

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)	Multiple-dose tranexamic acid for perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis : A single-blinded, randomized, parallel-controlled study protocol in China
AUTHORS	Kang, Bing-xin; Xu, Hui; Gao, Chen-xin; Zhong, Sheng; Zhang, Jing; Xie, Jun; Sun, Song-tao; Ma, Ying-hui; Zhai, Wei-tao; Xiao, Lian-bo

VERSION 1 – REVIEW

REVIEWER	Guanghua Lei Department of Orthopaedics, Xiangya Hospital, Central South University
REVIEW RETURNED	23-Oct-2019

GENERAL COMMENTS	The paper described a RCT protocol to evaluate the effects of multiple doses of tranexamic acid on perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis. The topic is interesting, and I only have several minor comments. Minor comments: 1. The title should indicate this is a study protocol. 2. Line 55: If IV was not used as an abbreviation in other places in the manuscript, it is recommended not to use the abbreviation here. 3. Line 98: Please check the reference and make sure that it is appropriate to say "joint replacement surgery accounts for the majority for these surgeries". 4. Line 103-107: It is recommended to reconstruct this section, because the flow is confusing. 5. Line 111: The sentence that "it can cause systemic blood cells" is confusing.
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REVIEWER	Fuxing Pei Department of Orthopedics, West China Hospital, Sichuan University, Chengdu, People's Republic of China
REVIEW RETURNED	12-Dec-2019

GENERAL COMMENTS	General comments: We have recommended editing to better conform to word selection, grammar, and understanding in the predominant English-speaking readers of the Journal. The study will be the most useful to orthopedic surgeons performing TKAs on RA patients. However, the study's generalizability to surgical populations is limited by its exclusion
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	criteria and overall population size, especially as related to potential adverse effects of the TXA use. Specific comments: Introduction: 1. Despite its scarcity, consider including a brief summary of current available literature/evidence regarding effectiveness of TXA in patients with RA. 2. Please clarify and provide more information regarding why we cannot apply TXA use in OA to RA patients- eg what mechanisms or pathophysiology is different and how that will apply 3. How often do patients with RA actually require TKA? 4. Consider also providing how prevalent RA is globally Methods: 1. Consider elaborating on the timing of discontinuing biologic DMARDs in relation to TKA procedure 2. Please give more specifics on when patients were told to stop their biologics in front of surgery. It would be interesting to know how many patients were on the biologics. 3. The method used for recording of intraoperative blood loss should be carefully detailed. 4. Page 12, line 242-243: Low molecular weight heparin was administrated once? How long was the total time of prophylaxis? 5. How were complications recognized/recorded during the follow-up? Discussion: 1. Appropriately re-emphasized that results can only be extrapolated to Chinese RA population and cannot be recommended for general use. 2. Should include OA articles showing lower blood loss and LOS and compare to results of your study. 3. While the study has enough statistical power to detect the difference in blood loss, it may not have the power to detect potential severe complications related to high dose TXA regimens.
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1 report:

1. The title should indicate this is a study protocol.

A: The title has indicated this is a study protocol. (Page 1 line 1)

2. Line 55: If IV was not used as an abbreviation in other places in the manuscript, it is recommended not to use the abbreviation here.

A: We agree with the Reviewer that no IV abbreviation used. (Page 3, Line 64,65)

3. Line 98: Please check the reference and make sure that it is appropriate to say “joint replacement surgery accounts for the majority for these surgeries”.

A: The manuscript has been replaced as” Total knee arthroplasty (TKA) is effective in treating flexion contracture and maintaining the stability of RA knee.” (Page 5, line 91-93)

4. Line 103-107: It is recommended to reconstruct this section, because the flow is confusing.

A: The confusing flow has been reconstructed as” However, after the release of the tourniquet, local tissue may be damaged by ischemia reperfusion injury, and fibrinolytic system activated. As a consequence, peripheral blood circulation is accelerated, plasma fibrinolysis enhanced, and

postoperative HBL increased". (Page 5-6, line 110-113)

5. Line 111: The sentence that "it can cause systemic blood cells" is confusing.

A: This confusing sentence in the original manuscript has been deleted.

Reviewer 2 report:

Introduction:

1. Despite its scarcity, consider including a brief summary of current available literature/evidence regarding effectiveness of TXA in patients with RA.

A: We agree with the Reviewer2 that a brief of summary of current evidence in effectiveness of TXA in RA patients has been included.(Page 6, line 120-123)

2. Please clarify and provide more information regarding why we cannot apply TXA use in OA to RA patients- eg what mechanisms or pathophysiology is different and how that will apply.

A: OA and RA have different pathogenesis. RA is a chronic, progressive disease characterized by synovial inflammation and systemic inflammation with not only destruction of joints and supporting soft tissues but also can be accompanied by hematological diseases and cause anemia. OA is a degenerative joint disease. Pathological changes seen joints include progress loss and destruction of articular cartilage, thickening of subchondral bone, formation of osteophytes, variable degrees of inflammation of the synovium, degeneration of ligaments and menisci of the knee and hypertrophy of the joint capsule. Local joint symptoms are predominant and rarely accompanied by systemic symptoms. Patients with RA are more likely to have anemia than OA (Page 5 ,line 100-102). Existing literature proves that high-dose TXA acid can reduce blood loss in TKA. However, patients undergoing surgery are mainly OA patients and only have a small amount of RA patients. Therefore, this study wanted to explore the effectiveness multiple doses of TXA on perioperative blood loss in TKA in patients with RA.

3. How often do patients with RA actually require TKA?

A: About 0.005% of RA patients receive TKA. (Page 5, line 93). Knee Joint severe pain with dysfunction, X-ray examination suggests Stage III or IV according to the Kellgren-Lawrence classification, and medical management is ineffective, TKA management will be considered.

4. Consider also providing how prevalent RA is globally

A: The prevalent RA in global has been provided.(Page 5,Line 90-91.)

Methods:

1. Consider elaborating on the timing of discontinuing biologic DMARDs in relation to TKA procedure.

A: The timing of discontinuing biologic DMARDs in relation to TKA procedure has been provided in the manuscript. (Page 9-10, Line 193-200)

2. Please give more specifics on when patients were told to stop their biologics in front of surgery. It would be interesting to know how many patients were on the biologics.

A: Specific methods of using perioperative biologics have been added to the manuscript. (Page -109, Line 193-200). We will also register patients using biologics during the trial.

3. The method used for recording of intraoperative blood loss should be carefully detailed.

A: The use of tourniquet during the operation, less intraoperative bleeding, and both groups used TXA before and during the operation. Preoperative and intraoperative baselines are the same in both groups.

The amount of postoperative blood loss= the total volume of fluid in the negative pressure drain—the volume of normal saline. (Page 10-11, Line 220-222)

4. Page 12, line 242-243: Low molecular weight heparin was administrated once? How long was the total time of prophylaxis?

A: Six hours after the surgery, perioperative enoxaparin sodium (60mg, once a day for 14 days) is injected for preventing deep vein thrombosis. (Page 11, line 240-241)

5. How were complications recognized/recorded during the follow-up?

A: Patients are usually discharged at 14 days after surgery. During hospitalization, we monitor and record the patient's adverse reactions in the CRFs.(Page14,line 291) If adverse reactions occur, we

will investigate the correlation between adverse reactions and TXA.

Discussion:

1. Appropriately re-emphasized that results can only be extrapolated to Chinese RA population and cannot be recommended for general use.

A : We have emphasized the results can only be extrapolated to Chinese RA population.(Page 15-16, line 332-333. Page 4, line 86)

2. Should include OA articles showing lower blood loss and LOS and compare to results of your study.

A: We cite the provenTXA in reducing blood loss after TKA in OA patients(Page 6,line 120-122).This article is a clinical protocol, there is no research data at present. For the early postoperative recovery of patients, in general, the LOS is 14 days after surgery. At the end of the clinical trial, we will compare the results of RA with OA patients.

3. While the study has enough statistical power to detect the difference in blood loss, it may not have the power to detect potential severe complications related to high dose TXA regimens .

A : We totally agree with the reviewer that blood loss may not have the power to detect potential severe complications related to high dose TXA regimens, relevant sentences in the manuscript have been deleted.

VERSION 2 – REVIEW

REVIEWER	Fuxing Pei West China Hospital, China
REVIEW RETURNED	02-Feb-2020

GENERAL COMMENTS	The authors have revised their manuscript. The revisions are generally satisfactory. However, I have three questions for the authors to answer. 1) Page 38, Line 105-106 This statement suggests HBL often leads to the postoperative pain, lower limb swelling, poor wound healing, postoperative inflammation, and even wound infections. Please supply relevant references to support this statement. 2) Was this study registered on Clinical Trial Registry? If was, please provide registration number. 3) Page 41, Line 171 Why only patients aged 55 - 75 years will be enrolled in this trial?
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Fuxing Pei

1) Page 38, Line 105-106

This statement suggests HBL may leads to the postoperative pain, higher limb swelling, poor wound healing, postoperative inflammation, and even wound infections. Please supply relevant references to support this statement.

A:The original statement is changed to “HBL often leads to the joint swell, postoperative inflammation and pain.” and the relevant references have been provided with entries 11 and 12 in the references.

2) Was this study registered on Clinical Trial Registry? If was, please provide registration number.

A:This study was registered on Clinical Trial Registry and registration number is ChiCTR1900025013.

3) Page 41, Line 171

Why only patients aged 55 - 75 years will be enrolled in this trial?

A:The age range of this trial is 50-75 years old, which has been corrected and highlighted .For two reasons :1. statistics on RA patients undergoing TKA in our hospital in the past 5 years,more than eighty percent of patients between the ages of 50 to 75 years.2,we suspect that a large age difference may affect the accuracy of experimental results, aim to reduce the bias we will enroll RA patients age 50-75.