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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 ml[3] 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. NetMetaXL[17] 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 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

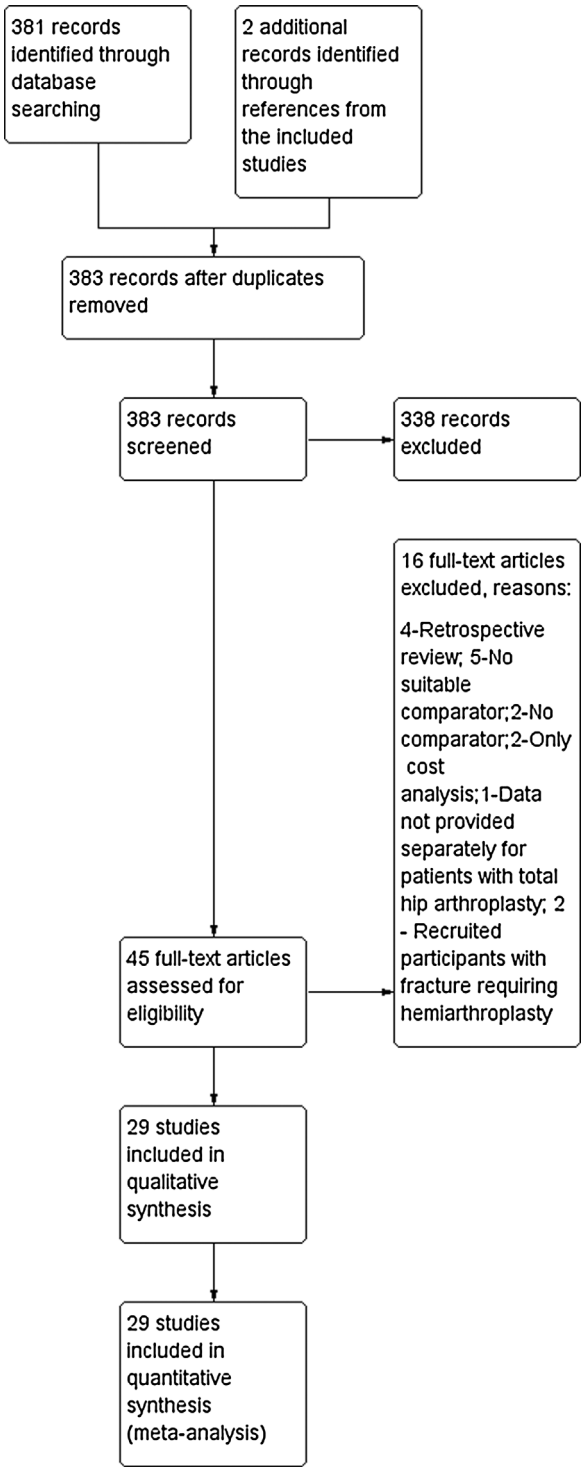

Fig. 1. PRISMA study flowchart.
A total of 383 articles were obtained and finally 29 studies were included in the network meta-analysis.

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