questions to be drawn. Another strong point of this study was that, comprehensive retrieval strategy was applied to reduce the risk of publication bias.

However, certain limitations in our network meta-analysis should be recognized and need to be addressed. First, the enrolled diagnoses, ages, Hb level and transfusion triggers varied from one study to another, which may cause considerable bias to the results. Second, only the most common treatments but not all available treatments were taken into the analysis. Third, although sham treatment was considered in this NMA, it was unable for us to account for the exact placebo effect on the results of this investigation. Fourth, the allocation concealment and details of blind method were not described in some of the included trails, which may limit the robustness of our findings. Fifth, only 1 direct comparison involving TXA+DEP was enrolled in this NMA, which may lead to large uncertainty regarding all estimates.

5. Conclusion

This is the first network meta-analysis to examine the comparative efficacy and safety of commonly used topical hemostatic agents in TKA and bring together available evidence in order to provide evidence-informed clinical decisions of postoperative blood management in TKA. Robust evidence supported that

TXA+DEP may be most likely to be the optimal topical hemostatic agent with higher efficacy and safety when compared with high or low dose TXA, FS and PRP, by significantly reducing total blood loss and Hb drop, decreasing the blood transfusion requirement. The use of common topical hemostatic agents (i.e., TXA+DEP, PRP, high or low dose of FS and TXA) would not add risk for thromboembolic events. Future multicenter and high-quality RCTs with large sample sizes are needed to further evaluate the results.

Author contributions

Conceptualization: Shaoshuo Li, Baixing Chen.
Data curation: Shaoshuo Li, Zhen Hua, Yang Shao.
Formal analysis: Shaoshuo Li, Baixing Chen, Zhen Hua, Yang Shao.
Methodology: Shaoshuo Li, Baixing Chen.
Supervision: Shaoshuo Li, Heng Yin, Jianwei Wang.
Validation: Shaoshuo Li, Baixing Chen, Heng Yin.
Writing – original draft: Shaoshuo Li, Baixing Chen.
Writing – review & editing: Shaoshuo Li, Baixing Chen, Zhen Hua, Yang Shao, Heng Yin, Jianwei Wang.

References

[1] Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010;92:2503–13.

[2] Carling MS, Jeppsson A, Eriksson BI, et al. Transfusions and blood loss in total hip and knee arthroplasty: a prospective observational study. J Orthop Surg Res 2015;10:48.

[3] Prasad N, Padmanabhan V, Mullaji A. Blood loss in total knee arthroplasty: an analysis of risk factors. Int Orthop 2007;31:39–44.

[4] Sehat KR, Evans R, Newman JH. How much blood is really lost in total knee arthroplasty? Correct blood loss management should take hidden loss into account. Knee 2000;7:151–5.

[5] Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet (London, England) 1996;348:1055–60.

[6] Kirksey M, Chiu YL, Ma Y, et al. Trends in in-hospital major morbidity and mortality after total joint arthroplasty: United States 1998-2008. Anesth Analg 2012;115:321–7.

[7] Ponnusamy KE, Kim TJ, Khanuja HS. Perioperative blood transfusions in orthopaedic surgery. J Bone Joint Surg Am 2014;96:1836–44.

[8] Bedard NA, Pugely AJ, Lux NR, et al. Recent trends in blood utilization after primary hip and knee arthroplasty. J Arthroplasty 2017;32:724–7.

[9] Napolitano LM, Cohen MJ, Cotton BA, et al. Tranexamic acid in trauma: how should we use it? J Trauma Acute Care Surg 2013;74:1575–86.

[10] Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet (London, England) 2010;376:23–32.

[11] Dai WL, Zhou AG, Zhang H, et al. Most effective regimen of tranexamic acid for reducing bleeding and transfusions in primary total knee arthroplasty: a meta-analysis of randomized controlled trials. J Knee Surg 2018;31:654–63.

[12] Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The efficacy of tranexamic acid in total knee arthroplasty: a network meta-analysis. J Arthroplasty 2018;33:3090–8.

[13] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

[14] Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA 2015;313:1657–65.

[15] 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.

[16] Dias S, Welton NJ, Caldwell DM, et al. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010;29:932–44.

[17] Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342:d549.

[18] Peters JL, Sutton AJ, Jones DR, et al. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat Med 2007;26:4544–62.

[19] Aguilera X, Martinez-Zapata MJ, Hinarejos P, et al. Topical and intravenous tranexamic acid reduce blood loss compared to routine hemostasis in total knee arthroplasty: a multicenter, randomized, controlled trial. Arch Orthop Trauma Surg 2015;135:1017–25.

[20] Alshryda S, Mason J, Vaghela M, et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial (TRANX-K). J Bone Joint Surg Am 2013;95:1961–8.

[21] Carvalho LHJr, Frois Temponi E, Machado Soares LF, et al. Bleeding reduction after topical application of tranexamic acid together with Betadine solution in total knee arthroplasty. A randomised controlled study. Orthop Traumatol Surg Res 2015;101:83–7.

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

[23] Drosos GI, Ververidis A, Valkanis C, et al. A randomized comparative study of topical versus intravenous tranexamic acid administration in enhanced recovery after surgery (ERAS) total knee replacement. J Orthop 2016;13:127–31.

[24] Morishita M, Ishida K, Matsumoto T, et al. Intraoperative platelet-rich plasma does not improve outcomes of total knee arthroplasty. J Arthroplasty 2014;29:2337–41.

[25] Gao F, Sun W, Guo W, et al. Topical administration of tranexamic acid plus diluted-epinephrine in primary total knee arthroplasty: a randomized double-blinded controlled trial. J Arthroplasty 2015;30:1354–8.

[26] Georgiadis AG, Muh SJ, Silverton CD, et al. A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. J Arthroplasty 2013;28(8 Suppl):78–82.

[27] Guerreiro JP, Danieli MV, Queiroz AO, et al. Platelet-rich plasma (PRP) applied during total knee arthroplasty. Rev Bras Ortop 2015;50:186–94.

[28] Guzel Y, Gurcan OT, Golge UH, et al. Topical tranexamic acid versus autotransfusion after total knee arthroplasty. J Orthop Surg 2016;24:179–82.

[29] Horstmann WG, Slappendel R, van Hellemondt GG, et al. Autologous platelet gel in total knee arthroplasty: a prospective randomized study. Knee Surg Sports Traumatol 2011;19:115–21.

[30] Peerbooms JC, de Wolf GS, Colaris JW, et al. No positive effect of autologous platelet gel after total knee arthroplasty. Acta Orthop 2009;80:557–62.

[31] Keyhani S, Esmailiejah AA, Abbasian MR, et al. Which route of tranexamic acid administration is more effective to reduce blood loss following total knee arthroplasty? Arch Bone Jt Surg 2016;4:65–9.

[32] Levy O, Martinowitz U, Oran A, et al. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. A prospective, randomized, multicenter study. J Bone Joint Surg Am 1999;81:1580–8.

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

[34] Morales Santias M, Mas Martinez J, Sanz-Reig J, et al. Topical tranexamic acid in cemented primary total knee arthroplasty without tourniquet: a prospective randomized study. Eur J Orthop Surg Traumatol 2020;DOI: 10.1007/s00590-020-02656-9.

[35] Molloy DO, Archbold HA, Ogonda L, et al. Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement: a prospective, randomised controlled trial. J Bone Joint Surg Br 2007;89:306–9.

[36] Notarnicola A, Moretti L, Martucci A, et al. Comparative efficacy of different doses of fibrin sealant to reduce bleeding after total knee arthroplasty. Blood Coagul Fibrinolysis 2012;23:278–84.

[37] Oztas S, Ozturk A, Akalin Y, et al. The effect of local and systemic application of tranexamic acid on the amount of blood loss and allogeneic blood transfusion after total knee replacement. Acta Orthop Belg 2015;81:698–707.

[38] Roy SP, Tanki UF, Dutta A, et al. Efficacy of intra-articular tranexamic acid in blood loss reduction following primary unilateral total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2012;20:2494–501.

[39] 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 2011;3:e12.

[40] 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.

[41] Sarzaeem MM, Razi M, Kazemian G, et al. Comparing efficacy of three methods of tranexamic acid administration in reducing hemoglobin drop following total knee arthroplasty. J Arthroplasty 2014;29:1521–4.

[42] Seo JG, Moon YW, Park SH, et al. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2013;21:1869–74.

[43] Mochizuki T, Yano K, Ikari K, et al. Platelet-rich plasma for the reduction of blood loss after total knee arthroplasty: a clinical trial. Eur J Orthop Surg Traumatol 2016;26:901–5.

[44] Tammachote N, Raphiphan R, Kanitnate S, et al. (3 g) topical tranexamic acid has higher potency in reducing blood loss after total knee arthroplasty compared with low dose (500 mg): a double-blind randomized controlled trial. Eur J Orthop Surg Traumatol 2019;29:1729–35.

[45] Tzatzairis TK, Drosos GI, Kotsios SE, et al. Intravenous vs topical tranexamic acid in total knee arthroplasty without tourniquet application: a randomized controlled study. J Arthroplasty 2016;31:2465–70.

[46] Wang CG, Sun ZH, Liu J, et al. Safety and efficacy of intra-articular tranexamic acid injection without drainage on blood loss in total knee arthroplasty: a randomized clinical trial. Int J Surg (London, England) 2015;20:1–7.

[47] Wang GJ, Hungerford DS, Savory CG, et al. Use of fibrin sealant to reduce bloody drainage and hemoglobin loss after total knee arthroplasty: a brief note on a randomized prospective trial. J Bone Joint Surg Am 2001;83:1503–5.

[48] Wang G, Wang D, Wang B, et al. Efficacy and safety evaluation of intra-articular injection of tranexamic acid in total knee arthroplasty operation with temporarily drainage close. Int J Clin Exp Med 2015; 8:14328–34.

[49] Wang J, Wang Q, Zhang X, et al. Intra-articular application is more effective than intravenous application of tranexamic acid in total knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty 2017;32:3385–9.

[50] Yang Y, Lv YM, Ding PJ, et al. The reduction in blood loss with intra-articular injection of tranexamic acid in unilateral total knee arthroplasty without operative drains: a randomized controlled trial. Eur J Orthop Surg Traumatol 2015;25:135–9.

[51] Yen SH, Lin PC, Chen B, et al. Topical tranexamic acid reduces blood loss in minimally invasive total knee arthroplasty receiving rivaroxaban. Biomed Res Int 2017;2017:9105645.

[52] Yuan X, Li B, Wang Q, et al. Comparison of 3 routes of administration of tranexamic acid on primary unilateral total knee arthroplasty: a prospective, randomized, controlled study. J Arthroplasty 2017;32: 2738–43.

[53] Randelli F, D'Anchise R, Ragone V, et al. Is the newest fibrin sealant an effective strategy to reduce blood loss after total knee arthroplasty? A randomized controlled study. J Arthroplasty 2014; 29:1516–20.

[54] Song SJ, Lee HW, Bae DK, et al. Daily blood loss transition after total knee arthroplasty with topical administration of tranexamic acid: paradoxical blood loss after action of tranexamic acid. J Orthop Surg (Hong Kong) 2020;28:2309499019895816.

[55] Okamoto S, Sato S, Takada Y, et al. AN active stereo-isomer (trans-form) of amcha and its antifibrinolytic (antiplasminic) action in vitro and in vivo. Keio J Med 1964;13:177–85.

[56] Jackson MR, MacPhee MJ, Drohan WN, et al. Fibrin sealant: current and potential clinical applications. Blood Coagul Fibrinolysis 1996;7:737–46.

[57] Gardner MJ, Demetrakopoulos D, Klepchick PR, et al. The efficacy of autologous platelet gel in pain control and blood loss in total knee arthroplasty. An analysis of the haemoglobin, narcotic requirement and range of motion. Int Orthop 2007;31:309–13.

[58] Everts PA, Devilee RJ, Brown Mahoney C, et al. Platelet gel and fibrin sealant reduce allogeneic blood transfusions in total knee arthroplasty. Acta Anaesthesiol Scand 2006;50:593–9.

[59] Gao F, Ma J, Sun W, et al. Topical fibrin sealant versus intravenous tranexamic acid for reducing blood loss following total knee arthroplasty: a systematic review and meta-analysis. Int J Surg (London, England) 2016;32:31–7.

[60] Zhang H, Chen J, Chen F, et al. The effect of tranexamic acid on blood loss and use of blood products in total knee arthroplasty: a meta-analysis. Knee Surg Sports Traumatol Arthrosc 2012;20:1742–52.

[61] Jans O, Grevstad U, Mandoe H, et al. A randomized trial of the effect of low dose epinephrine infusion in addition to tranexamic acid on blood loss during total hip arthroplasty. Br J Anaesth 2016;116:357–62.

[62] Yun-Choi HS, Park KM, Pyo MK. Epinephrine induced platelet aggregation in rat platelet-rich plasma. Thromb Res 2000;100:511–8.

[63] Bakovic D, Pivac N, Eterovic D, et al. The effects of low-dose epinephrine infusion on spleen size, central and hepatic circulation and circulating platelets. Clin Physiol Funct Imaging 2013;33:30–7.

[64] Sasanuma H, Sekiya H, Takatoku K, et al. Efficient strategy for controlling postoperative hemorrhage in total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2011;19:921–5.