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Review Article

Tranexamic acid in total hip arthroplasty: A recursive cumulative meta-analysis of randomized controlled trials and assessment of publication bias

Kannan Sridharan[a,*], Gowri Sivaramakrishnan[b]

[a] Associate Professor in Pharmacology, School of Health Sciences, College of Medicine, Nursing and Health Sciences, Fiji National University, Suva, Fiji
[b] Assistant Professor in Prosthodontics, School of Oral Health, College of Medicine, Nursing and Health Sciences, Fiji National University, Suva, Fiji

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ABSTRACT

Introduction: TXA has been evaluated in THA in several randomized controlled trials for the past 16 years. We attempted to evaluate the trends in the evidence using recursive cumulative meta-analysis and publication bias using Rosenthal and 'Trim and Fill' methods

Methods: Electronic databases were searched for randomized controlled clinical trials comparing TXA with either placebo (or no TXA administration) or TXA, administered through different routes in patients with osteoarthritis or osteonecrosis of the hip who underwent THA. We considered the total number of patients requiring blood transfusion as the clinical outcome for both the analyses and used quality effects model for assessing the changes in the pooled estimates with addition of new clinical trial data. We also assessed the publication bias by plotting individual study estimates with the standard errors using Rosenthal and 'Trim and Fill'methods.

Results: A total of 20 studies were included. The pooled cumulative meta-analysis indicates that from 2014 the addition of estimate from new studies in the following years is only narrowing the confidence interval without any significant change in the point estimate. Rosenthal fail-safe-N for the comparisons of intravenous bolus TXA, intra-operative and post-operative intravenous TXA and topical with control groups were 54, 6 and 16 respectively. Fail-safe-N for the combined intravenous and topical TXA with intravenous TXA alone was 13.

Conclusion: Adequate evidence exists supporting the use of intravenous TXA in reducing the need for blood transfusion in THA. There is possible existence of small studies with null effects evaluating the use of TXA in THA.

1. Introduction

Total hip arthroplasty [THA] is associated with a blood loss ranging between 1000 and 2000 ml and nearly 37% of patients undergoing THA require blood transfusion.1 Tranexamic acid (TXA) to reduce the bleeding and the need for blood transfusion in THA as well as in total knee arthroplasty is proven in randomized controlled trials and meta-analyses. 2,3 The earliest evidence evaluating the efficacy of TXA was in the 1987 in thyroid surgeries and in 2000 for THA.4 However, till date nearly 30 randomized clinical trials and several observational studies are being carried out on TXA in THA. A common limitation observed in the meta-analyses evaluating TXA in THA is publication bias. Most of the studies did not assess publication bias and its impact on the effect estimates. 5,6 Presence of unpublished literature may obscure the real findings and so it is vital to identify the extent or guesstimate the risk. 7 TXA has been evaluated in several routes and time of administration and there are no consensus as to which is the best route and time.8 Despite many randomized controlled trials and meta-analyses from 2000, recent clinical trials evaluating TXA is continuing.9

Cumulative meta-analysis is used to calculate the summary effect estimates from the results of studies that have accrued till date. 10 This helps us identify the trends and robustness of the accumulated evidence. This identifies the usefulness of studies conducted with indirect effect on the utility of the resources in a better way. Cumulative meta-analysis by precision also can be used to identify the presence of any publication bias. 11 The Rosenthal

* Corresponding author.
E-mail address: skannandr@gmail.com (K. Sridharan).

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method also known as 'file drawer analysis' calculates the number of studies required to be added to the given set, in order to average the null results for a given level of confidence. 12 Additionally, 'Trim and Fill' method estimates the number of missing studies by using the effect estimates of the included studies in a meta-analysis. 13 With this background, we tried to assess the changes in the summary estimates with the addition of new randomized clinical trials using recursive cumulative meta-analysis. Additionally, we also assessed the publication bias using Rosenthal and, Trim and Fill methods.

2. Methods

2.1. Information sources and search strategy

The protocol for this review was registered with PROSPERO with the registration number CRD42017058116. A thorough literature search was completed on 01 March 2017 with the search strategy: Tranexamic acid [tiab] AND arthroplasty [tiab]. Databases searched for potential articles include Medline (through PubMed), Cochrane CENTRAL and Google Scholar. No limits were placed with respect to either language or year of publication. The references from the screened literature were also searched for eligible studies.

2.2. Eligibility criteria

Only randomized controlled clinical trials comparing TXA with either placebo (or no TXA administration) or TXA administered through any route in patients with osteoarthritis or osteonecrosis of the hip who underwent THA were included for the assessment of trend analysis. We attempted to assess the trends and publication bias for only those comparisons that had a minimum of three studies. We considered the total number of patients requiring blood transfusion as the clinical outcome for both the analyses.

2.3. Study procedure and statistical considerations

Two authors independently performed literature search in the above mentioned databases. Both the authors independently extracted the following data from each eligible study: trial site, year, trial methods, participants, interventions, and outcomes. 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 guidelines (PRISMA). 14 We analysed the risk of bias of the included studies using Cochrane risk of bias tool under seven domains. 15 Odds ratio [95% confidence interval] was used as the effect estimate. MetaXL 16 was used to generate pooled estimates for the cumulative meta-analysis wherein the result of each trial is added to the previous pooled estimates in a repetitive fashion using quality effects model. The quality effects model 16 links the quality of each randomized controlled trial to the corresponding effect estimate. The quality of each trial was assessed based on the risk of bias tool wherein a score of 3 was given low risk, 2 for intermediate and 1 for high risk in each domain. We assessed the publication bias by 'Rosenthal' and 'Trim and Fill' methods using Meta-Essentials. 17

3. Results

3.1. Search results

A total of 383 articles were obtained with the above mentioned search strategy and references from the screened literature. Finally 20 studies 18–37 were included (Fig. 1). Eight studies compared the intravenous bolus administration of TXA either at the time of induction of anaesthesia or just before surgery, four compared TXA during surgery and post-operatively, and one study compared topical TXA with the control group. Four studies compared topical combined with intravenous bolus TXA to intravenous bolus TXA. One study compared intravenous bolus TXA at the time of

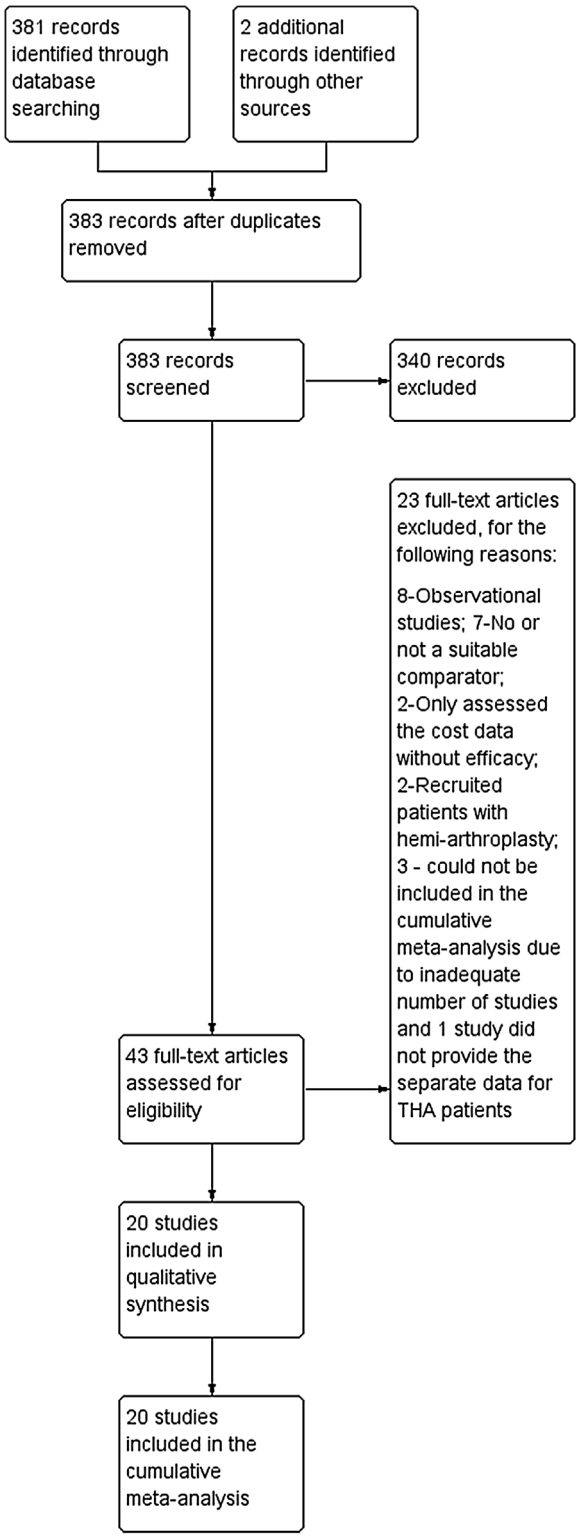

Fig. 1. PRSIMA flow chart.
A total of 383 articles were identified of which finally 20 studies were included in this cumulative meta-analysis.