

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	COMPARISON OF INTRAVENOUS, TOPICAL, OR COMBINED ROUTES OF TRANEXAMIC ACID ADMINISTRATION IN PATIENTS UNDERGOING TOTAL KNEE AND HIP ARTHROPLASTY: A META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS
AUTHORS	Sun, Qi; Li, Jinyu; Chen, Jiang; Zheng, Chenying; Liu, Chuyin; Jia, Yusong

VERSION 1 – REVIEW

REVIEWER	Zhihu Zhao Tianjin University General Hospital
REVIEW RETURNED	10-Jun-2018

GENERAL COMMENTS	Thank you for inviting me to review this manuscript. As far as we know, many meta-analysis have been published in recent years. This meta-analysis has no novelty. Though the author make a lot of efforts for this meta-analysis. The conclusion has no clinical practice. In my opinion, the current perspective was to find the optimal dose of TXA. Based on the novelty of the meta-analysis, I think current meta-analysis should be rejected.
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REVIEWER	Xia Wang The George Insitute for Global Health, Australia
REVIEW RETURNED	06-Jul-2018

GENERAL COMMENTS	This is a meta analysis to examine effects of tranexamic acid on blood loss and transfusion requirements in patients undergoing total knee and hip arthroplast. The study is with high quality and adhere to PRISMA checklist. Only minor issues noted: 1) please provide a detailed search strategy as a supplementary material. 2) please describe PICO clearly in both abstracts and methods. 3)pubmed should be medline.
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REVIEWER	Dr. Yun-feng RUI, MD. Ph.D Associate Consultant Orthopaedic Surgeon, Department of Orthopaedics, Zhongda Hospital, Southeast University, Nanjing, Jiangsu, China. Executive Deputy Director, Trauma Center, Zhongda Hospital, Southeast University, Nanjing, Jiangsu, China. Deputy Director, Orthopaedic Trauma Institute (OTI), Southeast University, Nanjing, Jiangsu, China.
REVIEW RETURNED	18-Sep-2018

GENERAL COMMENTS	<p>Total joint arthroplasty (TJA) is associated with substantial blood loss which can lead to postoperative anemia. As a synthetic amino acid that carries out its effects through an antifibrinolytic action, tranexamic acid (TXA) has been utilized in an intravenous route, a topical route or an oral route in the peri-operation period for blood salvage. However, whether the intravenous regime or the topical regime show an advantage over the other is not definite. So the authors conducted the meta-analysis to compare the efficacy and safety of the topical TXA and systematic TXA dosage. Overall, this review is original and the topic is interesting. However, there are some points needing to be addressed.</p> <ol style="list-style-type: none"> 1. In the Title and Objective part, you intend to compare the differences in terms of the clinical effect of tranexamic acid between different routes. However the oral route, which has also been studies in TJA, is not included. 2. As for the Method part, in the section of “Selection of studies”, you didn’t select the main outcome definitely. So it was not clarified whether the studies selected evaluated the main outcome. 3. In the Results part, an inconsistency between the titles of Figure 6, 7, 8 and your description in the results part were found, for the studies analyzed in the these figures contained the one by Lin(2015), where the combination utilization of TXA was compared with topical route, not the intravenous route. This may influence the accuracy and the credibility of your results greatly. Please recheck it carefully. 4. In the Discussion part, you concluded that the combined delivery method using IV and topical TXA show a more effective result comparing with the single regime. I do suggest that the discussion in depth should be done and an explanation to illuminate the potential mechanism for this result should be presented in this part.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 (Prof Zhihu Zhao)

General comments: Thank you for inviting me to review this manuscript. As for as we know, many meta-analysis have been published in recent years. This meta-analysis has no novelty. Though the author make a lot of efforts for this meta-analysis. The conclusion has no clinical practice. In my opinion, the current perspective was to find the optimal dose of TXA. Based on the novelty of the meta-analysis, I think current meta-analysis should be rejected.

Response: Thanks for this suggestion. We have already introduce previous meta-analyses in Introduction and Discussion section. All of changes are listed as follows: “Several previous trials or meta-analyses have mainly focused on comparing TXA and non-TXA, proving that oral, intravenous (IV) and topical TXA were associated with significantly reduced perioperative blood loss volume and blood transfusion requirements.[13-19] Furthermore, two important meta-analysis showed comparable haemostatic effects between oral and IV TXA.[20-21] Moreover, another two studies showed that patients who received combined IV and topical TXA experienced more benefit than those with single-route TXA administration.[22-23] However, few studies have directly compared the different TXA administration routes, and they were limited due to combination of various study design types and relatively small number of included studies.[24]”; “Several meta-analyses have been published on TXA use during arthroplasty. Both IV and intra-articular administration of TXA have been demonstrated to reduce the blood loss volume without increased risk of thromboembolic

complications, and the use of IV TXA is considerably more common.[13,14,16,21-24,63-68] However, most of these meta-analyses compared TXA with a placebo. We only identified two meta-analyses that performed a head-to-head comparison between the topical and IV routes, including one on TKA[24] and the other on THA.[61] Both analyses included only a very small number of studies. In addition, a methodological flaw was observed because they included non-randomised or retrospective studies.”

Reviewer: 2 (Prof Xia Wang)

General comments: This is a meta analysis to examine effects of tranexamic acid on blood loss and transfusion requirements in patients undergoing total knee and hip arthroplast. The study is with high quality and adhere to PRISMA checklist. Only minor issues noted:

Response: We appreciate your kindly suggestion. We have already addressed the comments in the revised manuscript and highlighted the changes in “RED.” All of changes have listed as follows:

Question 1: please provide a detailed search strategy as a supplementary material.

Response: Thanks for this suggestion, and the full search strategy in PubMed have already listed in supplementary file 1.

Question 2: please describe PICO clearly in both abstracts and methods.

Response: Thanks for this suggestion, the PICO have already changed in Methods section. Further, the PICO in Abstract section have already marked “RED”.

Question 3: pubmed should be medline.

Response: Thanks for this suggestion, and we searched in PubMed but not Medline due to the most recently studies were updated in PubMed, and the searching results of PubMed are containing medline. Therefore, we still searched PubMed in the current meta-analysis.

Reviewer: 3 (Prof Yun-feng RUI)

General comments: Total joint arthroplasty (TJA) is associated with substantial blood loss which can lead to postoperative anemia. As a synthetic amino acid that carries out its effects through an antifibrinolytic action, tranexamic acid (TXA) has been utilized in an intravenous route, a topical route or an oral route in the peri-operation period for blood salvage. However, whether the intravenous regime or the topical regime show an advantage over the other is not definite. So the authors conducted the meta-analysis to compare the efficacy and safety of the topical TXA and systematic TXA dosage. Overall, this review is original and the topic is interesting. However, there are some points needing to be addressed.

Response: We appreciate your kindly suggestion. We have already addressed the comments in the revised manuscript and highlighted the changes in “RED.” All of changes have listed as follows:

Question 1: In the Title and Objective part, you intend to compare the differences in terms of the clinical effect of tranexamic acid between different routes. However the oral route, which has also been studies in TJA, is not included.

Response: Thanks for this suggestion. The current study did not include oral route due to numerous meta-analysis have already demonstrated the clinical effect of oral tranexamic acid. Therefore, we changed the title and Objective part in the revised manuscript and marked “RED”.

Question 2: As for the Method part, in the section of “Selection of studies”, you didn’t select the main outcome definitely. So it was not clarified whether the studies selected evaluated the main outcome.

Response: Thanks for this suggestion, we have already changed this sentence into “the main outcomes included intraoperative and total blood loss, transfusion rate, low postoperative haemoglobin (Hb) level and postoperative Hb decline. However, the secondary outcomes included length of hospital stay (LOS) and/or the occurrence of venous thromboembolism (VTE) which may present as PE or DVT”

Question 3: In the Results part, an inconsistency between the titles of Figure 6, 7, 8 and your description in the results part were found, for the studies analyzed in the these figures contained the one by Lin (2015), where the combination utilization of TXA was compared with topical route, not the intravenous route. This may influence the accuracy and the credibility of your results greatly. Please

recheck it carefully.

Response: Thanks for the reviewer point out this mistake, and the titles of Figures 6-8 were not accuracy. We have already changed the titles of Figures 6-8 and listed as follows: “Figure 6. Forest plot comparing the efficacy of single versus combined routes of TXA on total blood loss.

Figure 7. Forest plot comparing the efficacy of single versus combined routes of TXA on blood transfusion rate.

Figure 8. Forest plot comparing the safety of single versus combined routes of TXA on postoperative venous thromboembolism.”

In addition, we have already rechecked the results of stratified analyses and found the results are corrected.

Question 4: In the Discussion part, you concluded that the combined delivery method using IV and topical TXA show a more effective result comparing with the single regime. I do suggest that the discussion in depth should be done and an explanation to illuminate the potential mechanism for this result should be presented in this part.

Response: Thanks for this suggestion, we have already added several sentences in Discussion and listed as follows: “Moreover, the antifibrinolytic effect of topical TXA is limited to postoperative bleeding. Preoperatively, IV TXA was associated with lower blood loss volume during arthroplasty, which explains the greater benefit of combined regimen of using IV along with topical routes.[62]”

VERSION 2 – REVIEW

REVIEWER	Xia Wang The George Institute for Global Health / Australia
REVIEW RETURNED	23-Oct-2018
GENERAL COMMENTS	No additional comments.

