International Journal of Surgery Protocols 22 (2020) 15–18

Contents lists available at ScienceDirect

International Journal of Surgery Protocols

journal homepage: www.elsevier.com/locate/isjp

The use of intra-operative tranexamic acid in shoulder surgery: Protocol for a systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 7 June 2020
Received in revised form 15 June 2020
Accepted 16 June 2020
Available online 23 June 2020

Keywords:
Systematic review
Meta-analysis
Protocol
Tranexamic acid
TXA
Shoulder surgery

ABSTRACT

Introduction: Blood loss is an important consideration in all types of shoulder surgery. Excessive bleeding is associated with increased morbidity. Tranexamic acid (TXA) is an antifibrinolytic agent. It has been demonstrated to be effective in reducing blood loss across multiple surgical specialties. The aim of this systematic review and meta-analysis is to review the literature evaluating clinical outcomes associated with the use of TXA in shoulder surgery.

Methods: The study protocol was designed and registered prospectively on PROSPERO (International prospective register for systematic reviews). Literature search will include the MEDLINE, EMBASE, PsycINFO, and Cochrane Library databases. Randomised controlled trials (RCTs) evaluating the use of TXA against placebo, in all types of shoulder surgery, will be included. Our primary outcome is total blood loss (ml). Secondary outcomes include patient-reported outcome measures (PROMs), adverse events, and number of blood transfusions required. Risk of bias will be assessed within each study using The Cochrane Risk of Bias Tool 2.0 and the Jadad score. Inconsistency and bias across included studies will be assessed statistically. Data from comparable outcomes will be pooled and analysed quantitatively or descriptively as appropriate.

Ethics and dissemination: No ethical clearances required for this study. This systematic review and meta-analysis will be published in a peer-reviewed journal. It will be presented a various national and international conferences.

1. Introduction

Perioperative blood management is an important consideration in all types of shoulder surgery. With increasing incidence [1,2] and in some cases, complexity of shoulder surgery, the effects of perioperative blood loss have become more obvious.

The rate of blood transfusion following shoulder surgery is relatively low [3,4]. There is significant increased morbidity associated with whole blood transfusion [5,6]. Excessive bleeding during shoulder surgery may influence length of stay, postoperative pain, swelling, and wound healing. The use of tranexamic acid (TXA) is one method of attempting to reduce blood loss. TXA is synthetic derivative of the amino acid lysine. It is an antifibrinolytic agent that binds reversibly to plasminogen, inhibiting its conversion to plasmin. It therefore stabilises formed clots by preventing fibrin degradation [7–9].

TXA has been used effectively across different specialties in surgery to reduce blood loss [7,9]. Recent systematic reviews have demonstrated TXA to be effective in reducing blood loss and transfusion rates in lower limb arthroplasty and spinal surgery [10–12]. Most recently, clinical trials investigating its use in shoulder arthroplasty have shown favourable results [13–18]. The overall clinical effectiveness of tranexamic acid use in shoulder surgery is of interest.

The aim of this systematic review is to comprehensively review the literature evaluating clinical outcomes associated with the use of TXA in shoulder surgery. Our primary outcome will be total blood loss (ml) as it has the most clinical relevance to both patients and surgeons. Secondary outcomes will include patient reported outcome measures (PROMs), operative time (mins), hospital length of stay, adverse events, and number of blood transfusions.

2. Methods

This study protocol was designed and registered prospectively on the PROSPERO (International prospective register for systematic

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https://doi.org/10.1016/j.isjp.2020.06.003
2468-3574/

reviews) database (Ref: CRD42020185482) [19]. The protocol is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocol (PRISMA-P) [20,21].

2.1. Eligibility criteria

2.1.1. Study design

Only randomised controlled trials will be included. All other trial designs will be excluded.

2.1.2. Participants

We will include studies with humans of any age undergoing any type of surgery to the shoulder girdle. This will include both open and arthroscopic techniques.

2.1.3. Intervention and comparators

The intervention of interest is intraoperative use of tranexamic acid. We will include all individual methods of delivery, timing, and dose of TXA. The comparator can include any form of placebo or no treatment.

2.1.4. Outcomes

The primary outcome of interest will be total blood loss (in ml). Other measures of bleeding may include post-operative blood loss via drain output, or reduction in serum haemoglobin.

Secondary outcomes examined will include patient reported outcome measures (PROMs), operative time, hospital length of stay, incidence of adverse events, and number of blood transfusions.

2.1.5. Timing

No restrictions regarding timing of the study.

2.1.6. Setting

No restrictions regarding setting of the study.

2.1.7. Language

Studies of all languages will be included. Any titles requiring translation into English will be included in the appendix.

2.2. Information sources

Our search strategy involved using the following bibliographic databases; MEDLINE, EMBASE, PsycINFO and The Cochrane Library.

2.2.1. Search strategy

No restrictions were placed on publication date or language. The Cochrane group randomised controlled trial filters for each database were utilised to increase sensitivity and maximise precision in the search strategy. Search terms utilised are included in the appendix. References from published systematic reviews investigating the same or similar topic were also manually searched for included studies. The PROSPERO database was searched, which revealed no ongoing or recently completed systematic reviews on this exact topic.

2.3. Study records

2.3.1. Data management

All literature search results will be combined and collected in Microsoft Excel. Duplicate articles will be removed. Two independent reviewers will screen titles and abstracts of returned search results. Both reviewers will complete this process independently and consensus will be sort prior to full text review. The resulting full text review of articles meeting eligibility criteria will then determine final inclusion.

2.3.2. Data collection process

Data extraction will involve two independent reviewers. One person will extract the data using a standardised proforma. The other reviewer will check the extracted data for inaccuracies. Any disagreement in data extraction will be resolved by discussion and the involvement of a third reviewer as necessary. We will attempt to contact study authors regarding unclear or missing data or for any additional details that may be required. Microsoft Excel will be used for data capture and Review Manager (RevMan version 5.3) used as a software tool for data management.

2.3.3. Data items

Data extraction will include study design, patient cohort, study characteristics, tranexamic acid dose/method of delivery, control group intervention, primary outcome measures, and any secondary outcome measures. Mean and standard deviations will be extracted for all outcome measures.

2.4. Outcomes and prioritisation

2.4.1. Primary outcome

The primary outcome of interest will be total blood loss (ml). Other outcome measures relevant to bleeding will include post-operative blood loss via drain output (ml), and/or reduction in serum haemoglobin (g/dL).

2.4.2. Secondary outcomes

Secondary outcomes examined will include patient reported outcome measures (e.g. Visual Analogue Score VAS, Oxford Shoulder Score OSS, and American Shoulder and Elbow Surgeons ASES shoulder score), operative time (minutes), hospital length of stay (days), incidence of adverse events, and number of blood transfusions required.

2.5. Risk of bias of individual studies

We will use the Cochrane collaboration Risk of Bias tool 2.0 to assess each trial for potential bias [22]. Bias is categorised into 5 domains. Each domain will be assigned a level of risk of bias (high risk, low risk, or some concerns). Signalling questions within each domain will guide interpretation of bias. The tool generates an overall risk of bias for each study. Each study will also be assessed using the Jadad scale as a supplementary method for assessing bias [23]. The Jadad scale gives a maximum of 5 points. Up to 2 points are given for randomisation – 1 point for mentioning randomisation and an additional point if the method of randomisation is appropriate. Up to 2 points are given for blinding – 1 point for mentioning blinding and an additional point if the method of randomisation is appropriate. A final point is given for an account of all patients involved in the trial.

2.6. Data synthesis

2.6.1. Quantitative synthesis

We expect a paucity of level I RCTs looking at the use of TXA in shoulder surgery. Data from a minimum of three studies will be synthesised for each outcome of interest. Data on outcomes related to bleeding from included studies will only be synthesised if the method in which they were recorded is comparable. Continuous variables, such as blood loss and haemoglobin reduction, will be summarised using standardised mean differences and inverse variance statistical analysis. We expect to perform most analyses using a random effects model due to some expected heterogeneity across the studies. Heterogeneity will be quantified using the using chi-square test for heterogeneity and the I^2 statistic. Any dichotomous data presented will be measured for effect using odds ratios.

2.6.2. Qualitative synthesis

Outcomes reported in less than three studies will not be synthesised and will be reported descriptively only. The inclusion of all surgical procedures involving the shoulder may provide unique outcomes in individual studies.

We will also describe outcomes reported when the incidence of the event is too low for pooled statistical analysis. This may include rate of blood transfusion and adverse events.

2.6.3. A priori subgroup analyses

Analysis will be performed in 2 categories based on the outcome measures reported. These include our primary outcome, total blood loss, and key secondary outcomes, not directly related to bleeding. There are no predetermined subgroup analyses. It is anticipated that the outcome measures used may differ between studies. We will pool data with comparable outcomes based on similarity of the methods used to capture the data.

2.6.4. Meta-bias

Publication bias will be assessed using a funnel plot of included studies investigating our primary outcome. We aim to assess for selective reporting by reviewing any trial protocol or trial registrations available to compare the pre-defined intended outcomes with those analysed and reported in the final manuscript. Each individual study will be assessed for risk of bias as previously described. Bias across studies will be assessed using statistical analysis of heterogeneity, as a measure of inconsistency.

2.6.5 Confidence in cumulative estimate

Description of the strength of the body of evidence provided will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [24–26]. Outcomes will be assessed as being of very low, low, moderate or high certainty.

Registration

PROSPERO 2020 CRD42020185482.

Ethical approval

No ethical approval was required for this review.

Funding

No funding received.

Authors' contributions

All authors contributed equally to this work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix. Search terms for MEDLINE

1. Clinical trials.mp.
2. Randomised.ab,ti.
3. Placebo.ab,ti.
4. Randomly.ab,ti.
5. Trial.ti.
6. Controlled clinical trial.pt.
7. Randomised controlled trial.pt.
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. Shoulder.ab,ti.
10. Glenohumeral.ab,ti.
11. Humerus.ab,ti.
12. Humeral.ab,ti.
13. Glenoid.ab,ti.
14. Scapula.ab,ti.
15. Acromion.ab,ti.
16. Coracoid.ab,ti.
17. Acromioclavicular.ab,ti.
18. Tranexamic acid.ab,ti.
19. TXA.ab,ti.
20. Antifibrinolytic.ab,ti.
21. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
22. 18 OR 19 OR 20
23. 8 AND 21 AND 22

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