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Full Length Article

The safest and most efficacious route of tranexamic acid administration in total joint arthroplasty: A systematic review and network meta-analysis

Sheng Xu[a,*], Jerry Yongqiang Chen[a], Qishi Zheng[b], Ngai Nung Lo[a], Shi-Lu Chia[a], Keng Jin Darren Tay[a], Hee Nee Pang[a], Luming Shi[b], Edwin Shih Yen Chan[b], Seng Jin Yeo[a]

[a] Department of Orthopaedic Surgery, Singapore General Hospital, Singapore
[b] Cochrane Singapore, Singapore Clinical Research Institute, Singapore

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ABSTRACT

Introduction: Blood loss in Total Joint Arthroplasty can be significant and often under-estimated. This study aims to investigate the safety and efficacy of different routes of tranexamic acid (TXA) administration in reducing blood transfusion after Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA). The secondary aim is to find the safest and most efficacious route and dose of TXA.

Material and methods: PubMed, Embase, Cochrane library, China National Knowledge Infrastructure, and OpenGrey were systemically searched for randomised controlled trials investigating the efficacy and/or safety of TXA for THA and/or TKA. Network meta-analysis, comparing the number of transfusion and deep vein thrombosis (DVT) among different interventions, was performed using a multivariate meta-regression model with random-effects, adopting a frequentist approach.

Results: 211 publications (20,639 individuals) were included. For outcome of transfusion, all interventions showed significantly lower transfusion rates compared to placebo. When compared to placebo, TXA via intra-venous and topical showed statistically significant lowest risk ratio (RR = 0.11, 95CI: 0.03, 0.41). For safety, TXA via topical showed relatively lowest risk ratio (RR = 0.75, 95CI 0.44, 1.30). TXA via topical and intra-articular had the highest but statistically insignificant RR (RR = 1.10, 95%CI: 0.51, 2.38). Therefore, current studies did not reveal any significant safety issue in using TXA.

Conclusion: All forms of TXA administration showed significantly lower transfusion rate compared to control. There is a trend towards better efficacy with intra-venous and topical. In patients with higher risk of thrombosis, physicians may consider topical alone for its best safety profile.

1. Introduction

Blood loss in primary total joint arthroplasty (TJA), especially total hip arthroplasty, can be significant and are often under-estimated due to hidden blood loss. Post-operative blood transfusion rate due to blood loss is estimated to be about 11% for Total Knee Arthroplasty (TKA) and 18% for Total Hip Arthroplasty (THA) [1]. Intra-operative blood loss from TKA can range from 700 to 800 ml [1,2] while that of THA can range from 700 to 900 ml [3]. This is further compounded by hidden blood loss due to extravasation into the tissues, residual blood in the joint and loss due to hemolysis which can account for up to 50% of total blood loss [2].

Tranexamic acid (TXA), an indirect fibrinolytic inhibitor, was deemed by many as the holy grail of post-operative blood conservation. The antifibrinolytic properties of TXA were first discovered by a Japanese husband and wife team, Shosuke and Utako Okamoto, in 1960s. Initially studied for its antifibrinolytic property to combat maternal death due to postpartum haemorrhage, TXA has since been widely studied and utilised in a wide range of clinical situations to diminish bleeding in different settings [4–7]. TXA exerts its anti-fibrinolytic effect in an indirect way by reversible and competitive binding and thereby blocking the lysine-binding sites on plasminogen

Abbreviations: CI, confidence interval; CNKI, China National Knowledge Infrastructure; DVT, deep vein thrombosis; IA, intra-articular; IV, intra-venous; MeSH, Medical Subject Headings; PE, pulmonary embolism; PRIMSA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomised control trial; RR, risk ratio; SC, standard of care; SUCRA, surface under the cumulative ranking; THA, Total Hip Arthroplasty; TJA, Total Joint Arthroplasty; TKA, Total Knee Arthroplasty; TXA, tranexamic acid

* Corresponding author at: Singapore General Hospital, Department of Orthopaedic Surgery, 20 College Road, Academia, Level 4, Singapore 169865, Singapore.
E-mail address: sheng.xu@mohh.com.sg (S. Xu).

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molecules, therefore inhibiting the activation of plasminogen to plasmin, the enzyme responsible for degradation of fibrin clots [8]. However, it is also due to this antifibrinolytic and clot stabilising effect of TXA that concerns have risen regarding possible prothrombotic adverse events such as deep vein thrombosis (DVT) and pulmonary embolism (PE).

In the field of orthopaedic surgery, TXA has been widely utilised in TKA and THA to minimise the risk of bleeding and need for post-operative blood transfusion. A growing body of literature has been published on the efficacy and safety of intravenous (IV), intra-articular (IA), topical and oral TXA in TKA and THA. To date, there is a lack of clinical trials with sufficient population size to not only proof its efficacy, but also support its safety in incidence of thromboembolism. While meta-analysis in recent literature were able to prove efficacy of TXA, none were able to draw meaningful conclusion on the most efficacious and safest mode and dose of TXA to prevent post-operative transfusion in total joint arthroplasty.

The aim of this systematic review and network meta-analysis was to investigate the safety and efficacy of the different route of TXA administration in reducing blood transfusion after TKA and THA. The secondary aim is to find the most efficacious and safest mode and dose of TXA administration.

2. Material and methods

The systematic review and network meta-analysis was designed and conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and registered in PROSPERO database (Register ID: CRD42018096891) [9].

2.1. Literature search and eligibility criteria

A comprehensive literature search was performed on electronic databases: PubMed (1946 onwards), Embase (1974 onwards), Cochrane library (1992 onwards), China National Knowledge Infrastructure (CNKI; 1994 onwards) and OpenGrey (2000 onwards) until 31 March 2018. The searching strategy was developed to combine the concepts of "total hip arthroplasty (THA)", "total knee arthroplasty (TKA)" and "tranexamic acid (TXA)". We conducted literature search using Medical Subject Headings (MeSH) or Emtree, and free text terms. There were no restrictions on language. All the bibliography listed in review papers and included publications were also checked.

Two investigators (XS and QZ) independently screened for eligible studies based on pre-defined eligibility criteria. Only randomised controlled trials that examined the efficacy and/or safety of TXA for THA and/or TKA were included. Non-randomised or observational studies, case reports, commentaries and letters-to-editors were excluded.

2.2. Data extraction and quality assessment

The following data were extracted from the included studies: (1) study characteristics (publication year and patient population); (2) baseline characteristics (mean age, number of males, follow-up time, patient type and route of TXA administration); and (3) outcome events (number of transfusion as measured by proportion of patients who received blood transfusion, and number of deep vein thrombosis [DVT]).

The quality of each study was evaluated, using the Cochrane Collaboration Risk of Bias tool, by two independent investigators (QZ and LS). Six domains were assessed for each RCT, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Each domain would be assigned a judgement of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias. Any disagreement in quality assessment was resolved by discussion and consensus.

2.3. Statistical analysis

A network geometry was constructed based on the included studies for each intervention. TXA administration was further classified by the route, e.g. intravenous (IV), intra-articular (IA), topical, oral and their combinations. IV refers to intravenous injection TXA, and can be performed either before the start of operation, during operation, or post-operatively. IA refers to TXA that was injected via a hypothermic needle either through the joint capsule after closure or retro-grade through surgical drains that were inserted during the operation. Topical refers to TXA that was applied topically to the exposed joint surface before closure of joint capsule. Oral refers to TXA that was taken as a tablet either before the operation or post-operatively. Each node represented an intervention and its size was weighted by the number of subjects of each intervention. The connecting line between two nodes meant direct comparison was existed and its thickness was determined by the number of studies included.

Network meta-analysis, comparing the number of transfusion and number of DVT among different interventions, was performed using a multivariate meta-regression model with random-effects, adopting a frequentist approach [10,11]. This allows for estimation of the effect size (i.e. proportion of blood transfusion and incidence of deep vein thrombosis) of each comparison group (e.g. IV vs Placebo, IA vs Placebo etc.). In the analysis, "Placebo" was used as the reference group, hence, 10 comparison group were formed based on the available interventions. In this model, the effect size of each comparison group formed a matrix of the outcome, i.e. the outcome "proportion of blood transfusion" and "incidence of deep vein thrombosis" were modelled across 10 comparison groups at the same time. Within each sub-model, variables capturing the observed comparison group-based effect sizes from all the studies, heterogeneity, and error term were included. This model allows for the inclusion of potential covariates, and accounts for the correlations from multi-arm trials, and risk ratio (RR) for both outcomes were estimated [12].

To rank the prognosis for all the groups, we used surface under the cumulative ranking (SUCRA) values [13]. Rank probabilities of all the groups were first estimated under a Bayesian framework. A step function was then applied to summarize the cumulative ranking for estimating the SUCRA values of each group, ranging from 0 to 1. Thus, large SUCRA values indicated a better prognosis. An efficacy-safety plot based on SUCRA results was constructed to evaluate the rank of interventions by both aspects.

The node-splitting approach and inconsistency model were used to test the consistency assumption [14]. The former method involved fitting a series of node-splitting models, with one model for each subgroup pairing for which there was direct and indirect evidence [15]. The latter method first fits an inconsistency model and then conducts a Wald test to check whether there is significant inconsistency among the included studies [16].

The network meta-analyses were implemented by Stata/MP 15 with network and network graphs package [16–18].

3. Results

3.1. Study characteristic and network geometry

From 1534 potential studies identified from the initial search, 211 randomised controlled trials (n = 20,639 individuals) satisfied inclusion/exclusion criteria and were included in this meta-analysis (Fig. 1; Sup Table 1). The mean age was 66.0 years old and 31.1% (n = 6426) were males.

There were 141 studies that reported the efficacy and/or safety of TXA via IV, 68 via IA, 19 via Topical, 14 via IV and IA, 6 via Topical and IA, 5 via Oral, 4 via Oral and IV and 3 via Topical and IV. Most of the studies (n = 151) used placebo as parallel comparison, while 67 used route homeostasis (standard of care, SC). Comparisons, including knee

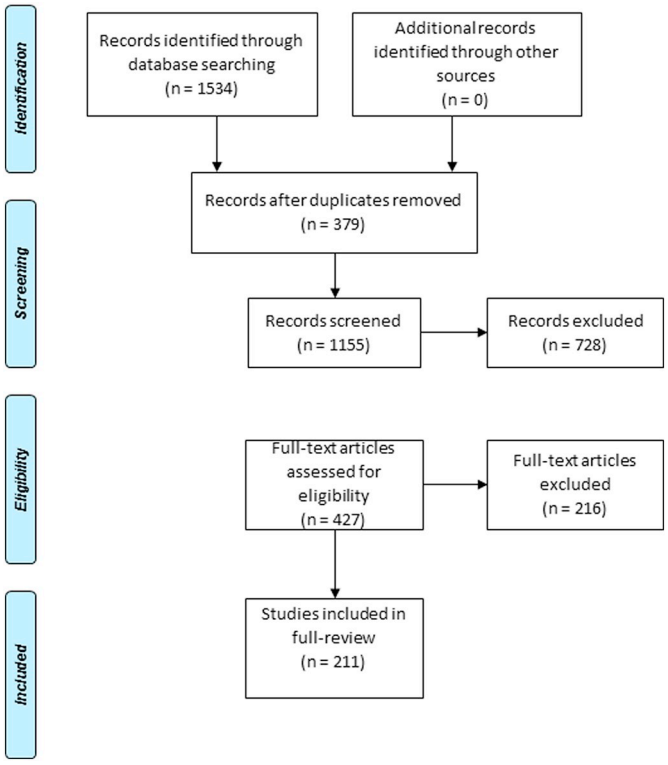

Fig. 1. PRISMA flowchart of study selection.

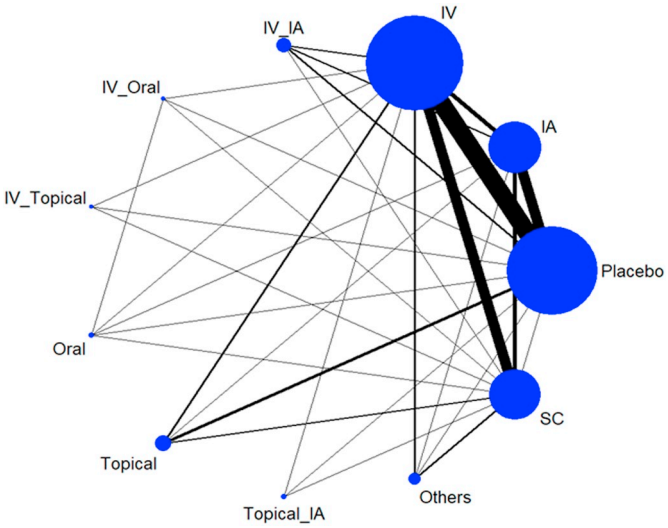

Fig. 2. Network geometry of included studies.

flexion, fibrin, anticoagulant, bipolar sealer system, aminocaproic acid, desmopressin and autotransfusion, were classified as "Others" and were reported in 11 studies. The network geometry was constructed based on the above information (Fig. 2).

Most of the studies demonstrated low risk of bias in the six domains assessed. However, due to open-label fashion and other break of blinding in the study design, around 25% of the included studies were ranked as "Unclear" or "High risk" in Both "blinding of participants and personnel" and "blinding of outcome assessment" (Sup Fig. 1).

3.2. Efficacy on number of transfusion compared to placebo

For outcome of number of transfusion, of which 164 studies (7674 transfusions) included for the analysis, all interventions, except "Others", showed significant lower number of transfusion comparing to "Placebo". All interventions, except "Others", also showed significant lower transfusion rate compared to routine hemostasis ("SC").

3.3. Most efficacious mode of administration

When compared to "Placebo", TXA administration via IV and Topical showed the lowest relative risk ratio for transfusion (RR = 0.11, 95%CI: 0.03, 0.41), followed by TXA via Topical and IA (RR = 0.35, 95%CI: 0.20, 0.60) and TXA via IA alone (RR = 0.36, 95%CI: 0.31, 0.43) (Table 1). When compared to routine hemostasis ("SC"), TXA via IV and Topical again showed the lowest relative risk ratio for transfusion (RR = 0.09, 95%CI: 0.02, 0.34). When TXA via IV and Topical were compared to other mode of administration, IV and Topical showed significant lower number of transfusion compared to TXA via IV alone (RR = 3.98, 95%CI: 1.02, 15.5), IV and Oral (RR = 5.16, 95%CI 1.27, 21.0), and Topical alone (RR = 0.24, 95%CI: 0.06, 0.98). All other forms of TXA showed no significant difference in terms of transfusion rate compared to each other.

When comparing effectiveness on varying dose of TXA within the same mode of administration, although TXA via IV and Topical showed the best efficacy, there appears to be no additional benefit with increasing dose (Fig. 4). There was a total of 3 studies investigating the effectiveness of TXA via IV and Topical, 2 of the studies used 15 mg/kg of IV TXA prior to skin incision together with 1 g of TXA mixed with normal saline that is applied before wound closure while the other study used a multiple IV TXA dosing regimen together with topical TXA. As the dose response graph shows no significant additional benefit with increasing dose when TXA is administered via IV and Topical, the 15 mg/kg IV together with 1 g topical dose is sufficient to bring about significant reduction in transfusion. On the other hand, TXA with Topical and IA and TXA with Oral alone showed the most significant dose dependent relationship with a higher dose giving rise to a lower risk ratio.

Results from both node-splitting method and inconsistency model showed no evidence on the violation of consistency assumption between direct and indirect comparisons. To estimate the rank of efficacy on number of transfusion, SUCRA values were calculated (Table 2).

3.4. Safety on number of DVT compared to placebo

To assess the safety of interventions, of which 191 studies (379 cases) included for the analysis, we estimated the pooled RR for all interventions comparing to placebo. All pooled RR had wide 95% CI, due to the relatively low frequency of DVT complications in each of the included study. No intervention showed significant increased number of DVT compared to "Placebo" or routine hemostasis ("SC").

3.5. Safest mode of administration

When compared to "Placebo", TXA via Topical showed the lowest risk ratio (RR = 0.75, 95%CI: 0.44, 1.30). TXA via Topical again showed the lowest risk ratio when compared to routine hemostasis ("SC") (RR = 0.90, 95%CI: 0.46, 1.77). However, both of these were statistically insignificant. When TXA via Topical is compared to all other mode of administration, TXA via Topical showed the lowest relative risk for DVT, albeit statistically insignificant. There was a total of 19 studies investigating the safety of TXA via Topical application, 6 using 1 g mixed with normal saline, 3 using 1.5 g, 3 using 2 g, 4 using 3 g, and 3 others using < 500 mg. Therefore, up to 3 g of TXA applied topically can be considered safe and since the dose response graph (Fig. 4) showed no significant additional benefit with increasing dose when TXA is administered via Topical alone, the most commonly used dosage, 1 g, can be chosen for its safety and efficacy profile. TXA via Topical and IA had the highest but statistically insignificant risk ratio (RR = 1.10, 95%CI: 0.51, 2.38). All other forms of TXA showed no

Table 1
Summary of results on number of transfusion and DVT.

IA	0.98 (0.66,1.45)	0.92 (0.41,2.05)	0.93 (0.14,6.07)	0.94 (0.11,8.20)	1.08 (0.30,3.90)	1.17 (0.61,2.24)	0.80 (0.35,1.83)	0.99 (0.41,2.40)	1.06 (0.64,1.75)	0.88 (0.61,1.27)
0.87 (0.72,1.05)	IV	0.94 (0.43,2.04)	0.95 (0.15,6.05)	0.96 (0.11,8.19)	1.11 (0.32,3.84)	1.20 (0.67,2.13)	0.82 (0.38,1.76)	1.01 (0.45,2.29)	1.08 (0.72,1.62)	0.90 (0.72,1.13)
1.01 (0.64,1.60)	1.16 (0.75,1.81)	IV_IA	1.01 (0.14,7.41)	1.02 (0.11,9.85)	1.18 (0.28,5.00)	1.27 (0.50,3.23)	0.87 (0.30,2.49)	1.08 (0.36,3.26)	1.15 (0.51,2.60)	0.96 (0.45,2.06)
0.67 (0.45,1.00)	0.77 (0.53,1.12)	0.66 (0.38,1.16)	IV_Oral	1.01 (0.06,16.9)	1.16 (0.14,9.87)	1.25 (0.18,8.55)	0.86 (0.12,6.25)	1.06 (0.14,7.97)	1.13 (0.17,7.39)	0.95 (0.15,5.97)
3.46 (0.88,13.6)	3.98* (1.02,15.5)	3.41 (0.82,14.2)	5.16* (1.27,21.0)	IV_Topical	1.15 (0.10,13.6)	1.24 (0.14,11.3)	0.85 (0.09,8.13)	1.05 (0.11,10.4)	1.12 (0.13,9.69)	0.94 (0.11,7.98)
0.87 (0.49,1.55)	1.00 (0.57,1.77)	0.86 (0.43,1.75)	1.30 (0.67,2.53)	0.25 (0.06,1.10)	Oral	1.08 (0.28,4.18)	0.74 (0.18,3.09)	0.91 (0.21,3.99)	0.97 (0.28,3.45)	0.81 (0.23,2.83)
0.84 (0.59,1.20)	0.97 (0.70,1.35)	0.83 (0.49,1.41)	1.26 (0.77,2.04)	0.24* (0.06,0.98)	0.96 (0.51,1.83)	Topical	0.68 (0.27,1.74)	0.85 (0.32,2.28)	0.90 (0.46,1.77)	0.75 (0.44,1.30)
1.04 (0.59,1.82)	1.19 (0.69,2.06)	1.02 (0.51,2.03)	1.55 (0.81,2.96)	0.30 (0.07,1.29)	1.19 (0.55,2.58)	1.23 (0.66,2.29)	Topical_IA	1.24 (0.42,3.69)	1.32 (0.63,2.78)	1.10 (0.51,2.38)
0.33* (0.23,0.49)	0.38* (0.27,0.55)	0.33* (0.19,0.57)	0.50* (0.30,0.83)	0.10* (0.02,0.39)	0.38* (0.20,0.73)	0.39* (0.25,0.63)	0.32* (0.17,0.61)	Others	1.07 (0.46,2.49)	0.89 (0.39,2.06)
0.30* (0.24,0.37)	0.34* (0.28,0.41)	0.29* (0.19,0.46)	0.44* (0.29,0.67)	0.09* (0.02,0.34)	0.34* (0.19,0.60)	0.35* (0.25,0.49)	0.29* (0.17,0.50)	0.89 (0.64,1.26)	SC	0.84 (0.54,1.29)
0.36* (0.31,0.43)	0.42* (0.37,0.47)	0.36* (0.23,0.56)	0.54* (0.38,0.78)	0.11* (0.03,0.41)	0.42* (0.24,0.73)	0.43* (0.31,0.60)	0.35* (0.20,0.60)	1.09 (0.76,1.58)	1.22* (1.01,1.49)	Placebo

Top right panel reported the pooled risk ratio (RR) of number of DVT from network meta-analysis, and the name below each RR was the reference group.
Bottom left panel reported the pooled risk ratio (RR) of number of transfusion from network meta-analysis, and the name to the right of each RR was the reference group.
*Statistical significant with P value < 0.05.

Table 2
Summary of results from SUCRA.

Mode of TXA	Number of transfusion		Number of DVT	
	SUCRA	Rank	SUCRA	Rank
IA	73.8	2	53.2	4
IV	56.1	6	51.1	6
IV_IA	71.5	4	45.5	9
IV_Oral	36.6	8	47.6	8
IV_Topical	97.8	1	48.9	7
Oral	58.7	5	55.8	3
Topical	53.7	7	67.3	1
Topical_IA	71.6	3	34	11
Others	10.7	10	51.4	5
SC	2.8	11	59.5	2
Placebo	16.6	9	35.8	10

significant difference in terms of DVT rate compared to each other. Therefore, current studies did not reveal any evidence of significant safety issue by using the TXA.

A two-dimensional graph of efficacy and safety based on RR and 95%CI was plotted (Fig. 3). As indicated in Fig. 3, the x axis represented the RR from worse (left, > 1.00), indifference (1.00) to better (right, < 1.00) and y axis represented the RR from worse (lower, > 1.00), indifference (1.00) to better (upper, < 1.00). Consistent to Table 1 on safety outcome, all but TXA via Topical and IA had a point estimate (red hexagram) lower than the horizontal indifference line. For efficacy outcome, TXA via IV and Topical (pink diamond) showed an excellent efficacy but similar safety among all interventions, and TXA via Topical (grey diamond) alone showed the best safety result but moderate efficacy.

4. Discussion

Total joint replacement is one of the most common elective surgical procedure performed worldwide and an estimate of 2%, or 7 million individuals in the United States are living with a total hip or total knee arthroplasty [19], with over 1 million replacement procedures performed each year [20]. However, one of the key concerns regarding TJA is the intra- and post-operative blood lose as well as cost and complications associated with blood transfusions. Since the first pilot study by Benoni et al. [21] in 1995 on the effect of TXA on TKA, a growing body of literature has attempted to investigate the safety and efficacy of TXA in total knee and total hip arthroplasty.

According to the Centre of Evidence Based Medicine (CEBM), “one of the fundamental skills required for practising EBM is the asking of well-built clinical questions. To benefit patients and clinicians, such questions need to be both directly relevant to patients' problems and phrased in ways that direct your research to relevant and precise answer.” This systematic review and network meta-analysis aims to specifically investigate the role of TXA in TJA to allow a better understanding of not only the safety and efficacy of TXA in TJA, but also the safest and most efficacious mode of administration.

The efficacy of TXA on TJA has been well investigated in the literature, with numerous randomised controlled trials and meta-analysis concluding that IV, topical, oral, and any combination of these are efficacious in reducing post-operative blood transfusion. Similarly, the results of our study showed that any mode of administration of TXA is more efficacious in reducing post-operative transfusion when compared with placebo or routine hemostasis. However, to the understanding of the authors, there is currently no literature that concludes which mode of administration is the most efficacious. In the most recent and largest meta-analysis published to date by Fillingham et al. [6] in 2018 with 67 randomised controlled trials investigating the efficacy of TXA in TKA, their results demonstrated a treatment effect significantly favouring all available forms of TXA compared to placebo. However, they were unable to draw conclusion regarding a clearly superior route of TXA administration. One of the key limitations of meta-analysis is that often insufficient data is available to perform subgroup analysis, especially if one of the subgroups is infrequently reported in the literature. In this meta-analysis, the authors attempted to overcome this by performing the largest volume of meta-analysis to date. This was made possible by the inclusion of Chinese literature from the China National Knowledge Infrastructure which formed a substantial proportion of the randomised controlled trials available. This resulted in the inclusion of 211 publications that reported the influence of TXA on post-operative blood transfusion and/or DVT prevalence, allowing further subgroup analysis

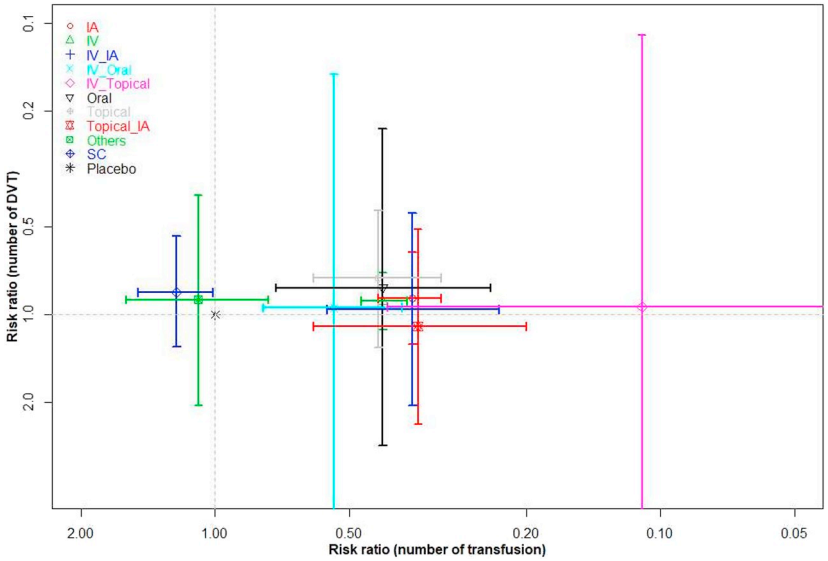

Fig. 3. Two-dimensional graph of efficacy and safety.

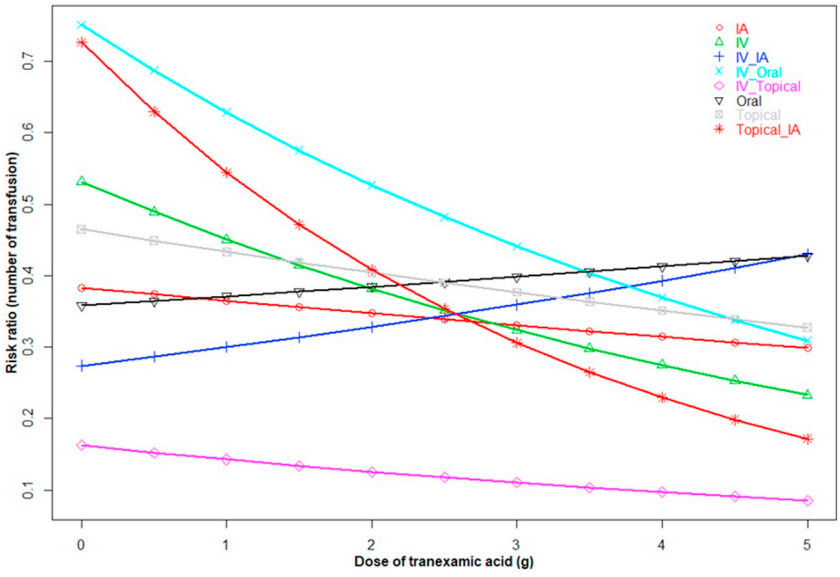

Fig. 4. Dose response plot.

on the different mode of administration. This study demonstrated that TXA administration via IV with topical not only have the lowest risk ratio for transfusion when compared with placebo and routine hemostasis, it also resulted in significantly lower transfusion compared to IV alone, IV with Oral, or Topical alone.

On safety of TXA in TJA, another recent meta-analysis published by Fillingham et al. [7] in 2018 with the largest included randomised controlled trials of 79 publications with 7164 patients, they concluded that in patients undergoing a hip or knee arthroplasty, IV, topical, and oral TXA lack any observed influence on the risk of venous thromboembolism. Similarly, in this study, no intervention showed significant increased number of DVT compared to placebo or routine hemostasis. In this study, attempts were made to compare the different mode of TXA administration to investigate the safest mode possible. However, even with such a large cohort of publications and patients, the authors were unable to detect significant difference between the different modes of administration. What could be inferred from this study is that topical administration had the lowest risk ratio for DVT when compared to placebo and routine hemostasis and when topical administration was compared with all other mode of administration, it had the lowest relative risk for DVT, albeit statistically insignificant.

One of the main strength of this study is that, to the knowledge of the authors, this is the largest network meta-analysis available to date investigating the safety and efficacy of TXA on TJA. With a total of 20,639 patients from 211 randomised controlled trials, the authors were able to perform subgroup analysis with significant statistical power to analyse the influence of different mode of TXA administration on efficacy of reducing post-operative blood transfusion. However, in an attempt to provide a larger patient population, hip and knee arthroplasty populations were combined in our study and this may introduce heterogeneity in the results. A similar method of combining total hip and knee arthroplasty studies were used by Fillingham et al. [7] in the study of safety of TXA in TJA to give a higher statistical power and they found no observed heterogeneity in their results as all individual and combined analyses have no statistical evidence of heterogeneity on I-squared testing.

5. Conclusion

To the knowledge of the authors, this was the largest systematic review and meta-analysis performed on safety and efficacy of TXA in total joint arthroplasty. This was made possible by the inclusion of Chinese literatures which formed a substantial proportion of the randomised controlled trials available. All forms of TXA administration showed significant lower transfusion rate compared to routine hemostasis and placebo. There is a trend towards better efficacy in reducing post-operative blood transfusion using IV with Topical application. In patients with higher risk of thrombosis, physicians may consider Topical alone for its best safety profile.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.02.006.

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A

Search strategies:
MEDLINE/PubMed

#1 Arthroplasty, Replacement, Knee [Mesh]
#2 Total Knee Arthroplasty
#3 Total Knee Replacement
#4 TKA
#5 TKR
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 Tranexamic Acid [Mesh]
#8 Tranexamic Acid
#9 “cyklokapron”[Title/Abstract]) OR “transamin”[Title/Abstract]) OR “cyclo f”[Title/Abstract]) OR “exacyl”[Title/Abstract]
#10 #7 OR #8 OR #9
#11 #6 AND #10

References

[1] M.S. Carling, A. Jeppsson, B.I. Eriksson, H. Brisby, Transfusions and blood loss in total hip and knee arthroplasty: a prospective observational study, J. Orthop. Surg. Res. 10 (1) (2015) 48.
[2] K.R. Sehat, R. Evans, J.H. Newman, How much blood is really lost in total knee arthroplasty?: correct blood loss management should take hidden loss into account, Knee 7 (3) (2000) 151–155.
[3] X. Liu, X. Zhang, Y. Chen, Q. Wang, Y. Jiang, B. Zeng, Hidden blood loss after total hip arthroplasty, J. Arthroplast. 26 (7) (2011) 1100–1105.
[4] C.J. Dunn, K.L. Goa, Tranexamic acid, Drugs 57 (6) (1999) 1005–1032.
[5] I. Roberts, Tranexamic acid in trauma: how should we use it? J. Thromb. Haemost. 13 (2015) S195–S199.
[6] Y.A. Fillingham, D.B. Ramkumar, D.S. Jevsevar, A.J. Yates, P. Shores, K. Mullen, S.A. Bini, H.D. Clarke, E. Schemitsch, R.L. Johnson, S.G. Memtsoudis, The efficacy of tranexamic acid in total knee arthroplasty: a network meta-analysis, J. Arthroplast. 33 (10) (2018) 3090–3098.
[7] Y.A. Fillingham, D.B. Ramkumar, D.S. Jevsevar, A.J. Yates, P. Shores, K. Mullen, S.A. Bini, H.D. Clarke, E. Schemitsch, R.L. Johnson, S.G. Memtsoudis, The safety of tranexamic acid in total joint arthroplasty: a direct meta-analysis, J. Arthroplast. 33 (10) (2018) 3070–3082.
[8] L. Tengborn, M. Blombäck, E. Berntorp, Tranexamic acid–an old drug still going strong and making a revival, Thromb. Res. 135 (2) (2015) 231–242.
[9] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (4) (2009) 264–269.
[10] J.P. Higgins, D. Jackson, J.K. Barrett, G. Lu, A.E. Ades, I.R. White, Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies, Res. Synth. Methods 3 (2) (2012) 98–110.
[11] I.R. White, J.K. Barrett, D. Jackson, J.P. Higgins, Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression, Res. Synth. Methods 3 (2) (2012) 111–125.
[12] I.R. White, Multivariate random-effects meta-regression: updates to mvmeta, Stata J. 11 (2) (2011) 255.
[13] G. Salanti, A.E. Ades, J.P. Ioannidis, Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial, J. Clin. Epidemiol. 64 (2) (2011) 163–171.
[14] S. Dias, N.J. Welton, D.M. Caldwell, A.E. Ades, Checking consistency in mixed treatment comparison meta-analysis, Stat. Med. 29 (7–8) (2010) 932–944.
[15] S. Donegan, P. Williamson, U. D'Alessandro, C. Tudur Smith, Assessing key assumptions of network meta-analysis: a review of methods, Res. Synth. Methods 4 (4) (2013) 291–323.
[16] I.R. White, Network meta-analysis, Stata J. 15 (4) (2015) 951–985.
[17] A. Chaimani, J.P. Higgins, D. Mavridis, P. Spyridonos, G. Salanti, Graphical tools for network meta-analysis in STATA, PLoS One 8 (10) (2013) e76654.
[18] Stata Statistical Software [Computer Program], StataCorp LLC, College Station, TX, 2017.
[19] H.M. Kremers, D.R. Larson, C.S. Crowson, W.K. Kremers, R.E. Washington, C.A. Steiner, W.A. Jiranek, D.J. Berry, Prevalence of total hip and knee replacement in the United States, J. Bone Joint Surg. Am. 97 (17) (2015) 1386.
[20] C. Steiner, R. Andrews, M. Barrett, A. Weiss, HCUP projections: mobility/orthopedic procedures 2003 to 2012, HCUP Projections Report# 2012-03 2012, US Agency for Healthcare Research and Quality, 2012.
[21] G. Benoni, A. Carlsson, C. Petersson, H. Fredin, Does tranexamic acid reduce blood loss in knee arthroplasty? Am. J. Knee Surg. 8 (3) (1995) 88–92.