Original Article

Tranexamic acid in total hip arthroplasty: Mixed treatment comparisons of randomized controlled trials and cohort studies

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ABSTRACT

Background: The present study is a network meta-analysis of various routes of tranexamic acid (TXA) in patients with total hip arthroplasty (THA).

Methods: Randomized controlled trials and cohort studies evaluating TXA in patients with THA were included. Number of patients requiring blood transfusion was the primary outcome.

Results: Pooled estimate for TXA use against placebo for blood transfusion rate was 0.30 [0.23, 0.39] favoring TXA. Maximum reduction in the risk of blood transfusion was observed with topical plus intra-operative intravenous TXA.

Conclusion: Combined topical and intravenous TXA during surgery may perform better than other modes in patients undergoing THA.

1. Introduction

Joint replacements are widely carried with nearly 1 million surgeries in United States alone annually.¹ Due to increase in the life expectancy worldwide, there is an increase in the total number of joint replacements. Total hip arthroplasty (THA) is commonly performed in patients with osteoarthritis hip followed by patients with other conditions such as osteonecrosis of femoral head, rheumatoid arthritis, fracture and dysplasia.² Blood loss during total hip arthroplasty (THA) has been estimated to range between 1000 and 1500 ml³ with blood transfusion rates ranging between 21 and 70%.⁴ Despite being life-saving, blood transfusions are associated with known adverse events that are sometimes life-threatening.⁵

TXA, an anti-fibrinolytic, is widely used in patients undergoing THA, total knee arthroplasty and shoulder arthroplasty.^{6–10} With regard to THA, TXA is used in various doses and routes for managing blood loss. Direct comparison meta-analyses evaluated the various routes of administration of TXA in THA.^{11,12} However, the variations in the routes of administration of TXA in patients undergoing THA are huge that only a network meta-analysis can compare all the possibilities both by direct and indirect comparisons. Hence, we carried out the present network meta-analysis to compare the efficacy and safety of TXA in THA.

2. Methods

2.1. Information sources and search strategy

The protocol for this review was registered with PROSPERO with the registration number CRD42017058116. We did a thorough literature search on Medline (through PubMed), Cochrane CENTRAL, Google Scholar and ClinicalTrials.gov with the search strategy: Tranexamic acid [tiab] AND arthroplasty [tiab] and was completed on 01 March 2017.

2.2. Eligibility criteria

We included either randomized controlled clinical trials (RCTs) or cohort studies comparing different routes of TXA or TXA with placebo. Those studies that included patients with osteoarthritis or osteonecrosis of the hip and had THA were included. Number of patients requiring blood transfusion was considered as the primary outcome. Total blood loss and number of patients developing thrombosis (deep vein thrombosis/pulmonary embolism/myocardial infarction) were the secondary outcomes.

2.3. Study procedure and statistical considerations

Two authors independently performed literature search in the above

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mentioned databases. Disagreement between the authors was resolved through discussion. The present review and network meta-analysis has been reported as per the preferred reporting items for systematic reviews and meta-analysis for network meta-analysis guidelines (PRISMA-NMA).¹³ The risk of bias of the included studies was analyzed using Cochrane risk of bias tool.¹⁴ The Newcastle-Ottawa scale was used to assess the quality of cohort studies.¹⁵ We assessed the publication bias for the comparison of intravenous TXA with placebo and also performed cumulative meta-analysis with the same search strategy and published elsewhere.¹⁶ Random effects model was used and the direct comparisons were performed using Revman 5.3 following heterogeneity assessment using Chi-square and I^2 tests. Odds ratio [95% confidence interval] was the effect estimate for categorical outcomes and weighted mean difference [95% confidence interval] was used for numerical outcomes. NetMetaXL¹⁷ and WinBUGS statistical analysis program version 1.4.3 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK) were used for generating results for the categorical outcomes. We evaluated the sensitivity of the network to individual trials by removing each trial one at a time and investigated the impact on the probability of which intervention was 'best'. We intended to analyze the changes in the primary outcomes with respect to the following variables: cohort studies; bilateral arthroplasty; different thromboprophylaxis; revision surgery; cementless arthroplasty; without tourniquet, transfusion criterion and computer assisted surgeries. The pooled estimates were obtained by means of Markov Chain Monte Carlo simulation method. Inconsistencies between direct and indirect comparisons for the primary outcome were evaluated by plotting the posterior mean deviance of individual data points for consistency and inconsistency model.¹⁷ Inconsistencies for the secondary outcomes were evaluated by statistics wherein a value of < 3 was considered as minimal, 3–6 as modest and > 6 as gross inconsistency.¹⁸ Step plot was used to compare treatment arms and a cumulative rankogram was generated based on the surface under cumulative ranking curve (SUCRA).¹⁹ Under Bayesian approach, SUCRA estimates the probability of a treatment being the best. Generalized pairwise modeling was used though MetaXL for generating the pooled estimates of total blood loss in indirect comparison analyses. Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group approach was used to assess the quality of evidence for key comparisons with the primary outcome.¹⁴

3. Results

3.1. Search results

A total of 383 articles were obtained and we finally included 29 studies in the present review (Fig. 1).^{20–48} The NMA included assessment of the pooled estimates from 2878 participants and the total number of events for the primary outcome were 413. The network diagram is shown in Fig. 2 and the key characteristics of the included studies are mentioned in the Electronic Supplementary Table 1. Of the 29 studies, 25 were RCTs and four were cohort studies. Majority of the randomized controlled trials were observed to carry low risk as observed in the summary of risk of bias (Fig. 3). The scores of all the Cohort studies exceeded six indicative of moderate to good quality studies. Key details of the studies registered in ClinicalTrials.gov are presented in the Electronic Supplementary Table 2.

3.2. Primary outcome

3.2.1. Direct comparisons

Pair-wise direct comparisons with placebo were carried out with the following interventions: Intra-operative and post-operative intravenous TXA, Pre-operative TXA, intravenous bolus dose of TXA either at the time of induction of anesthesia or just before surgery, TXA both in the pre-operative period and during the surgery, topical TXA, TXA in the

Fig. 1. PRISMA study flowchart.

A total of 383 articles were obtained and finally 29 studies were included in the network meta-analysis.

pre-operative and post-operative periods and topical along with intravenous bolus administration of TXA. The pooled estimate of TXA interventions against placebo was 0.30 [0.23, 0.39] favoring the use of TXA. Additionally, topical TXA was compared with intravenous bolus either at the time of induction or just before surgery, two intravenous doses administered intra-operatively, and intravenous bolus dose at the time of induction or just before surgery and, only topical administration. Intravenous TXA both during surgery and post-operatively was also directly compared with pre-operative TXA administration. The

Fig. 2. Network diagram.
The diagram depicts the treatment arms included in this network meta-analysis. There were nine types of interventions of which TXA was administered as a single intravenous bolus at induction or just before surgery in 18 studies, six studies with intra-operative and post-operative administration, seven topical, five topical with intravenous routes intra-operatively and one each evaluated TXA intravenous bolus with continuous infusion intra-operatively, pre-operative and intra-operative administration, pre-operative and two doses intra-operatively. Out of the total 29 studies, 23 studies compared the interventions with placebo.

pooled estimates of these individual comparisons are mentioned in Table 1.

3.2.2. Mixed treatment comparisons

The pooled estimates of the mixed treatment comparisons of the interventions with respect to the blood transfusion rate are depicted in Table 1. Significant reductions in the risk of blood transfusion were observed with topical plus intra-operative intravenous TXA, two doses of intra-operative intravenous TXA, topical TXA, TXA intravenous pre-operatively along with intra-operative intravenous TXA and intravenous TXA intra-operatively and post-operatively in comparison to placebo. Also, the same combination performs better than topical alone, intravenous bolus during surgery, pre-operative intravenous TXA and intra-operative with post-operative intravenous TXA. Assessment of rankogram concluded that the combination of topical with intravenous TXA during surgery had the highest probability of being the ‘best’ in the pool with maximum SUCRA (Fig. 4). No gross inconsistencies were observed between direct, indirect and mixed treatment comparison effect estimates (Fig. 5 and Table 1).

3.2.3. Sensitivity analyses

Both the pooled estimates and rankogram did not differ significantly when each trial was removed one at any time. No significant changes in both the pooled estimates and rankogram were observed when cohort studies were excluded from the overall analysis. Similarly, no significant changes were observed in the pooled estimates with respect to the following variables: bilateral THA; anticoagulants other than low molecular weight heparin; revision and type of prosthesis. None of the included studies reported either on the use of computer assisted surgery or without use of tourniquet and considering the variability of the transfusion criteria observed in the included studies, we did not carry out any sensitivity analysis for these variables.

3.3. Secondary outcomes

Incidence of complications related to thrombosis and total blood loss following the use of TXA in THA was reported in 24 (2482 participants) and 22 (2246 participants) respectively. Forest plot of the pooled estimates of the comparisons with placebo are depicted in Figs. 6 and 7 respectively for the thrombotic complications and blood loss. No significant differences were observed between the interventions in the risk of thrombosis. The combination of topical and intravenous TXA is associated with minimal blood loss.

3.4. Grading the evidence

The quality of evidence for key comparisons in the primary outcome was graded separately for direct estimates and mixed treatment comparison estimates (Table 2). Moderate quality was observed for topical TXA, intravenous bolus either at induction of anesthesia or just before surgery and administration of TXA during both intra-operative and post-operative period in comparison to placebo. Either low or very low quality was observed for other estimates and the reason for downgrading are listed in Table 2.

4. Discussion

We conducted the present NMA to evaluate the blood transfusion rate, total blood loss and thrombotic complications when TXA was administered through different routes and timing for patients undergoing THA. We included 29 studies and from the pooled estimates from mixed treatment comparisons, the combination of topical and intravenous TXA was found to perform better than other modes of TXA administration. No significant differences were observed in the risk of thrombotic complications between the interventions. Quality of evidence for most of the comparisons of primary outcome was either low or very low. This is the first NMA that evaluated the efficacy and safety of TXA in THA. A network meta-analysis offers the advantage of comparing multiple treatments not only directly but also indirectly through a common comparator.⁴⁸ Especially when head-to-head trials are scant,

Fig. 3. Risk of bias of the randomized clinical trials included in this review.
Red circles with minus symbol indicate high risk of bias of the concerned domain; Green circle with plus symbol indicate a low risk of bias and yellow circle with question symbol indicate an unclear risk of bias.

Fig. 4. SUCRA estimates of the interventions evaluated in the present meta-analysis. The combination of topical and intra-operative intravenous TXA has the highest probability of being the best amongst the interventions.

this type of analysis may shed light on the efficacy of interventions if such trials are conducted. By doing so, it may be possible to identify the best amongst a basket of agents that can be used for treating a particular disease in case of limited clinical evidence.⁴⁹ Several direct comparison meta-analyses were conducted comparing two different routes of TXA both in patients with THA and total knee arthroplasty.^{11,12,50} Zhang et al¹¹ did a direct comparison meta-analysis of seven studies that compared the combination of topical and intravenous TXA with either placebo, topical or intravenous TXA alone in patients with THA. Several pitfalls were observed in the previous meta-

analysis that could undermine the conclusion of the study such as inclusion of a retrospective study along with randomized controlled trials due to limited number of the latter studies. However, the conclusion of the study is similar to our network meta-analysis that the combination was found to be better than the comparator groups. Additionally, we also observed that the combination of topical and intravenous TXA was better than other modes of administering TXA and have a high probability of being the best. Also, we conducted several sensitivity analyses and also included cohort studies in addition to randomized controlled trials.

Fig. 5. Consistency plot of the estimates between direct and indirect comparisons. No gross deviation was observed between the estimates in consistency and inconsistency models.

Fig. 6. Forest plot of the pooled estimates of mixed treatment comparisons for the risk of thrombosis.

Topical – Topical administration of TXA in the joint cavity; Intra-Op + Post-Op – TXA administration intravenously both during surgery and in the post-operative period; IV bolus – TXA administration as a bolus intravenous dose either during induction of anesthesia or just before surgery; IV bolus with infusion – TXA administered as intravenous bolus followed by continuous infusion; Topical + IV-bolus – TXA administered both topically in the joint space and intravenously during surgery; Pre-Op – TXA administered pre-operatively.

Fig. 7. Forest plot of mixed treatment comparisons for the difference in total blood loss between the interventions.

IV bolus + Top – TXA administered intravenously as bolus injection along with topically in the joint space; Topical – TXA administered topically in the joint space; IV bolus – TXA administered as single bolus intravenously; Intra-Op + Post-Op – TXA administered intravenously both intra-operatively and post-operatively; Two intra-Op – TXA administered at two doses during the surgery; Pre-Op – TXA administered intravenously pre-operatively.

With regards to the safety of TXA, results of our meta-analysis are corroborative to the above mentioned direct comparison meta-analyses thus further strengthening the safety profile of TXA. A nationwide database review from Sweden over a period of six years in patients with menorrhagia who reported the use of TXA revealed a high risk for developing deep vein thrombosis although not observed statistically.⁵¹ Recent evidences have confirmed the safety of TXA in patients without thromboprophylaxis and also reduction in the incidence of arterial thrombosis.^{52,53}

The strength of the present network meta-analysis is that we compared the various routes of administering TXA reported in the literature in a single platform. We also used robust techniques wherein we combined generalized linear pair-wise modeling that does not have any assumptions with frequentist approach for direct comparisons and Bayesian approach for mixed treatment comparison of primary outcome. The overall analyses and interpretations did not change significantly during sensitivity analyses and publication bias was not observed. Minimal inconsistencies were observed between the estimates of direct, indirect and mixed treatment comparisons. However, the results of this meta-analysis have to be considered with the following limitations: We have not evaluated the difference in response with respect to dose of TXA administered by each route; The onset of action of TXA depends on the route of administration wherein oral administration will take about 2 h and when administered intravenously, the onset of action ranges between 5 and 15 min.^{54,55} Hence, we considered studies that administered TXA within 15 min prior to surgery together with studies that administered TXA during induction of anesthesia as a single entity; Differences in the ways of topical administration of TXA

were observed between the studies but this is not accounted; Studies that recruited patients with fracture were not included for the present review; and the differences in techniques, surgical set-ups and skills of operating surgeons between the studies are some of the inevitable limitations of our analysis.

To conclude, from the present mixed treatment comparisons we observed that the combination of topical and intravenous TXA is better than placebo and other modes of administering TXA in terms of reducing the rate of blood transfusion and total blood loss in patients with THA. No significant differences exist for the risk of thrombotic complications between TXA and placebo.

Conflict of interest

The authors have none to declare.

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Table 2

Grading the quality of evidence for comparisons in the primary outcome.

Comparisons	Illustrative comparative risks (95% confidence intervals)		Effect estimate and quality of evidence for direct comparisons	Effect estimate and quality of evidence for mixed treatment comparisons
	Assumed risk ^b	Corresponding risk ^a		
Topical plus intra-operative dosing of TXA with placebo	260 per 1000	27 per 1000 (7–115)	0.08 [0.02, 0.37] ⊕⊕⊕⊕ Very low ^{c,d} NA	0.06 [0.02, 0.14] ⊕⊕⊕⊕ Low ^{c,f} 0.13 [0.02, 0.51]
Two intra-operative doses of TXA administered intravenously with placebo	260 per 1000	ND		⊕⊕⊕⊕ Very low ^{c,f} 0.16 [0.02, 0.93]
Intravenous TXA both pre-operatively and during surgery with placebo	260 per 1000	57 per 1000 (10–230)	0.17 [0.03, 0.85] ⊕⊕⊕⊕ Very low ^{c,d} NA	⊕⊕⊕⊕ Very low ^{c,f} 0.19 [0.02, 1.12]
TXA intravenous bolus with continuous infusion during surgery with placebo	260 per 1000	ND		⊕⊕⊕⊕ Very low ^{c,f} 0.20 [0.09, 0.38]
Topical TXA with placebo	260 per 1000	57 per 1000 (27–107)	0.17 [0.08, 0.34] ⊕⊕⊕⊕ Moderate ^e	⊕⊕⊕⊕ Low ^{c,f} 0.22 [0.14, 0.37]
TXA intravenous bolus either at induction of anesthesia or just before surgery with placebo	260 per 1000	95 per 1000 (59–146)	0.30 [0.18, 0.49] ⊕⊕⊕⊕ Moderate ^g	⊕⊕⊕⊕ Moderate ^f 0.31 [0.06, 1.24]
Pre-operative TXA intravenously with placebo	260 per 1000	92 per 1000 (37–201)	0.29 [0.11, 0.71] ⊕⊕⊕⊕ Low ^{c,g}	⊕⊕⊕⊕ Very low ^{c,f} 0.29 [0.12, 0.70]
Intra-operative and post-operative TXA intravenously with placebo	260 per 1000	98 per 1000 (53–173)	0.31 [0.16, 0.60] ⊕⊕⊕⊕ Moderate ^g	⊕⊕⊕⊕ Low ^{f,g} 0.33 [0.12, 0.79]
Topical and intra-operative intravenous TXA with topical TXA	58 per 1000	6 per 1000 (1–109)	0.10 [0.01, 1.98] ⊕⊕⊕⊕ Very low ^{c,d}	⊕⊕⊕⊕ Low ^{f,g} 0.28 [0.11, 0.60]
Topical and intra-operative intravenous TXA with intravenous TXA alone	55 per 1000	15 per 1000 (6–34)	0.26 [0.11, 0.60] ⊕⊕⊕⊕ NA	⊕⊕⊕⊕ Very low ^{c,f} 0.21 [0.06, 0.69]
Topical and intra-operative intravenous TXA with intra-operative and post-operative intravenous TXA	75 per 1000	ND		⊕⊕⊕⊕ Very low ^{c,f}

ND – Not determined because the direct estimate is not available for that comparison; NA – Not available.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^a Corresponding risks are based on the effect estimates from direct comparisons.^b Assumed risk was the median control group risk across the studies.^c Downgraded two levels for imprecision as evident by a wide confidence interval.^d Downgraded one level for inconsistency which could not be assessed.^e Downgraded one level for imprecision.^f Downgraded one level for indirectness as assessed through one loop indirectly.^g Downgraded one level for small number of events.

generate pooled results for indirect comparisons of categorical variables. We are grateful to EpiGear for using MetaXL in generating mixed treatment comparison results for secondary outcomes in this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jor.2018.01.051>.

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