

Prophylactic tranexamic acid use in orthognathic surgery: a systematic review

Submitted by

Dr. Hooman Baghaie

BOH, BDSc (Hons), MD

A thesis submitted in total requirements for the degree of

Master of Clinical Science

JBI, Faculty of Health and Medical Sciences

The University of Adelaide

July 2023

Table of contents

List of tables	5
List of figures	6
Abbreviations	7
Declaration	8
Acknowledgements	9
Executive summary	10
Background	10
Objectives	10
Inclusion criteria	10
Methods	11
Results	11
Conclusion	11
CHAPTER 1: INTRODUCTION	13
Orthognathic surgery	13
Mandibular osteotomy	13
LeFort I osteotomy	14
Genioplasty	14
Blood loss in orthognathic surgery	14
Haemorrhage minimisation	15
Overview of evidence synthesis	17
Review question	19
Current literature	19
CHAPTER 2: SYSTEMATIC REVIEW PROTOCOL	22
Objectives and statement of review question	22
Inclusion criteria	22
Types of studies	22
Types of participants	22
Types of interventions	23
Comparators	23
Types of outcome measures	23
Review methods	25
Search strategy	25
Assessment of methodological quality/critical appraisal	26
Data extraction	26
Data synthesis	26
Deviations from the protocol	27
CHAPTER 3: RESULTS	29

Description of studies	29
Methodological quality	37
Review of results	40
Intraoperative blood loss	40
Intraoperative blood loss sensitivity analysis:	46
Changes in haematocrit.....	46
Haematocrit sensitivity analysis	50
Changes in haemoglobin	50
Haemoglobin sensitivity analysis.....	54
Rate of perioperative blood transfusion	54
Rate of transfusion sensitivity analysis.....	58
Operative time	58
Operation time sensitivity analysis	62
Length of stay	62
Length of stay sensitivity analysis	62
Adverse effects.....	64
Publication bias	64
GRADE Summary of Findings.....	66
Summary of results	68
CHAPTER 4: DISCUSSION AND CONCLUSIONS.....	69
Intraoperative blood loss	69
Haematocrit.....	69
Haemoglobin	70
Rate of transfusion	70
Operation time	70
Length of stay	71
Overall completeness and applicability of evidence	71
Strengths and limitations of this review	72
Study inclusion and search strategy	72
Study design	73
Heterogeneity	73
Publication bias	74
Data extraction.....	74
Data analysis.....	75
Context within the literature	76
Implications for practice.....	78
Implications for research.....	78
REFERENCES	80
APPENDICES	88
Appendix 1: Initial search terms.....	88
Appendix 2: PubMed search strategy example.....	89
Appendix 3: PRISMA flowchart of study selection process	91
Appendix 4: Excluded full text studies.....	92
Appendix 5: Breakdown of risk of bias analysis	95

Appendix 6: Extended GRADE assessment of quality of evidence and strength of recommendations.....	155
--	------------

List of tables

Table 1. Characteristics of included studies	31
Table 2. GRADE Summary of Findings	67

List of figures

Figure 1. Risk of bias analysis summary.....	39
Figure 2. Forest plot for intraoperative blood loss – systemic or topical route	41
Figure 3. Forest plot for intraoperative blood loss – various systemic dosages.....	43
Figure 4. Forest plot for intraoperative blood loss – various surgery types.....	45
Figure 5. Forest plot for change in haematocrit – systemic or topical route	47
Figure 6. Forest plot for change in haematocrit – various surgery types.....	49
Figure 7. Forest plot for change in haemoglobin – systemic or topical route	51
Figure 8. Forest plot for change in haemoglobin – various surgery types (bimaxillary surgery only).....	53
Figure 9. Forest plot for rate of blood transfusion – systemic or topical route	55
Figure 10. Forest plot for rate of blood transfusion – various surgery types (bimaxillary surgery only).....	57
Figure 11. Forest plot for operative time – systemic or topical route.....	59
Figure 12. Forest plot for operative time – various surgery types	61
Figure 13. Forest plot for length of stay – systemic route.....	63
Figure 14. Funnel plot for intraoperative blood loss – systemic or topical route	64
Figure 15. Funnel plot for operative times – systemic or topical route	65

Abbreviations

MAP – mean arterial pressure

Bimax – bimaxillary osteotomy

BSSO – bilateral sagittal split osteotomy

RoB – risk of bias

JBI – Joanna Briggs Institute

PICO – population, intervention, control, outcome

TXA – tranexamic acid

EBH – evidence based healthcare

OS – orthognathic surgery

LA – local anaesthetic

RCT – randomised controlled trial

IOBL – intraoperative blood loss

LOS – length of stay

Hb – haemoglobin

Hct – haematocrit

ITT – intention to treat

PP – per protocol

NR – not reported

ASA – America Society of Anaesthesiologists Physical Status Classification System

OCP – oral contraceptive pill

BMI – body mass index

TMJ – temporomandibular joint

BP – blood pressure

LA – local anaesthetic

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree. I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time. I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Hooman Baghaie on 23/07/2023

Acknowledgements

I would like to express my sincere appreciation and deepest gratitude to the individuals who have played a vital role in making this thesis a reality:

First and foremost, I am immensely thankful to my dedicated supervisors, Professor Zachary Munn, Dr. Jennifer Stone, and Dr. Omar Breik, for their unwavering patience, invaluable advice, meticulous editing, and constant motivation. Their guidance and support have been instrumental in shaping this thesis into what it is today.

A special acknowledgment goes to my co-reviewer, Dr. Khilan Shukla, for readily assisting me with numerous requests and even enduring challenging deadlines. Your input has been immensely valuable to the final outcome.

I extend my gratitude to my colleagues, Professor Sakineh Hajebrahimi, Associate Professor Yuichiro Enoki, and Dr. Nariyoshi Miyata, for their kind assistance in translating non-English studies, which enriched the depth of my research.

I would like to thank Ms. Siew Siang Tay for her professional copyediting, adhering to the Australian Standards for Editing Practice (specifically sections D and E) in a timely manner. Your meticulous work ensured the clarity and accuracy of this thesis.

I am deeply indebted to my wife, Maya Morsico-Baghaie, for her unwavering support in every decision I've made. Her love, patience, and encouragement have been my driving force, and I dedicate all my achievements to her.

To my loving parents, Zia Baghaie and Beheshteh Baghaie, whose unwavering love and inspiration have been my pillar of strength since the beginning. Their wisdom and love continues to inspire me.

Gratitude goes to my sisters, Helya and Hasti Baghaie, for their constant support throughout my academic journey. Your encouragement and belief in me have been invaluable.

Last but not least, I am grateful to my son, Aurelius, and my daughter, Artemis, for their existence and sacrifice during this demanding period. Your love and support have meant the world to me, and I cherish every moment spent with you.

It is through the collective efforts and unwavering support of these exceptional individuals that this thesis has come to fruition. I am truly grateful for their presence in my life.

Executive summary

Background

Orthognathic surgery describes a group of surgical procedures primarily performed whereby one or both jaws are segmentalised via precise cuts (osteotomies) and then fixated in functionally and cosmetically ideal configurations. These elective procedures typically result in significant bleeding. The most widely studied pharmaceutical adjunct in reducing blood loss is tranexamic acid (TXA). Tranexamic acid is a synthetic amino acid that reversibly inhibits plasminogen activation, which in turn prevents the breakdown of microclots and reduces blood loss. It is widely used and validated in other surgical procedures to limit blood loss; however, its use is not yet a gold standard in orthognathic surgery.

Objectives

The primary goal of this thesis was to determine the role of prophylactic TXA use in minimising blood loss in orthognathic surgery. This was achieved by comparing the use of perioperative TXA (either topically or systemically) to no-treatment or a saline placebo in healthy patients undergoing a variety of orthognathic procedures. The primary outcomes of interest were the intraoperative volume of blood loss, perioperative changes in haematocrit or haemoglobin, and the postoperative need for blood transfusion. Secondary outcomes included operative time, duration of hospital stay, and any adverse effects reported from TXA administration.

Inclusion criteria

The inclusion criteria for this review were peer-reviewed randomised controlled trials published in any language over any date that utilised the correct population, intervention, control and outcome (PICO). The population of this review were healthy patients undergoing orthognathic surgery, defined as a minimum of LeFort I or bilateral sagittal split osteotomy of the maxilla or mandible, respectively. The intervention was use of TXA in any dose, route or regime with no treatment or saline as the control. The outcomes measured related to blood loss, either directly (intraoperative blood loss, change in haematocrit or haemoglobin, and need for perioperative blood transfusion) or indirectly (operative time, duration of stay and adverse effects).

Methods

Three electronic databases (PubMed, Embase and Cochrane Library) were searched from the date of database inception. Titles, abstracts and full-text papers were assessed against the inclusion criteria by two independent reviewers. Risk of bias was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool. Data was extracted independently by two reviewers. Meta-analysis was conducted for all outcomes, where appropriate, with weighted mean differences used for intraoperative blood loss, changes in haematocrit/haemoglobin levels, operation time, length of stay, transfusion rates and adverse outcomes. Certainty of the evidence was determined using the Grading of Recommendations, Assessment, Development and Evaluation approach.

Results

This review included 11 randomised controlled trials accounting for up to 406 participants from the experimental group and 398 controls. The results of the primary outcomes demonstrated that the use of TXA reduced intraoperative blood loss by a mean of 189.6 ml (95% CI -237.3, -141.9), and reduced postoperative drop in haematocrit by 1.7% (95% CI -2.6, -0.85) and in haemoglobin by 6.9 g/L (95% CI -9.6, -4.2). The use of TXA also reduced the absolute risk of postoperative blood transfusions by 2% (95% CI -0.05, 0.01), and reduced the duration of surgery by 8.9 minutes (95% CI -17.45, -0.31) and reduced length of stay by 0.3 days. The use of prophylactic TXA appeared most useful when it was given systemically, at a dosage of 20mg/kg when undergoing at least a LeFort I osteotomy. The secondary outcomes measured supported the use of TXA in reducing the overall operative time and length of hospital stay without increasing the risk of adverse effects. The operative time was decreased in cases of maxilla only or bimaxillary surgery but increased in mandible only surgery.

Conclusion

This systemic review and meta-analysis synthesise the current evidence on the use of prophylactic TXA in reducing blood loss in orthognathic surgery. The literature supports the benefits of prophylactic intraoperative use of TXA in reducing blood loss in orthognathic surgeries without increasing risk of adverse thromboembolic events.

CHAPTER 1: INTRODUCTION

Orthognathic surgery

Orthognathic surgery (OS) is a group of elective surgery for correcting dentomaxillofacial deformities. It entails performing intricate pre-planned mandibular and/or maxillary osteotomies and fixation of bony segments into ideal functional and cosmetic relationships. While the procedure is routinely performed in young patients without comorbidities, there is a growing indication for OS in the surgical management of obstructive sleep apnoea (1). An introduction to various orthognathic procedures is provided below.

Mandibular osteotomy

Descriptions of the first osteotomy of the lower jaw date back to Hullihen in 1849, however, it was in 1955 when Obwegeser described bilateral sagittal split osteotomy (BSSO), which, while slightly modified over the years, is still commonly practiced today (2). These osteotomies allow for three-dimensional repositioning of the mandible and maxilla in anteroposterior and superoinferior planes, with some movements across the horizontal plane. The osteotomies are performed on patients under general anaesthesia. The surgery involves exposure of the bone, performing the osteotomies, using the dental occlusion (bite) to determine the ideal three-dimensional positioning of the bone, and then fixating the osteotomy in the new position and finally closing the overlying soft tissues. The mandible is exposed by cutting through the mucosa down to the periosteum and retracting the oral mucosa and buccinator muscle in a subperiosteal plane. The attachment of the temporalis muscle is detached from the anterior aspect of the ramus. Utilising a variety of saws, a cut is made through the outer bony cortex extending from the lingula anteriorly to the anterior ramus, down the external oblique ridge, anteriorly to the first molar tooth and then inferiorly to the inferior border of the mandible. This cut is approximately 6-8 cm in length. The osteotomy is then propagated and formalised using a combination of chisel, mallet and bone spreaders. The same procedure is repeated on the other side (2, 3).

LeFort I osteotomy

In the maxillary LeFort I osteotomy, the bone is exposed in a similar fashion with an incision extending typically from the first molar to the contralateral first molar. The nasal mucosa from the floor and lateral nasal walls is elevated in a subperiosteal plane. Osteotomy is performed from the lateral nasal walls extending posteriorly to the posterior maxilla. The pterygoid plates are typically detached from the maxilla with a chisel and mallet, then the osteotomy is propagated and finalised through the nasal septum and lateral nasal walls, extending posteriorly to the descending palatine artery and vein. Finally, the maxilla is down-fractured and mobilised to ensure unhindered manipulation into its corrected location. In certain cases, the LeFort I osteotomy may be further divided into multiple segments to allow for more accurate correction of dentofacial deformities (2, 3).

Genioplasty

Augmentation or reduction of the bony chin (genioplasty) can sometimes be performed as a standalone procedure to alter the shape and position of the chin, or in combination with single or double jaw surgery to enhance the outcome. Anterior repositioning genioplasties can be used as a surgical treatment of obstructive sleep apnoea (4). Compared to other mandibular osteotomies, there is a much smaller potential for blood loss as there is a lesser degree of periosteal stripping, reduced exposure of cancellous bone and less risk of damage to blood vessels (2, 3).

Blood loss in orthognathic surgery

Historically, blood loss of up to 5000ml has been documented during orthognathic surgery(5). More recently, there are reports of mean intraoperative blood loss of approximately 800ml in both single and double jaw orthognathic surgery, with more than 40% of patients receiving postoperative blood transfusions (6). There are institutions that routinely collect multiple units of blood from patients preoperatively to use as an autologous transfusion (7).

There are several factors that contribute to excessive bleeding in orthognathic surgery. Firstly, the head and neck region is highly vascular, with the face receiving multiple tributaries from both internal and external carotid arteries. When gaining access to the bone to perform the

osteotomies, long 4-5cm incisions are made bilaterally in the mucosa. These wounds are the first contributors to blood loss. Secondly, the mandible receives its blood supply from the periosteum as well as the inferior alveolar artery which travels inside the inferior alveolar canal. This is situated within the ramus and body of the mandible. Damage to the inferior alveolar artery and vein is possible during osteotomy and mobilisation of the mandible. There are cases of traumatic pseudoaneurysms reported in the literature (8). Similarly, the osteotomies invariably expose the relatively vascular cancellous bone which leads to a slow continuous ooze of blood. Finally, there are various other vessels (pterygoid plexus of veins, maxillary and lingual artery) which may be inadvertently damaged intraoperatively.

Arguably maxillary osteotomy has the greatest potential for blood loss. When a similar sized mucosal incision is made, there is significantly more periosteal stripping required for a LeFort I osteotomy. Extensive bleeding is first encountered when mobilising the nasal mucosa, and again when performing maxillary osteotomies within very close proximity to the descending palatine vessels. If one side of the osteotomy iatrogenically damages any of the deep vessels in the midface, the haemorrhage cannot be locally managed until the contralateral osteotomy is completed and the maxilla is down-fractured. Similarly, in cases requiring segmentalisation of the maxilla, there are extensive regions of cancellous bone that contribute to a slow but constant ooze of blood.

Haemorrhage minimisation

Over the years, various tools and techniques have been trialled in minimising blood loss encountered during orthognathic surgery. These can be categorised as: surgical techniques and adjuncts, physiological modifications, or pharmaceutical adjuncts.

Surgical techniques have changed over the past decades. Dal Pont (9), Hunsuck (10) and Epker (11) proposed well-accepted modifications that make mandibular osteotomies more predictable and efficient that ultimately lead to reduced operative time and blood loss. Similarly, piezoelectric devices have been used to perform osteotomies with reduced risk of damage to the neurovascular bundles in the operative field. The challenge of using such

instruments lies in their expense, reduced availability and lower cutting efficiency, significantly increasing the duration of the operation (12).

Physiological modifications include the optimisation of patient haemodynamics perioperatively. This process starts with identifying and treating sources of anaemia preoperatively, withdrawing and storing a patient's own blood to use as an autologous blood transfusion, or diluting the patient's blood with fluids so as to reduce the concentration of haemoglobin lost intraoperatively. The most widely documented and accepted physiological modification is the intentional use of hypotensive anaesthesia while performing the osteotomies. Hypotensive anaesthesia has been defined in many different ways, ranging from a systolic blood pressure of 60-80% of that of preoperative blood pressure to aiming for a mean arterial pressure of 65-75mmHg (13-17). Finally, a commonly accepted and easy physiological modification is the placement of the patient's head in a reverse Trendelenburg position or in an upward position by 15 degrees to facilitate the venous drainage in the head and neck and reducing intraoperative blood loss when operating in the head and neck region (18, 19).

Pharmaceutical adjuncts include the use of adrenaline containing local anaesthetics to create vasoconstriction and to reduce blood loss from the superficial soft tissues. The most commonly used pharmaceutical adjunct is tranexamic acid (TXA). Tranexamic acid is a synthetic analogue of the amino acid lysine that exerts its antifibrinolytic effects by reversibly inhibiting the activation of plasminogen. By attaching to the lysine-binding sites on plasminogen, plasminogen cannot adhere to the fibrin clot and is thus less locally available to be activated by tissue-type plasminogen activators. As such, there is less activated plasminogen (plasmin) and less susceptibility to clot breakdown and ultimately reduced bleeding. There is some evidence that TXA may also offer anti-inflammatory properties by indirectly inhibiting plasmin-mediated activation of complements, monocytes and neutrophils (20). The clinical effect of TXA is well documented and meta-analyses have shown that TXA decreases overall intraoperative blood loss by up to 30% across various surgeries, including cardiothoracic, orthopaedic, obstetrics and gynaecology, as well as in general and maxillofacial trauma, and prolonged complex surgeries (21-24).

However the literature notes some concerns about the theoretical increased risk of thromboembolism from the use of TXA in oral and maxillofacial surgery. There has been one reported case of a 21-year-old female who developed deep vein thrombosis seven days after undergoing bimaxillary orthognathic surgery and received 500mg of TXA intravenously intraoperatively. Her BMI was 24.6, and she was otherwise healthy, apart from taking regular mefenamic acid for menorrhagia (25). Mefenamic acid is a non-steroidal anti-inflammatory medication that is a non-selective cyclooxygenase inhibitor. It is associated with increased risk of thromboembolic events (26). The authors attributed the deep vein thrombosis to the concurrent use of TXA and mefenamic acid. Nevertheless, a recent systematic review and meta-analysis conducted by Taeuber et al. (27), which included 216 randomised controlled trials and 125 550 patients, found that intravenous TXA, irrespective of dosing, was not associated with increased risk of any thromboembolic events. Of note, there were six trials (13, 14, 28-31) pertaining to maxillofacial surgery, none of which reported any thromboembolic events.

Overview of evidence synthesis

Based on the work of Guyatt in 1991, evidence-based healthcare (EBH) has been defined as clinical decision making that considers the feasibility, appropriateness, meaningfulness and effectiveness of healthcare practices, informed by the best available evidence, the context in which care is delivered, the individual patient, and the professional judgement and expertise of the health professional (32). Evidence-based healthcare marks a transition from anecdotal guided practice of healthcare towards a critical analysis of the evidence and the utilisation of such evidence to steer engagement and decision making with patients. One challenge that EBH faces is the enormity and exponentially increasing volume of published content that practitioners must navigate in order to make clinical decisions. The capacity for an individual or group of practitioners to summarise current best evidence is limited by the significant clinical and administrative demands many health professionals face.

In this context, the expanding role and relevance of reviews of the literature are apparent. Systematic reviews are a structured approach to summarising and synthesising existing knowledge relevant to a particular question. They began to appear in the literature in the

1970s and 1980s (33) and often included a meta-analysis. Meta-analysis is the quantitative synthesis of primary data to yield an overall summary statistic. Systematic reviews aim to minimise bias through following pre-defined processes and structured, explicit methods, thereby allowing practitioners to utilise their findings in a reliable and meaningful way (34). Ultimately, systematic reviews are the gold standard to search for, collate, critique and summarise the best available evidence regarding a clinical question. The quality of a systematic review is dependent on the minimisation of risk and error during the review process; this includes the methods used to conduct the review, analyse the data and assess the quality of the studies included (34). Thus, a well-conducted systematic review and meta-analysis of randomised controlled trials is the highest level of evidence available to practitioners on the effectiveness of an intervention.

In light of the rapid expansion of the published literature, with at times, varying quality of work, several systematic approaches to reporting and reviewing have been developed. These include the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) tool and the Consolidated Standards of Reporting Trials (CONSORT) checklist for reporting randomised controlled trials (35, 36). Transparent standards allow for clear reporting on the methodological conduct and results of a review. Methodological guidance also exists which support best practice in the conduct of these reviews (34, 37).

JBIs (formerly the Joanna Briggs Institute) approach to evidence-based practice is centred around clinical decision making that is informed by the best available evidence, delivered in a contextually and culturally appropriate manner, considers the preferences of the healthcare consumer, and accounts for the judgement of the health professional (38). Evidence-based practice is an iterative process that progresses through the generation, synthesis, transfer and utilisation of the evidence, to ultimately impacting health practices and outcomes globally (32). Evidence synthesis is the evaluation or analysis of research evidence and opinion on a specific topic to aid in decision making in healthcare. In the JBI model, the outputs of evidence synthesis are guidelines, evidence summaries and systematic reviews. As there are currently no up-to-date systematic reviews that assess TXA in orthognathic surgery, we aimed to address this gap in order to contribute to informed decision making in practice and to create evidence-based guidance for clinicians.

Review question

The review question was: what is the role of prophylactic TXA (both systemic or topical) in reducing blood loss in orthognathic surgery in healthy patients?

The population in mind was healthy patients, defined as those without coagulopathies, undergoing orthognathic surgery, defined as a minimum of BSSO or LeFort I osteotomy. The intervention was pre- or intraoperative use of TXA either topically or systemically at any dosage. The control was isotonic solution or no treatment. The outcomes of concern were volume of intraoperative blood loss, change of haematocrit, change of haemoglobin, need for blood transfusion, operative time, duration of hospital stay and any reported adverse (thromboembolic) effect.

As this was a review on the effectiveness of TXA, a quantitative systematic review design and meta-analysis was chosen to answer the review question. The review question was developed using the JBI (formerly called the Joanna Briggs Institute) Manual for Evidence Synthesis (34) and defended through a peer research panel. The protocol was formulated, peer-reviewed and published prior to commencement of the review (39).

Current literature

Amongst the literature, the latest review (40) on this topic assessed the role of TXA in reducing blood loss in craniomaxillofacial surgeries. Fu et al. included 16 studies, 12 of which were randomised controlled trials; one was a clinical trial and three were retrospective studies. Among the 958 included patients, 257 underwent craniofacial surgeries (125 in the TXA group and 132 in the placebo group) and 701 underwent maxillary surgeries (374 in the TXA group and 327 in the placebo group). Despite pooling results from a very heterogenous group of studies, their meta-analysis revealed that, compared with the placebo group, the TXA group showed a significant reduction in intraoperative blood loss of 139.81 mL (95% CI: -179.66 to -99.96 mL; $p < 0.01$), a shortening of the 'maxillary surgery' duration of 15.48 min (95% CI: -

21.03 to -9.92 min; $p < 0.01$), an elevation of the postoperative haemoglobin level of 7.4 mg/L (95% CI: 4.2 to 10.7 mg/L; $p < 0.01$), and a limited effect on increasing the postoperative haematocrit level of 1.77% (95% CI: 0.17 to 3.36; $p = 0.03$). However much of their analyses suffered from very significant heterogeneity ($I^2 > 95\%$).

Their review also had other limitations which necessitated this current review. The first issue pertained to the external validity of their results. Craniofacial operations, such as repair of cranial synostosis, are rare, technically and anatomically complex, and typically performed in paediatric patients with syndromal/genetic abnormalities. The results of these studies were not comparable to populations of older, healthy patients that typically undergo orthognathic surgery. Fu et al. included patients as young as two months of age in whom the total blood volume would likely be less than the intraoperative blood loss volume of an adult.

The second issue pertained to their data-analysis. In assessing the raw data analysed by Fu et al., it was found that they appeared to have inadvertently 'double-counted' by including the same cohort of patients across different studies. Firstly, they included data from Christabel 2014 and 2016. The data presented in Christabel 2014 was re-reported in their 2016 paper and as such only the data from 2016 should have been included. Similarly, Apipan, Rummasak and Narainthonsaene presented a sample of 60 experimental (20 with 10mg/kg of TXA, 20 with 15mg/kg and 20 with 20mg/kg) and a control group of 20 participants. Pooling data from all three experimental groups necessitated triplication of data from the control group and thus double-(triple)-counting. Finally, their subgroup analyses were limited to various dosages of TXA and not based on the surgeries performed.

Zhao et al. conducted a similar systematic review and meta-analysis in 2018 looking at role of prophylactic TXA in orthognathic surgery (41). Their review had similar findings to Fu et al., however that review is now several years old, and there have since been multiple novel randomised controlled trials published on this topic (16, 42). Similarly, their search was limited to publications in English.

It is assumed that the current review will build on the findings of previous reviews by providing a comprehensive review of the updated literature in assessing the role of prophylactic TXA in reducing blood loss in healthy patients undergoing orthognathic surgery.

CHAPTER 2: SYSTEMATIC REVIEW PROTOCOL

This systematic review was conducted according to the JBI methods for performing systematic reviews and meta-analysis. The systematic review protocol was prepared and defended through a panel of experts in the fields of research methodology and head and neck surgery. It was subsequently peer reviewed and published in a peer-reviewed journal, *JBI Evidence Synthesis* (39).

Objectives and statement of review question

The objective of this review was to evaluate the effectiveness of perioperative prophylactic tranexamic acid use in prevention of blood loss in orthognathic surgery in healthy patients.

The review question is as follows:

What is the effectiveness of prophylactic tranexamic acid versus placebo, usual care, or no intervention on blood loss in healthy patients receiving orthognathic surgery?

Inclusion criteria

Types of studies

This review considered randomised controlled trials and pseudo-randomised controlled trials, defined as those which used a systematic but non-random allocation method.

Types of participants

This review considered trials comparing TXA use (topical or systemic) to appropriate controls (placebo or no intervention). The population was healthy patients (15-70 years) and excluded those with pre-existing coagulopathies or taking anticoagulant/antiplatelet medications. This is because the benefits of TXA in patients with pre-existing coagulopathies or those on Vitamin K antagonists have already been reviewed (43, 44). Furthermore, orthognathic surgery is typically performed in healthy patients who do not present with these bleeding risk factors.

Orthognathic surgery was defined as a minimum of Le Fort I maxillary osteotomies or variations of bilateral mandibular ramus osteotomies. These osteotomies were used as a cut off for two reasons: [1] they are the two most common types of osteotomies performed in

orthognathic surgery; and [2] the inclusion of simpler osteotomies such as isolated genioplasty would be clinically inappropriate as they are less surgically complex and are quicker to perform. This could lead to underestimation of the true effect of TXA in orthognathic surgery. Studies including concurrent or additional surgeries were excluded. Invariably, the orthognathic surgery procedure is performed in the operating theatre setting under general anaesthetic. The procedure may be performed by surgeons of all levels of experience and surgical specialty. Surgeons with all levels of experience and studies from all countries will be included.

Types of interventions

This review considered studies that evaluated the use of TXA. While typically the intravenous dose was 10-20mg/kg and the topical dosage was 50mg/ml; there were no restrictions on the dosage used. Similarly, if a dosage was given around induction of anaesthesia or intraoperatively, there were no limitations regarding the specific timing or frequency of TXA administration.

Comparators

This review considered studies that compared the intervention to appropriate passive controls. This was in the form of a saline placebo or no treatment or usual care.

Types of outcome measures

This review considered studies that included the following primary outcomes:

- [1] Intraoperative blood loss, defined as the volume of bleeding during the surgical procedure. Typically, this is calculated by combining the amount of blood in the surgical suction canisters (after subtracting the estimated volume of irrigation fluid used in the operation) as well as the blood in the surgical sponges (dry weight subtracted from soaked weight, assuming specific gravity of 1.0, 1g of blood equates to 1ml of same). This direct outcome was considered an objective and clinically important outcome.
- [2] Haematocrit is the percentage volume of erythrocytes in whole blood. The change in haematocrit is typically calculated by subtracting the postoperative levels from

preoperative ones. It was accepted that the specific timing of measurements would vary among studies. Provided the timing was consistent among each arm within the study, any postoperative measurement within the first 24 hours was accepted and pooled.

- [3] Haemoglobin is the oxygen carrying molecule in erythrocytes. Haemoglobin concentration is the mass of haemoglobin in whole blood and is represented as grams per litre (g/L). Changes in haemoglobin are calculated in the same way and in the same time frame as haematocrit. There is no clinically significant difference between haematocrit and haemoglobin as both measure the amount of red blood cells in the whole blood and both are affected by the patients level of hydration (45). This is especially true if the outcome is the *change* in one of the parameters. In this review, both outcomes were reported as it was likely that some studies would report one index and not the other.
- [4] Another outcome of note was the need for blood transfusions. The indications and cut off for blood transfusion are different in most institutions. Nonetheless, each institution has their own transfusion protocol, which was presumably consistently applied to both arms of each study. Any blood transfusion given intra- or postoperatively during the surgical admission was considered and included.

The secondary outcomes considered in this review are as follows:

- [5] Operative time is typically calculated as from the time of first incision to the end of skin closure. Operative time is an indirect measurement of blood loss. Intraoperative bleeding prolongs the procedure by reducing visibility in the surgical field. Similarly, more time is needed to establish haemostasis at each surgical step. This outcome was included as an objective outcome that was clinically and economically important.
- [6] The duration of hospital stay is another clinically and economically important outcome that was sought. Both the amount of intraoperative blood loss as well as the duration of operation are statistically associated with a prolonged length of hospital stay (46). Finally receiving blood transfusions prolongs the duration of stay due to the need for post-transfusion monitoring and repeat blood tests.
- [7] Finally, adverse reactions are undesired effects that can be attributed to the use of TXA. Each study was assessed for any adverse reactions reported. Theoretically, TXA

can increase the risk of pathological thrombi and emboli formation. Similarly, the risk of hypersensitivity or anaphylaxis exists with any medication that is given to a patient.

Review methods

Search strategy

The systematic review was conducted in accordance with the JBI methodology for systematic reviews of effectiveness evidence (34). The review protocol was registered in PROSPERO (CRD42022314403). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020)(35) was used to guide the reporting of this review. The protocol was published in a peer-reviewed journal prior to conducting the review (39).

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilised in this review. An initial limited search (Appendix 1) of PubMed was undertaken followed by an analysis of the text words contained in the title and abstract, and index terms used to describe the relevant articles. A second search using all identified keywords and index terms was then undertaken across the three included databases (PubMed example in Appendix 2). Thirdly, the reference lists of all identified reports that underwent risk of bias assessment were searched for additional studies that may have been missed.

The databases searched included PubMed, Embase and Cochrane library (including CENTRAL) as these were the most important and relevant databases for this type of review (47). Each database was screened from the date of its inception.

Studies published in languages other than English were included in the screening. Where the title or abstract was not in English, they were translated into English via an online automated translation service (<https://translate.google.com/>). The full texts of appropriate studies were retrieved and translated with the aid of scientific translators. Finally, using appropriate keywords, the World Health Organization International Clinical Trial Registry Platform and the Clinicaltrials.gov database were searched for unpublished trials. The authors of any proposed or protocolled projects were contacted for further information, however results that were

not yet published in peer-reviewed publications were not included in this review. Such studies were referenced as upcoming trials for future reviews.

Assessment of methodological quality/critical appraisal

Eligible studies were critically appraised independently by two reviewers at the study and where appropriate the outcome level for risk of bias using the Risk of Bias 2.0 (RoB) tool from Cochrane Collaboration (37). Where required, authors of papers were contacted to request missing or additional data for clarification. Any disagreements between the reviewers were resolved through discussion. The results of risk of bias assessment are reported in the 'Results' section. All studies, regardless of their risk of bias, underwent data extraction and synthesis (where possible). The results of risk of bias assessment were used to inform the analysis and interpretation of the results of the individual studies and this review.

Data extraction

Data was extracted from studies included in the review by two independent reviewers using Covidence (Veritas Health Innovation, Melbourne, Australia). The data extracted included study details, participant characteristics, intervention and control details, outcome details and data, and conclusions from the study. The template used for data extraction in Covidence was trialled on several studies meeting the inclusion criteria and, after modification, was applied independently by the reviewers to the included studies (Appendix 3). The information extracted was compared between the two reviewers and any disagreements were resolved through discussion. Where information was missing, authors were contacted and if information was unavailable, a decision was made between the two reviewers whether to exclude the data. If an agreement could not be reached, a third reviewer's input was sought. The use of a third mediatory reviewer was not required in this review.

Data synthesis

Where feasible, individual study estimates were pooled in a meta-analysis using RevMan 5.4 (Copenhagen: The Nordic Cochrane Centre, Cochrane) and presented in forest plots. Effect estimates were expressed as weighted (or standardised) final post-intervention mean differences and standard deviation (for continuous) or relative risk (for dichotomous data)

with 95% confidence intervals. For continuous data that was collected using the same scale, the weighted mean differences were used. For data collected using different scales, the standardised mean difference was calculated. If the standard deviation was not reported, the authors were contacted for further information. In cases where this information could not be retrieved, it was calculated using the guidance in the Cochrane Handbook for Systematic Reviews of Interventions (37). Where it was not possible to calculate an approximate standard deviation, the highest standard deviation of the other studies included in the meta-analysis was imputed in place of the missing data. If there was suspicion that there were multiple publications for the same patient cohort, authors were contacted for clarification. In these cases, the publication with the larger sample size was included and the other excluded. The data was analysed using a random effects model (48). Subgroup analyses were conducted where there was sufficient data to investigate the effect of various dosage, various routes of administration and extent of orthognathic surgery. Sensitivity analyses were conducted to test the assumptions underpinning the meta-analysis, such as applying both random- and fixed-effect meta-analysis models, and strategies used for determining/imputing missing data. Heterogeneity was assessed via visual inspection of the forest plots and statistically via the standard χ^2 and I^2 value.

Where there were ten or more studies included in a meta-analysis, a funnel plot was generated in RevMan to assess publication bias. Statistical tests for funnel plot asymmetry (Egger test) were not performed as there was adequate visual symmetry. Where meta-analysis was not possible, the findings were presented in narrative form including tables and figures to aid in data presentation.

Deviations from the protocol

There were a few instances where deviations from the protocol took place. They pertained to estimation of standard deviations in studies that failed to provide this figure. Attempts were made to contact the authors in the first instance for clarification. After receiving no response, guidance was sought from The Cochrane Handbook for Systematic Reviews of Interventions (7.7.3.3). Obtaining standard deviations from standard errors, confidence

intervals, t values and p values for differences in means (37) was used to estimate such figures.

CHAPTER 3: RESULTS

Description of studies

After searching the three databases on 17/04/2022, a total of 259 references were imported into Endnote for screening. There were an additional six references located from a search of various trial registries, making a total of 265 references. Three references were removed due to being duplicates, leaving 262 studies to be screened against title and abstract. After independent screening, 230 studies were deemed as irrelevant and excluded, leaving 32 studies meeting full-text screening eligibility. Sixteen studies were excluded for the following reasons: 11 due to wrong study design (6, 7, 49-57), two due to wrong patient group (58, 59), one due to use of duplicate data (60), one due to wrong intervention (61) and one due to reporting of wrong outcomes (62). A further five references belonged to trial protocols and were excluded. Three references (63-65) were already published studies (7, 17, 66); one trial was withdrawn due to lack of funding (67) and one had been abandoned (68). The contact person for the abandoned protocol was contacted multiple times to clarify their intent, however no response was received. Ultimately 11 studies were included for data extraction (13-17, 30, 42, 63, 69-71). Study inclusion is summarised in the PRISMA flowchart in Appendix 3. The references of excluded full text studies are available in Appendix 4.

To maintain a contemporaneous search, all three databases were searched again on 01/05/2023 using the previous key terms and selection criteria for any additional references. There were only three relevant references found. One was the protocol for this review, and the other two were protocol registrations for new randomised controlled trial protocols of studies which were yet to start recruitment (72, 73).

From the included studies, nine were based in Asia (Iran (66, 70, 71), India (15, 30, 42), Thailand (13, 69) and Hong Kong (14)), and the remaining two from Europe [Denmark (17) and France (16)]. Most studies were published in oral and maxillofacial surgery journals (13-17, 30, 42, 66). One study was published in an anaesthesia journal (70), and another in a medical sciences journal (71). All but one of the included studies were in English (71). Duration of patient recruitment was reported for seven studies (13, 14, 17, 66, 70, 71, 74) and ranged from five to 27 months. There were no possible conflicts of interest reported for six studies

(13, 15-17, 30, 74) and the remaining studies failed to mention any information on conflicts of interest. With regards to sources of funding, only four studies (13, 15, 16, 30) reported no source of funding while the remaining studies failed to give any information.

All studies had a randomised controlled trial study design. Sample sizes were generally small and ranged from 18 to 74 participants. Nine studies examined the effects of systemic TXA use (13-17, 30, 70, 71, 74) and two used topical TXA (66, 69). With regards to surgical experience, where reported, the surgery was done by either a single surgeon (16, 70), an 'experienced surgical team' (13, 17, 30), surgeons of 'similar experience level' (15) or senior surgical trainees (14). Where outcomes were presented for each type of surgery, studies included single jaw [mandibular (14), maxillary (14, 15)] or Bimax surgery (13, 14, 17, 30, 70, 71). A wide range of anaesthetic agents were used for induction and maintenance of anaesthesia. Where information on the anaesthesia was available, most studies reported the use of local anaesthetics with vasoconstrictor agents (15-17, 30, 70), all but two studies reported positioning the head up to reduce venous blood loss (42, 70); all studies aimed to use hypotensive anaesthesia (MAP of <75 or >20% below the preoperative baseline). With respect to outcomes reported, intraoperative blood loss was reported by all, operative time was the second most commonly reported outcome (13-17, 30, 42, 66, 69, 70), followed by rate of transfusion (13-16, 30, 66, 70); changes in haematocrit (13-15, 69); change in haemoglobin (14-16, 71) and length of stay (13, 14, 70). Incidence of adverse effects were reported in all included studies. The characteristics of the included studies are presented in Table 1.

Table 1. Characteristics of included studies

Study ID	Overall RoB score	Country in which the study was conducted	Study design	Start date	End date	Reported funding, conflict of interest	Eligibility criteria	Experiment details	Sample size	Surgeon experience	Surgery type	Anaesthesia type	Outcomes reported	Notes
Apipan, Rummasak and Narainthonsaene 2018 (13)	Low	Thailand	RCT	2012	2014	None, none	Inclusion: patients aged 18-35 years with ASA of I Exclusion: known allergy to TXA, at risk of thromboembolism (OCP), BMI>30, segmental Le Fort I, additional procedure (e.g. genioplasty, angle reduction)	Experimental group 1: single dose of TXA of 10 mg/kg in 100ml 0.9% Saline over 30 mins after the induction of anaesthesia Experimental group 2: single dose of TXA of 15 mg/kg in 100ml 0.9% saline over 30 mins after the induction of anaesthesia Experimental group 3: single dose of TXA of 20 mg/kg in 100ml 0.9% saline over 30 mins after the induction of anaesthesia. Control group: 100ml 0.9% saline over 30 mins after the induction of anaesthesia	Group control: 20 Group 10 mg/kg: 20 Group 15 mg/kg: 20 Group 20 mg/kg: 20	Experienced (>200 cases and >5 years' experience) or inexperienced surgeons	Bimax.	Induction: midazolam, fentanyl, propofol and cisatracurium. Maintenance: nitrous oxide, cisatracurium, fentanyl and sevoflurane. BP: MAP 65-75 mmHg LA: NR Positioning: head 15 degrees up	Blood loss Change in Hct Operative time Transfusion Hospital stay	
Choi, Irwin and Samman 2009 (14)	Some concerns	Hong Kong	RCT	2005	2008	NR, NR	Inclusion: patients aged 16-40 years with ASA of I undergoing bimaxillary osteotomy	Experimental group: 20 mg/kg TXA in 20ml 0.9% saline infused over 15	Group control: 29 Group TXA: 32	Multiple surgeons or senior trainees	Maxillary surgery: -Le Fort I with or without segmentalisation; -Anterior maxillary (Wunderer)	Induction: propofol + remifentanyl + rocuronium Maintenance: isoflurane	Blood loss Change in Hb Change in Hct Operative	

							Exclusion: bone diseases, craniofacial syndromes, other simultaneous non-orthognathic surgeries	minutes during induction Control group: 20 ml 0.9% saline at same regime			osteotomy; -Posterior maxillary (Schuchardt) osteotomy; or -Le Fort I maxillary distraction. Mandibular surgery: -Anterior subapical (Hofer) osteotomy; -Body (Step) osteotomy; -Sagittal split ramus osteotomy; -Vertical subigmoid osteotomy; -Genioplasty; or -Mandibular body osteotomy and distraction.	and remifentanil BP: BP maintained at 25% to 30% below the mean preoperative level by incremental doses of labetalol and/or metoprolol LA: NR Positioning: head up 15 degrees	time Transfusion Hospital stay	
Christabel 2016 (15)	Low	India	RCT	NR	NR	None, none	Inclusion: patients aged 18-35 years with ASA of I undergoing Le Fort I Exclusion: cleft lip and palate, syndromic deformities, pregnancy or lactation, medication that could alter bleeding, coagulopathies, allergy to TXA, intraoperative MAP >70 mmHg	Experimental group: 10mg/kg TXA infusion commenced 30 mins prior to induction and ceased at closure (rate NR) Control group: 0.9% saline at same regime	Group 1: saline + disjunction: 50 Group 2: saline + tuberosity: 50 Group 3: TXA + disjunction: 50 Group 4: TXA + tuberosity: 50	Three consultant surgeons with similar experience in performing orthognathic surgery	Isolated Le Fort I non-segmented osteotomies.	Induction: thiopental, fentanyl and vecuronium Maintenance: isoflurane, fentanyl and vecuronium BP: MAP 60-70 LA: 2% lignocaine with 1:80,000 adrenaline, Positioning: 15 degrees head up	Blood loss Operating time Change in Hb Transfusion	Includes participants of Christabel 2014 (60) Reported quality of surgical field
Eftekharian 2015 (66)	Some concerns	Iran	RCT	2011	2013	NR, NR	Inclusion: patients with ASA of I, requiring bimaxillary osteotomy Exclusion: coagulopathy, anticoagulant use or additional non-	Experimental group: 1g of TXA in 1020mL of 0.9% saline (0.098% TXA) for tissue irrigation Control group:	Group control: 28 Group TXA: 28	Multiple surgeons, level of experience NR	Bimax	Induction: propofol, fentanyl Maintenance: propofol, remifentanil, atracurium BP: MAP 30% less than	Blood loss Operating time Transfusion	

							orthognathic procedures	0.9% saline for tissue irrigation				patient's normal MAP LA: NR Positioning: NR		
Jozefowicz 2021 (16)	Low	France	RCT	NR	NR	None, none	Inclusion: patients undergoing a Le Fort I or bimaxillary osteotomies with a haemoglobin >120mg/L and ASA of I-II Exclusion: haemostasis disorders, anticoagulant or antiplatelet therapy, history of severe renal failure, seizures, or recent thromboembolic events	Experimental group: 1g of TXA in 30ml 0.9% saline over 30 mins during induction then 1g over 8 hours Control group: 0.9% saline at same regime	Group control: 73 Group TXA: 74 (intention to treat analysis)	Single senior surgeon	Le Fort I or Bimax 14:58 in experimental group and 10:58 in control group.	Induction: NR Maintenance: NR BP: MAP 65-75 mmHg LA: 5-10ml 1% lidocaine + adrenaline Positioning: supine position with head lift	Blood loss Operating time Change in Hb Transfusion	Reported rate of blood loss >1.2L
Kaewpradub 2011 (69)	Low	Thailand	RCT	NR	NR	NR, NR	Inclusion: patients with ASA of I undergoing bimaxillary osteotomy Exclusion: anticoagulants	Experimental group: irrigation with TXA solution 500 mg (10 mL) into 1000mL 0.9% saline Control group: 10 mL of 0.9% saline into 1000mL 0.9% saline	Group control: 20 Group TXA: 20	NR	Le Fort I + BSSO predominantly (75%) +/- genioplasty +/- multi-segmental maxillary osteotomy.	Induction: propofol, fentanyl and pancuronium. Maintenance: nitrous oxide in oxygen, sevoflurane, fentanyl, and pancuronium. LA: NR BP: MAP 65-75 mmHg. Positioning: head up 15 degrees.	Blood loss Operating time Change in Hct	
Karimi 2012 (70)	Low	Iran	RCT	2010	2011	NR, NR	Inclusion: patients aged 18-40 years with ASA of I, undergoing bimaxillary osteotomy Exclusion: uncontrolled	Experimental group: 20 mg/kg of TXA intravenously just before induction of anaesthesia Control group:	Group control: 16 Group TXA: 16	Single surgeon	Bimaxillary osteotomy (87.4% or 28), remainder also had genioplasty (4).	Induction: thiopental, atracurium and lidocaine. Maintenance: isoflurane and nitrous oxide.	Blood loss Operating time Transfusion Hospital stay	

							systemic diseases, anticoagulant consumption, simultaneous non-orthognathic surgery (TMJ, craniofacial, autologous bone graft) or bony diseases	0.9% saline at same regime				BP: MAP 20% below normal LA: adrenaline to surgical site. Positioning: NR		
Mortazavi 2016 (71)	High	Iran	RCT	2009	2010	NR, NR	Inclusion: patients with ASA of I undergoing bimaxillary osteotomy Exclusion: Le Fort II, III or genioplasty, bone-related diseases, cleft lips or palates, craniofacial syndromes, concurrent TMJ surgery, bone marrow transplant recipients	Experimental group: 20 mg/kg TXA administered intravenously just before induction of anaesthesia Control group: 0.9% saline at same regime	Group control: 24 Group TXA: 24	NR	Bimax	Induction: NR Maintenance: NR BP: normotensive to hypotensive (MAP 65-75 mmHg) LA: NR Positioning: head 15 degrees up	Blood loss (estimate)	Translated into English
Sankar 2012 (30)	Low	India	RCT	NR	NR	None, none	Inclusion: patients aged 17-30 years with ASA of I Exclusion: bone diseases, cleft lip and palate, craniofacial syndromes, patients requiring palatal expansion surgery, distraction osteogenesis, simultaneous rhinoplasty, genioplasty, bone graft or implant placement and endoscopically assisted surgeries	Experimental group: 10mg/kg of TXA infused over 20 mins before incision then 1mg/kg at every hour for the duration of surgery Control group: saline at the same regime	Group control: 25 Group TXA: 25	Same experienced surgical team	Maxillary procedures included: anterior maxillary osteotomy; Le Fort I osteotomy with or without anterior maxillary osteotomy. Mandibular procedures included: BSSO; anterior subapical osteotomy; and genioplasty.	Induction: thiopentone sodium and succinyl choline Maintenance: N2O and O2 (60:40 ratio), 0.5% halothane, vecuronium, midazolam and fentanyl. BP: MAP 70-75 until fixation of osteotomy LA: 5ml 2% lignocaine with 1:80000 adrenaline Positioning:	Blood loss Operating time Transfusion	Reported quality of surgical field

												head up 15 degrees		
Secher 2018 (17)	Some concerns	Denmark	RCT	2014	2016	None, none	Inclusion: patients aged above 18 years, undergoing bimaxillary osteotomy Exclusion: pregnancy, history of thromboembolism, cramps, diabetes, connective tissue disorders, cancers, known allergy to TXA, ocular complications, kidney deficiency, or intake of omega-3 fatty acids, garlic, ginseng, and ginkgo biloba up to 10 days preoperatively	Experimental group: 1g TXA or saline given at time of induction Control group: 0.9% saline given at equivalent time	Group control: 45 Group TXA: 51	One of two experienced specialist surgeons.	Bimax single vs segmented maxilla: TXA group 45/6 and control 42/3	Induction: sufentanil, propofol, remifentanil Maintenance: remifentanil, sufentanil, desflurane BP: MAP 60 LA: bupivacaine hydrochloride and 0.5% adrenaline at start Positioning: head 30 degree up	Blood loss Operative time	Both arms received subcutaneous heparin preop
Sharma 2020 (74)	Some concerns	India	RCT	2018	2019	None, none	Inclusion: patients aged 15-60 years, with ASA I or II, undergoing Le Fort I and/or BSSO Exclusion: simultaneous rhinoplasty, coagulopathy, allergy to TXA, abnormal liver/renal function, pregnancy or lactation	Experimental group: intravenous 15mg/kg TXA infusion over 10 mins during induction + 0.25-0.7 microg/kg/hr of dexomethodine during maintenance Control group: intravenous saline infusion over 10 mins during induction + 0.25-0.7 microg/kg/hr of dexomethodine during maintenance	Group control: 18 Group TXA: 18	NR	12/36 patients undergoing Le Fort I osteotomy, 11/36 patients undergoing BSSO, and 13/36 patients undergoing both Le Fort I and BSSO	Induction: morphine, propofol, vecuronium Maintenance: Isoflurane and nitrous oxide +/- Esmolol (to reduce MAP if needed) BP: MAP 55-70 mmHg LA: NR Positioning: NR	Blood loss (estimate) Operative time	

NR: not reported; ASA: American Society of Anaesthesiologists Physical Status Classification System; TXA: tranexamic acid; OCP: oral contraceptive pill; BMI: body mass index; MAP: mean arterial pressure; TMJ: temporomandibular joint; BSSO: bilateral sagittal split osteotomy; BP: blood pressure; LA: local anaesthetic; Hct: haematocrit

Methodological quality

There was a mixed overall quality of studies based on RoB 2.0 (Figure 1). The majority of studies had a low overall risk of bias (13, 15, 16, 30, 42, 69, 70), there were three studies with some risk of bias concerns (14, 17, 66) and there was one study with a high risk of bias (71). It should be noted that the study with high risk of bias was published originally in Farsi and was translated into English by medical translators.

At the study level, with regards to domain 1, Randomisation Process, all but one study (66) had low risk of bias. Where clearly reported, randomisation was achieved via computer generated numbers in five studies (13, 14, 16, 30, 70) and by the block method in two studies (15, 17).

Assessed at a study level, with respect to domain 2, the only deviation from the intended intervention was found in one study (16) where one of the control patients had a significant intraoperative bleed, had their allocation revealed and received the experimental drug. Because of this deviation, the risk of bias was elevated. With regards to domain 3, Missing Outcome Data, there were some concerns with two studies. The missing data was across all outcomes. Choi, Irwin and Samman reported exclusion of 15% (6/39) of their experimental participants and 7% (3/39) of controls due to missing data. Similarly, in the study by Secher et al. (17), seven participants dropped out from the control group but only one did from the experimental group. However, given that the allocation of participants was hidden from the investigators in both studies, the risk of bias was only raised to 'some concerns'.

From the included studies, two had pre-published protocols (17, 63, 65, 66) which allowed for assessment of reporting of all planned outcome data. Both Eftekharian and Secher et al. presented data on all outcomes they had set out to record (intraoperative blood loss: need for transfusion and adverse effects in Eftekharian et al. and intraoperative blood loss in Secher et al.).

With regards to the Measurement of the Outcome domain, while all other studies had measured and reported intraoperative blood loss volume via volumetric and/or gravimetric

means, Mortazavi et al. (71) and Sharma et al. (74) only estimated this outcome using pre- and post-operative haemoglobin. It was agreed by the reviewers that not reporting the blood loss is concerning, especially given that this would be a data routinely reported in the operative report. As such, risk of bias was initially increased to 'some concerns' for both these studies, however, it was later elevated to 'high' for Mortazavi et al. as it was unclear if the surgeon was blinded to the group allocations. All other outcomes across all studies were graded with low risk of bias. Finally, in the Selection of Reported Results domain, Jozefowicz 2021 (16) was graded with 'some concerns' due to the changing allocations of the abovementioned participant. The inter-rater agreement (Kappa) was 100% and the breakdown of risk of bias for each study is presented in Appendix 5.

<u>Study ID</u>	<u>Experimental</u>	<u>Comparator</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>
Apipan 2018	IV TXA 10, 15, 20 mg/kg	Saline	+	+	+	+	+	+
Choi 2009	IV TXA 20 mg/kg	Saline	+	+	!	+	+	!
Christabel 2016	IV TXA 10 mg/kg	Saline	+	+	+	+	+	+
Eftekharian 2015	Topical TXA 1mg/ml	Saline	!	+	+	+	+	!
Jozefowic 2019	IV TXA 2g	Saline	+	+	+	+	!	+
Kaewpradub 2011	Topical TXA 0.05%	Saline	+	+	+	+	+	+
Karimi 2012	IV TXA 20mg/kg	Saline	+	+	+	+	+	+
Mortazavi 2015	IV TXA 20mg/kg	Saline	+	+	+	-	+	-
Sankar 2012	IV TXA 10mg/kg bolus and 1mg/kg infusion	Saline	+	+	+	+	+	+
Secher 2018	IV TXA 1g	Saline	+	+	!	+	+	!
Sharma 2020	IV TXA 15mg/kg	Saline	+	+	+	!	+	!

 Low risk
 Some concerns
 High risk

D1 Randomisation process
 D2 Deviations from the intended interventions
 D3 Missing outcome data
 D4 Measurement of the outcome
 D5 Selection of the reported result

Figure 1. Risk of bias analysis summary

Review of results

Intraoperative blood loss

The first primary outcome was intraoperative blood loss. All 11 included studies reported this outcome. This outcome was measured in two different ways across the studies: volumetric/gravimetric (assuming specific gravity of blood as 1.0, intraoperative blood loss = [volume of fluid in the suction unit – volume of saline using for irrigation] + [weight of blood soaked gauze – weight of dry gauze] (13-17, 30, 66, 69, 70) or by assessing the change in haemoglobin (42, 71). Despite this, the same scale (millilitres) was used to describe this outcome in all studies, thus allowing use of weighted mean difference. As evident in the forest plot in Figure 2 (some data from Apipan, Rummasak and Narainthonsaene is presented in the forest plot to demonstrate a dose-dependent trend, however it was not pooled into the meta-analysis to avoid double counting), pooled data on 406 participants formed the experimental group and 398 controls, and the use of TXA, at any dosage and in any form, reduced the volume of blood loss by a mean of 189.6 ml (95% CI -237.3, -141.9). While this comparison was statistically significant ($P < 0.05$), as expected, there was significant heterogeneity with I^2 of 86%. The results of nine studies (13-17, 30, 42, 70, 71) (358 experimental and 350 controls) were pooled to show that the use of TXA via an intravenous route reduced the intraoperative blood loss by 189.9 ml (95% CI -240.6, -139.2). This comparison was also statistically significant ($p < 0.05$), with high heterogeneity (I^2 of 88%). Pooled results of two studies (66, 69) (48 experimental and 48 controls) assessing the effect of topical TXA revealed a reduction in blood loss by 191ml (95% CI -336.3, -45.9). This comparison was statistically significant ($P < 0.05$), with little heterogeneity (I^2 of 22%).

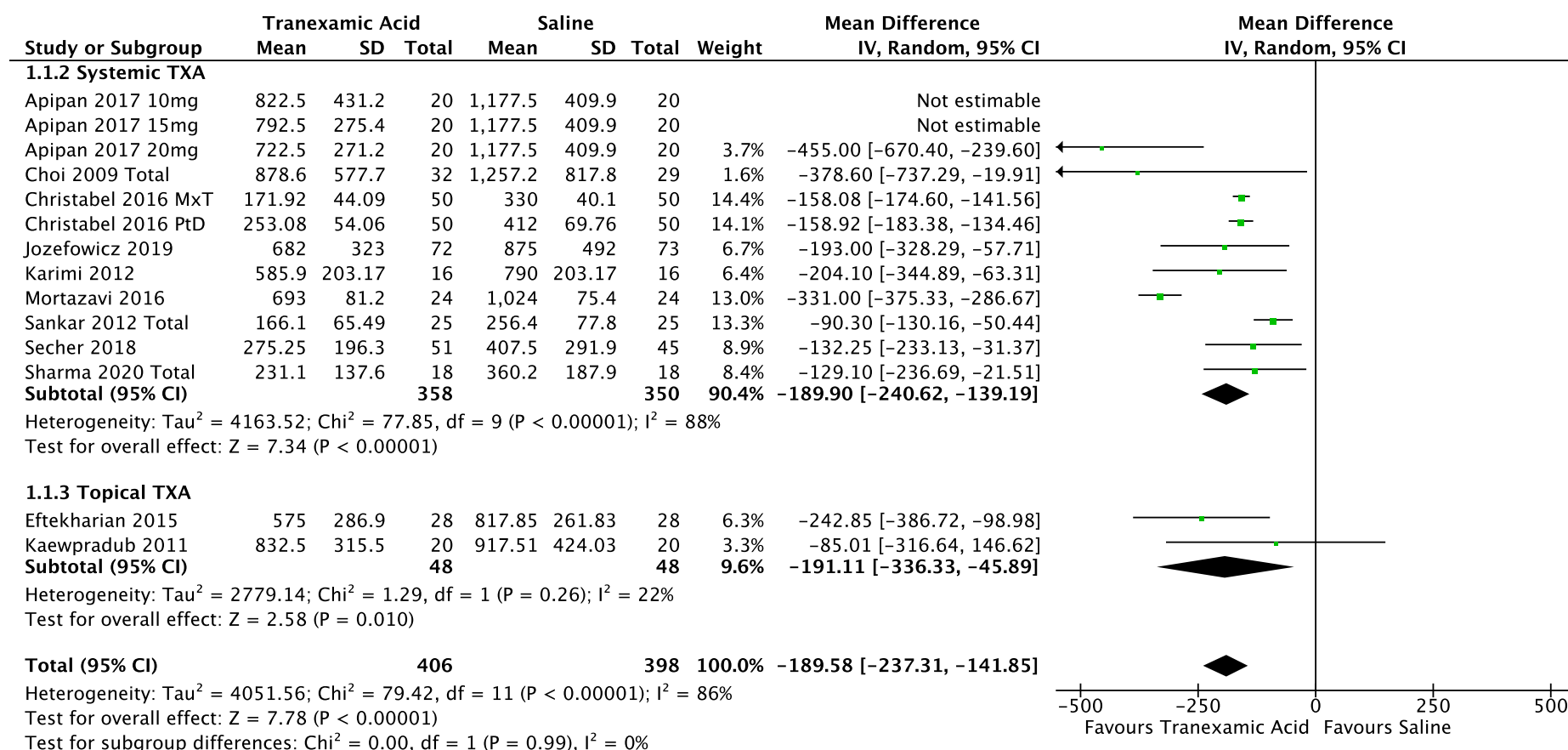


Figure 2. Forest plot for intraoperative blood loss – systemic or topical route

The intraoperative blood loss in various dosages of systemic TXA was also analysed. In general there were four different dose regimes: 10mg/kg reported in three studies (13, 15, 30) with 145 participants in each arm, 15mg/kg in two (13, 42) with 38 participants in each arm, 20mg/kg in four (13, 14, 70, 71) with 92 experimental participants and 89 controls, and finally a 1g dose in two studies (16, 17) with 123 in the experimental arm and 118 in the control arm. As evident in the forest plot in Figure 3, the lowest weight-based dose of TXA led to a mean reduction of 143.7ml (95% CI -178.3, -109.0) which was statistically significant ($P < 0.05$), with high heterogeneity (I^2 of 76%). The 15mg/kg dose resulted in a mean reduction of 239.1 ml (95% CI -487.4, 9.2) which was not statistically significant ($P > 0.05$), with high heterogeneity (I^2 of 77%). The 20mg/kg dose reduced mean intraoperative blood loss by 318.9ml (95% CI -402.0, -235.9) which was statistically significant ($P < 0.05$), with some heterogeneity (I^2 of 32%). Finally, the 1.0-gram subgroup analysis yielded a mean reduction of 154.0 ml (95% CI -234.8, -73.1), which was statistically significant ($P < 0.05$), with little heterogeneity (I^2 of 0%). We have not discussed the final pooled results for this analysis due to double counting of Apipan, Rummasak and Narainthonsaene.

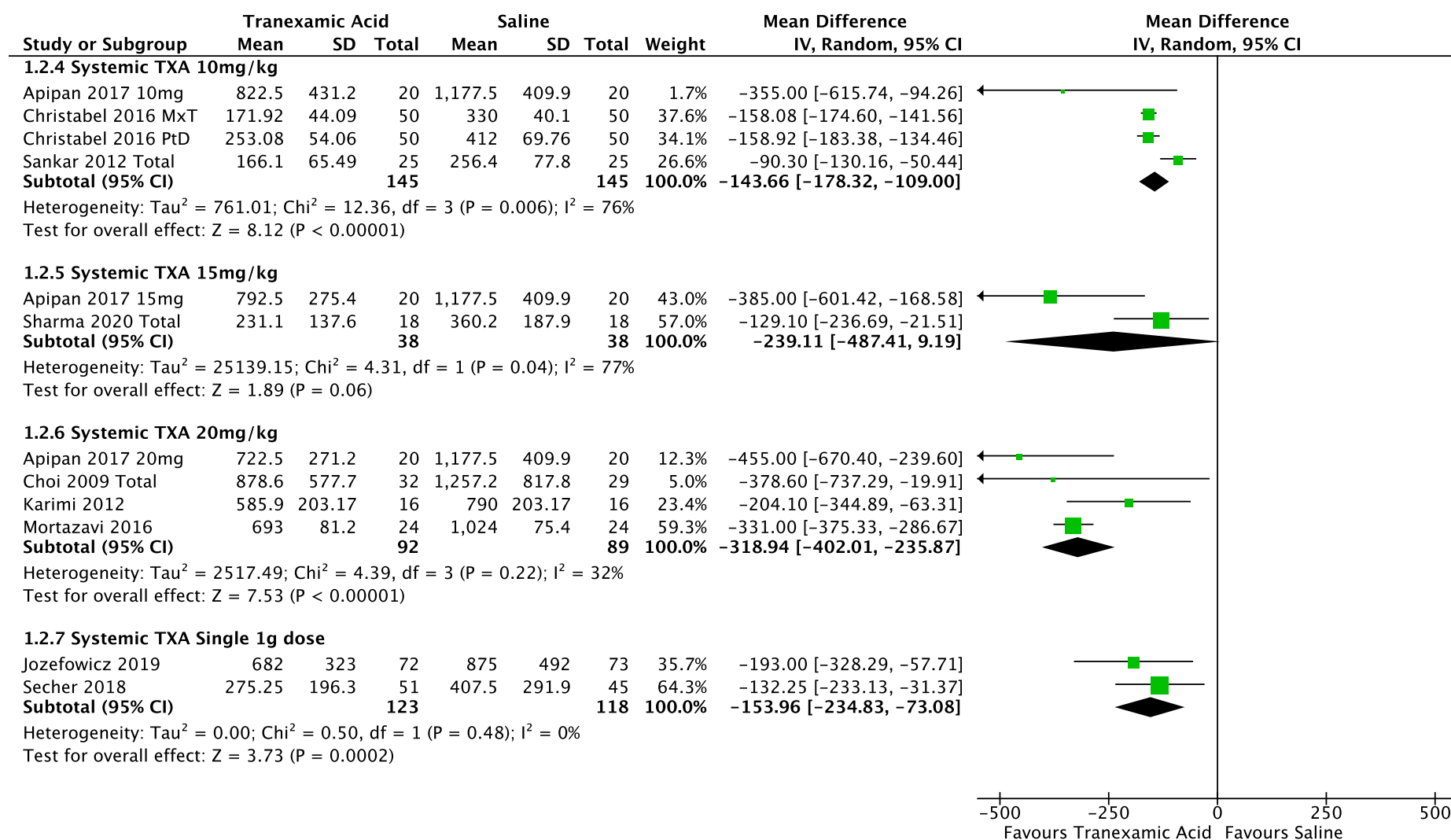


Figure 3. Forest plot for intraoperative blood loss – various systemic dosages

Finally intraoperative blood loss was analysed based on the type of surgery performed while on systemic TXA. As evident in the forest plot in Figure 4 (some data from Choi, Irwin and Samman and Apipan, Rummasak and Narainthonsaene is presented in the forest plot to show dose-dependent trend, however they are not pooled into the meta-analysis to avoid double counting). Two studies (14, 15) with 132 experimental and 129 control participants underwent maxilla-only surgery. Choi, Irwin and Samman additionally reported outcomes for blood loss in mandible-only surgery (14), and five studies that reported results for bimaxillary surgery (13, 14, 30, 70, 71). The pooled data for the bimaxillary subgroup included 75 participants in the experimental and 78 in the control arm. Some data from Choi, Irwin and Samman (14) and team and Apipan, Rummasak and Narainthonsaene (13) is presented in the table, however it was not included in the pooled data to avoid double-dipping. The use of systemic TXA in maxilla-only surgery resulted in a mean reduction of blood loss by 158.7ml (95% CI -172.3, -145.0) which was statistically significant ($P<0.05$), with no heterogeneity (I^2 of 0%). Mean reduction in blood loss was 256.4ml (95% CI -422.2, -90.7) was also seen in those receiving double jaw surgery. The double jaw subgroup analysis was statistically significant ($P<0.05$) but with significant heterogeneity (I^2 of 95%).

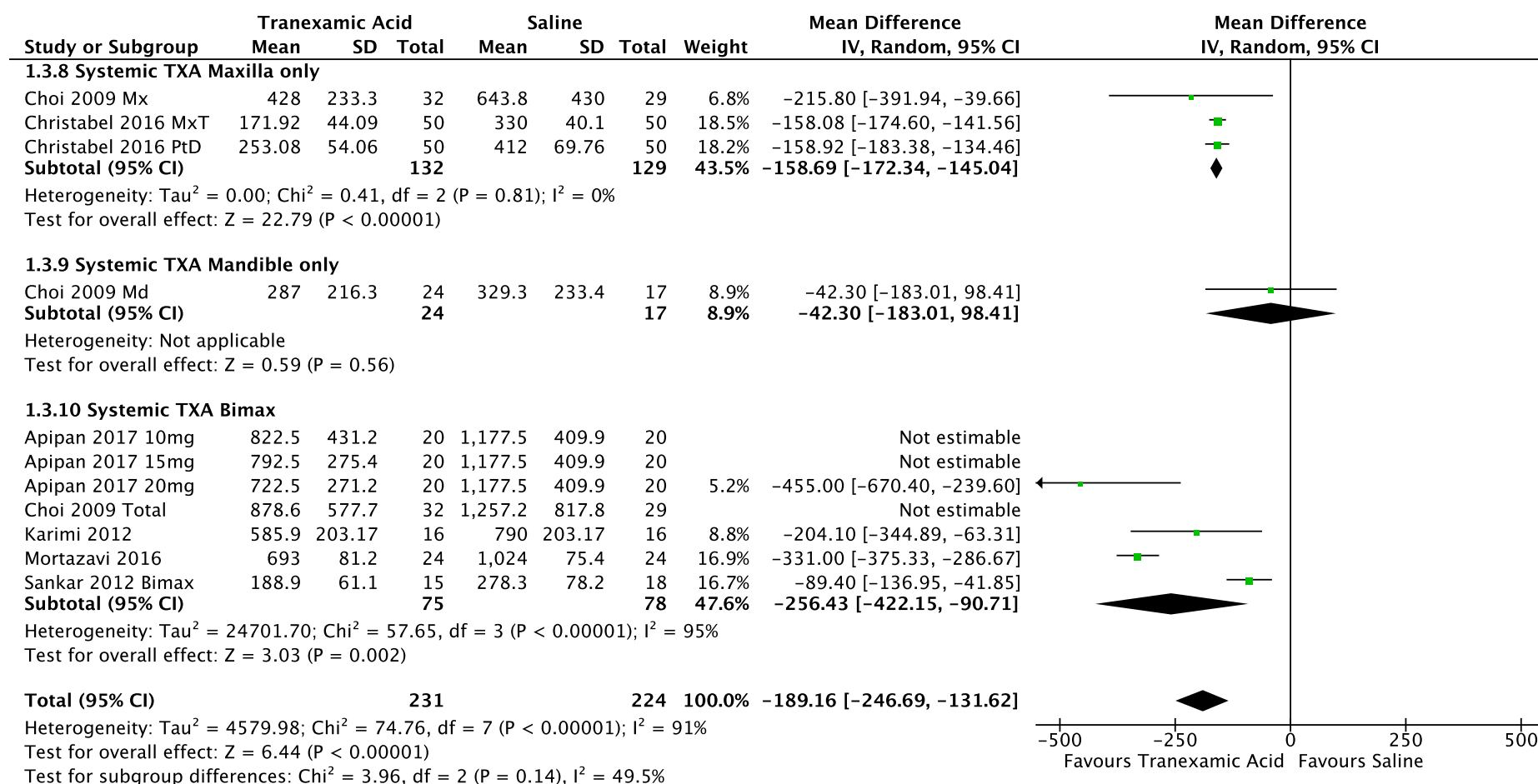


Figure 4. Forest plot for intraoperative blood loss – various surgery types

Intraoperative blood loss sensitivity analysis:

Excluding studies that did not directly measure intraoperative blood loss volume did not significantly change the results. Similarly, excluding studies with less-than-ideal overall risk of bias scores also did not significantly change the results.

Changes in haematocrit

Comparison of the drop in haematocrit was the second primary outcome of this meta-analysis. Data for this outcome was reported in four studies (13-15, 69) involving 172 experimental participants and 169 controls. As evident in the forest plot in Figure 5 (some data from Apipan, Rummasak and Narainthonsaene is presented in the forest plot to show dose-dependent trend, however it was not pooled into the meta-analysis), the mean difference between the haematocrit drop was 1.7% in favour of the experimental group (95% CI -2.6, 0.85). This comparison was statistically significant ($P < 0.05$), with some heterogeneity (I^2 of 46%).

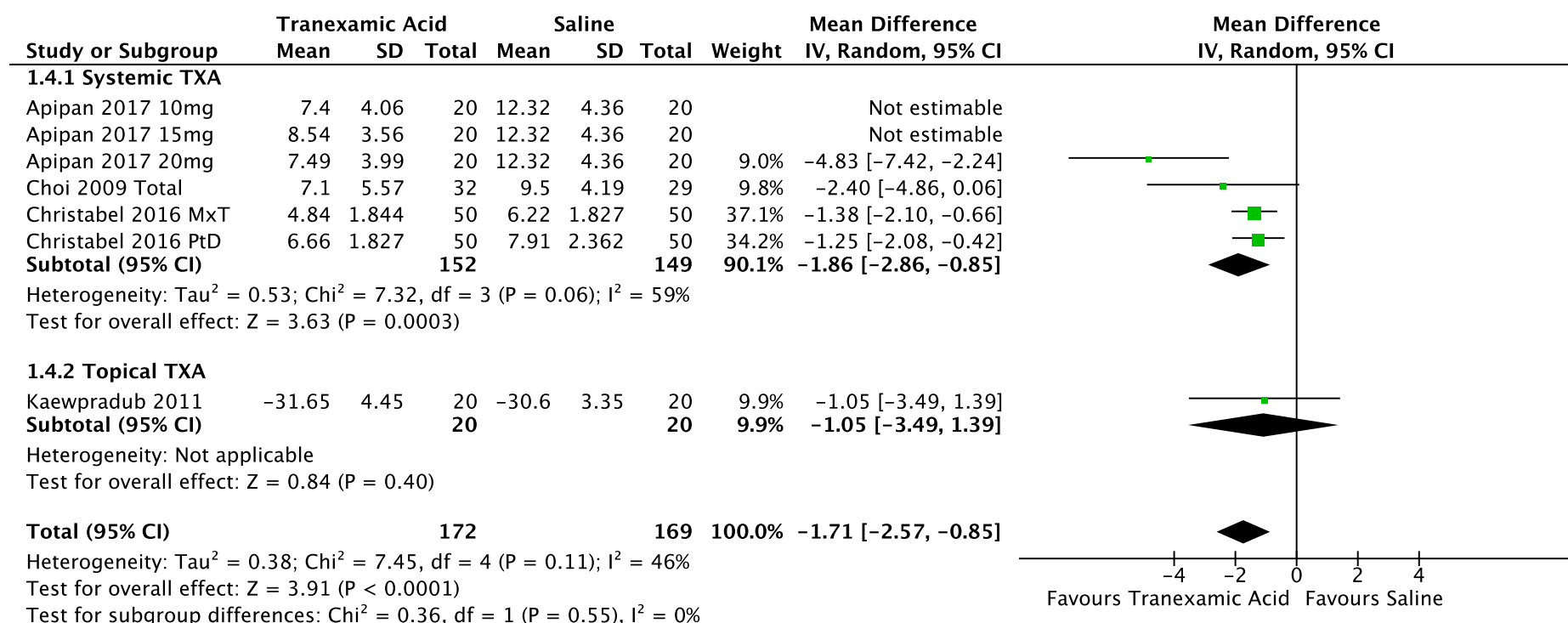


Figure 5. Forest plot for change in haematocrit – systemic or topical route

Analysis of changes in postoperative haematocrit in studies assessing systemic TXA in bimaxillary surgery was also possible – see forest plot in Figure 6 (part of Apipan, Rummasak and Narainthonsaene data is presented in the forest plot to show dose-dependent trend, however it was not pooled into the meta-analysis). Maxilla-only data was only present in one study (15) and there were no studies assessing haematocrit changes in mandible-only surgery. In the bimaxillary surgery analysis, pooled data for 52 experimental participants and 49 controls was available, resulting in a mean difference between the haematocrit drop of 3.6% in favour of the experimental group (95% CI -6.0, -1.2). This comparison was statistically significant ($P < 0.05$), with some heterogeneity (I^2 of 44%).

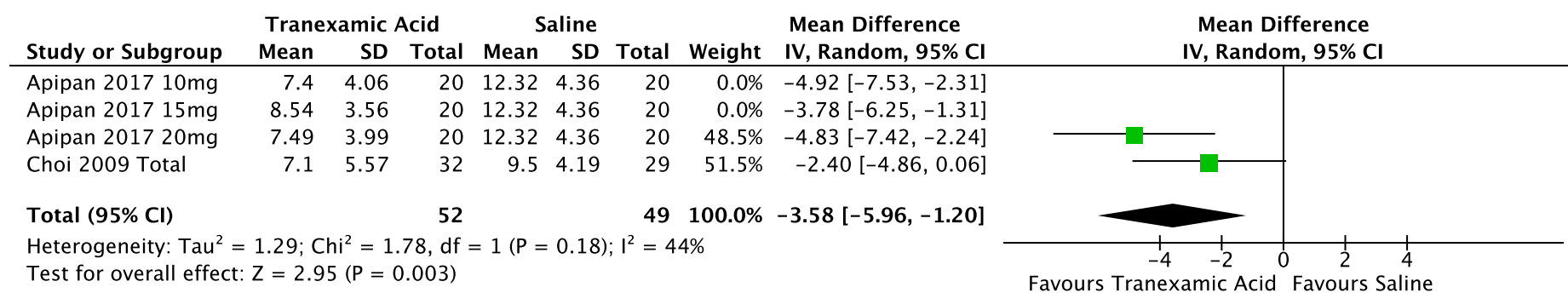


Figure 6. Forest plot for change in haematocrit – various surgery types

Haematocrit sensitivity analysis

Sensitivity analysis by exclusion of the studies with less-than-ideal risk of bias scores or those which did not have a clear reporting of when postoperative samples were collected did not significantly change the results.

Changes in haemoglobin

Postoperative change in haemoglobin was the third primary outcome. In studies assessing systemic use of TXA, changes in haemoglobin were reported in four studies (14-16, 71), pooling results from 228 experimental and 226 control participants (Figure 7). The pooled results showed reduction in the haemoglobin drop postoperatively by a weighted mean of 6.9 g/L (95% CI -9.6, -4.2). This result was statistically significant ($P < 0.05$), with high heterogeneity (I^2 of 80%).

It should be noted that Choi, Irwin and Samman (14) did not present changes in the haemoglobin in groups. Instead, they only presented postoperative haemoglobin mean and standard deviations. As per the Cochrane Handbook (9.4.5.2 Meta-analysis of Change Scores) (37), changes from baseline and post intervention measurements can be compared using a *non-standardised mean difference*. As such, the postoperative haemoglobin mean and standard deviation values from Choi, Irwin and Samman were used. To allow comparison to the other studies which showed *changes* in haemoglobin, Choi, Irwin and Samman's postoperative haemoglobin figures were converted to negative values.

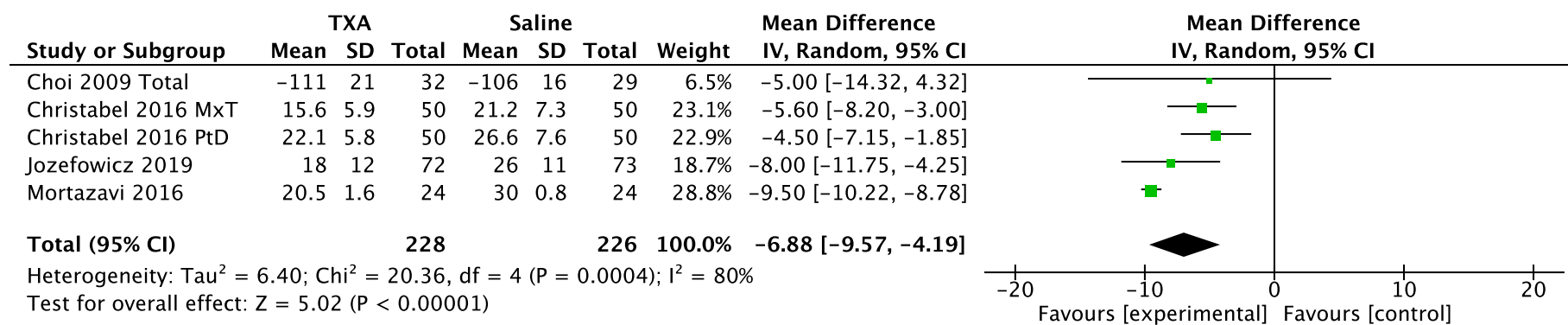


Figure 7. Forest plot for change in haemoglobin – systemic or topical route

There was only one study reporting haemoglobin change in maxilla-only surgery (15), with no studies in the mandible-only subgroup, and two studies in the bimaxillary surgery subgroup (14, 71). Analysis of the bimaxillary surgery group was possible for a total of 56 experimental and 53 control participants. The mean difference in postoperative haemoglobin drop was 9.5 g/L (95% CI -10, -8.8). This result was statistically significant ($P < 0.05$), with no heterogeneity (I^2 of 0%), and is presented in Figure 8.

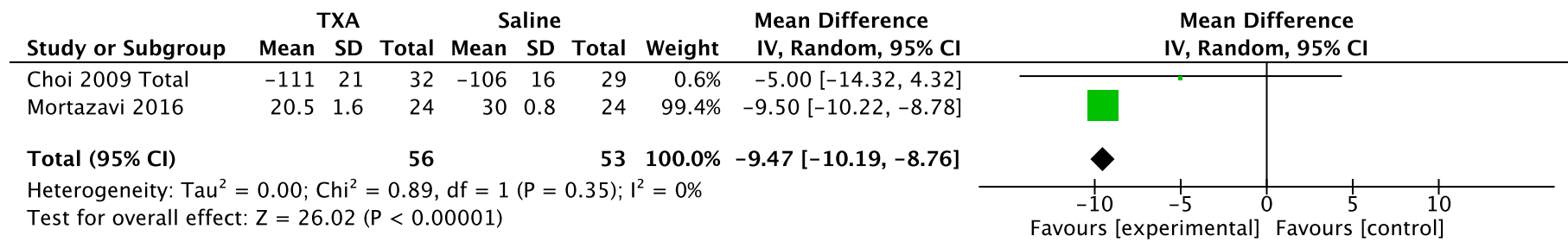


Figure 8. Forest plot for change in haemoglobin – various surgery types (bimaxillary surgery only)

Haemoglobin sensitivity analysis

Sensitivity analysis by exclusion of the studies with less-than-ideal risk of bias scores or those which did not have a clear reporting of when postoperative samples were collected did not significantly change the results.

Rate of perioperative blood transfusion

The need for postoperative blood transfusions was the final primary outcome of this review. Data on this outcome was reported in seven studies (13-16, 30, 66, 70), resulting in data for 295 experimental and 291 control participants. The overall need for transfusion was low: only four cases in the experimental group but 15 in the control group. The risk difference was 2% (95% CI -0.05, 0.01) which was not statistically significant ($P > 0.05$), with some heterogeneity (I^2 of 35%), as evident in Figure 9 (all of Apipan, Rummasak and Narainthonsaene data is presented, however only one set was included in the meta-analysis).

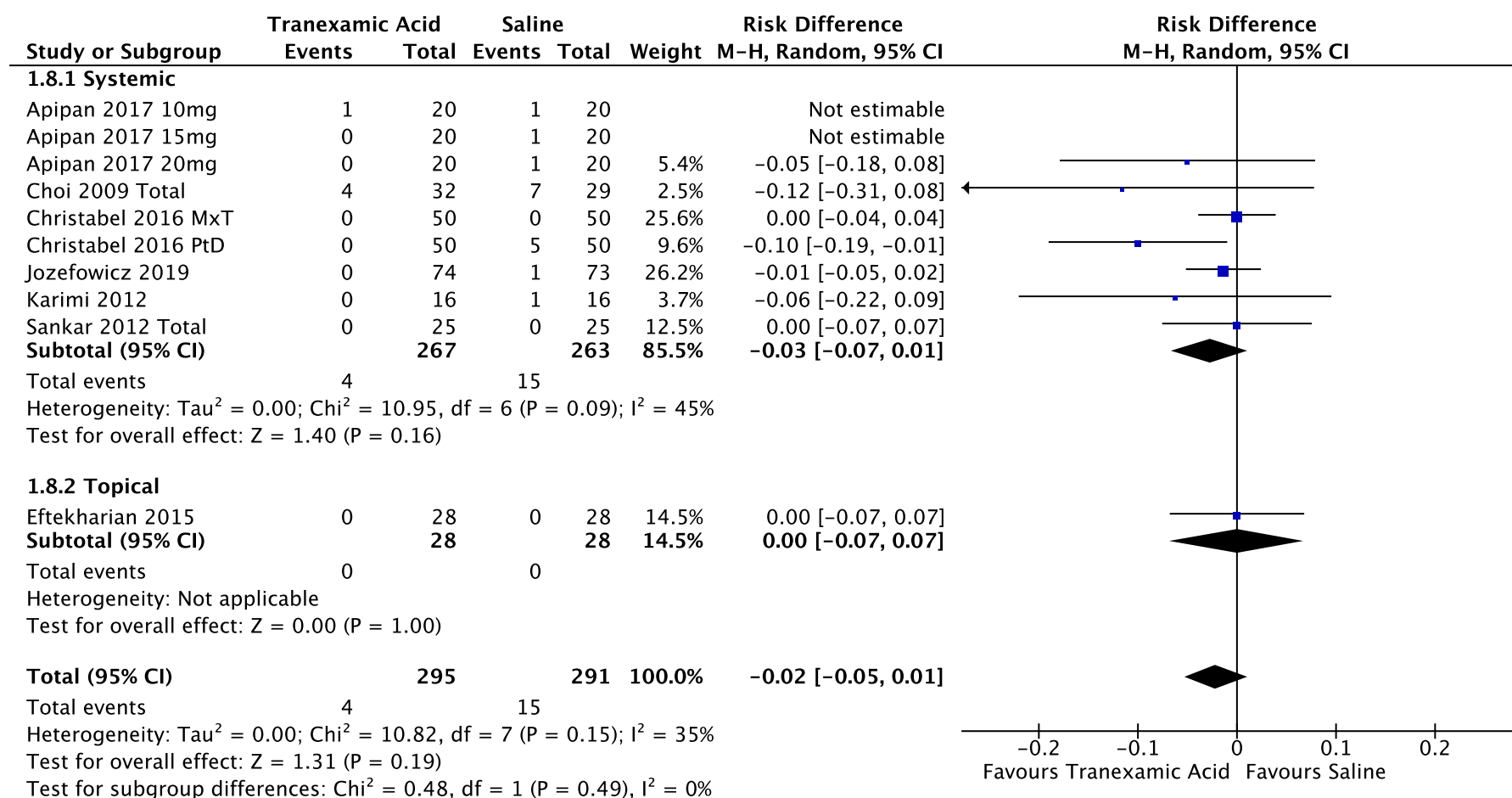


Figure 9. Forest plot for rate of blood transfusion – systemic or topical route

This outcome was re-categorised based on the type of surgery in studies utilising systemic TXA. Analysis for systemic TXA in mandible-only surgery was not possible due to the absence of studies in this group, and in the maxilla-only group there was only one study (15). As evident in the forest plot in Figure 10 (all of Apipan, Rummasak and Narainthonsaene data is presented, however only one set was included in the meta-analysis), results for systemic TXA in bimaxillary surgery followed similar results involving 51 experimental and 54 control participants from three studies (13, 30, 70), with a risk difference of 3% (95% CI -0.1, 0.04) which was not statistically significant ($P>0.05$), and with low heterogeneity (I^2 of 0%).

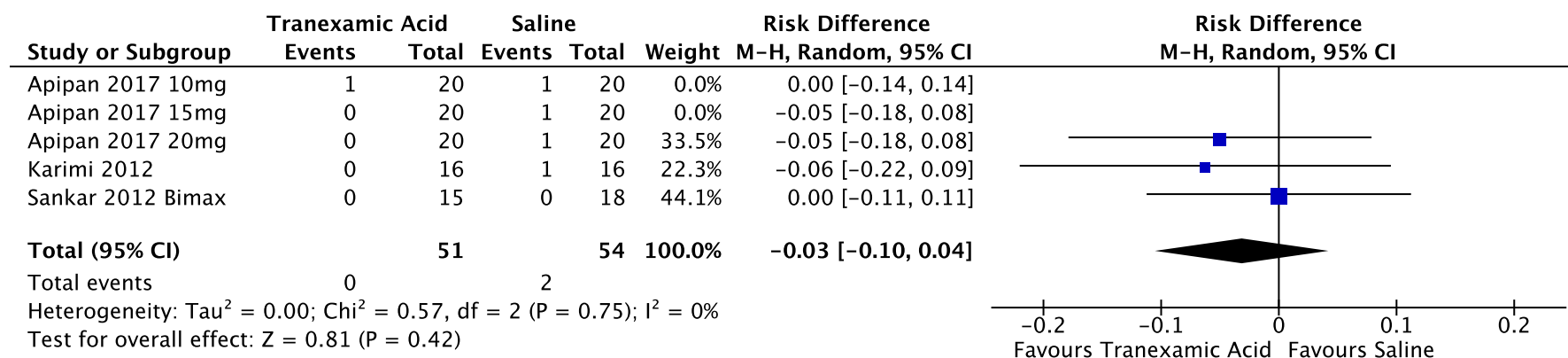


Figure 10. Forest plot for rate of blood transfusion – various surgery types (bimaxillary surgery only)

Rate of transfusion sensitivity analysis

Sensitivity analysis by exclusion of the less-than-ideal risk of bias score did not significantly change the results.

Operative time

The first secondary outcome was the effect of TXA on operative time. Data on this outcome was reported in ten studies (13-17, 30, 42, 66, 69, 70) involving 382 experimental participants and 374 control participants (Figure 11). Use of TXA in any dosage or route resulted in a mean reduction of operative time by 8.9 minutes (95% CI -17.45, -0.31) which was statistically significant ($P < 0.05$), with high heterogeneity (I^2 of 61%). Data for systemic TXA was included in eight studies, accounting for 334 experimental and 326 controls, which showed a mean reduction in operation time by 11.45 minutes (95% CI -20.0, -3.0). This comparison was statistically significant ($P < 0.05$), with high heterogeneity (I^2 of 60%). The use of topical TXA in 48 experimental and 48 control participants from two studies (66, 69) suggested a *prolonged* operating time in the experimental group by a mean of 10.7 minutes (95% CI -12.0, 33.4). This comparison was not statistically significant ($P > 0.05$), with no heterogeneity (I^2 of 0%).

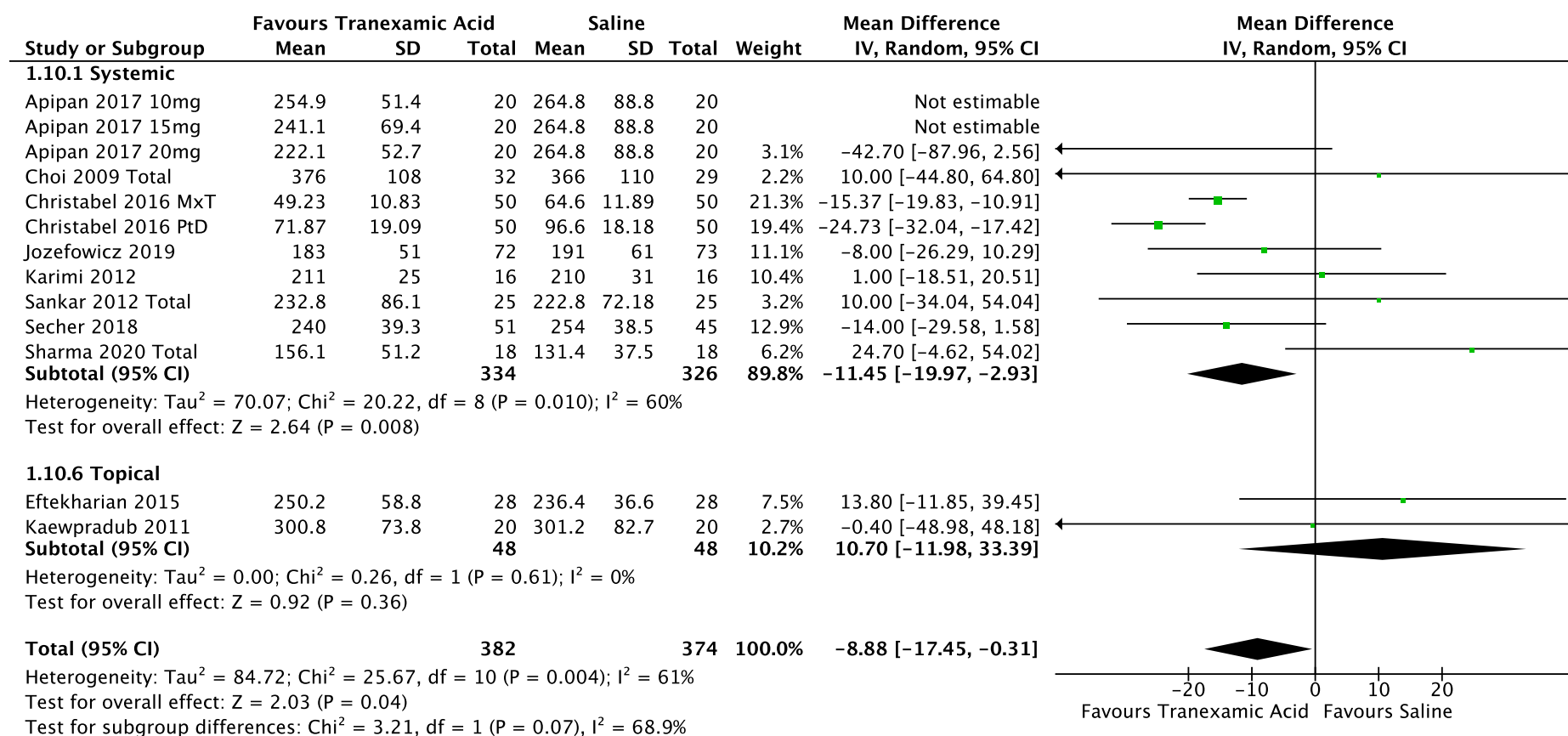


Figure 11. Forest plot for operative time – systemic or topical route

Figure 12 (all Apipan, Rummasak and Narainthonsaene data is presented, however only one set was included in the meta-analysis) re-categorises this outcome data based on various surgery types. Systemic TXA use in maxilla-only surgery subgroup was reported in three studies (14, 15, 42) involving 139 experimental participants and 134 controls, demonstrating a mean reduction of 16.3 minutes (95% CI -22.5, -8.2), which was statistically significant ($P < 0.05$), with high heterogeneity (I^2 of 59%). The pooled data for systemic TXA in mandible-only surgery included 26 participants in each arm from two studies (14, 42) and showed an *increase* in the operative time by 26 minutes (95% CI 5.4, 46.7) and this comparison was statistically significant ($P < 0.05$), with no heterogeneity (I^2 of 0%). In the bimaxillary subgroup, there were six studies (13, 14, 17, 30, 42, 70), producing pooled results for 143 experimental and 132 control participants. This subgroup demonstrated a mean reduction of 6.3 minutes (95% CI -20.2, 7.6), however these results were not statistically significant ($p > 0.05$), with little risk of heterogeneity (I^2 of 0%).

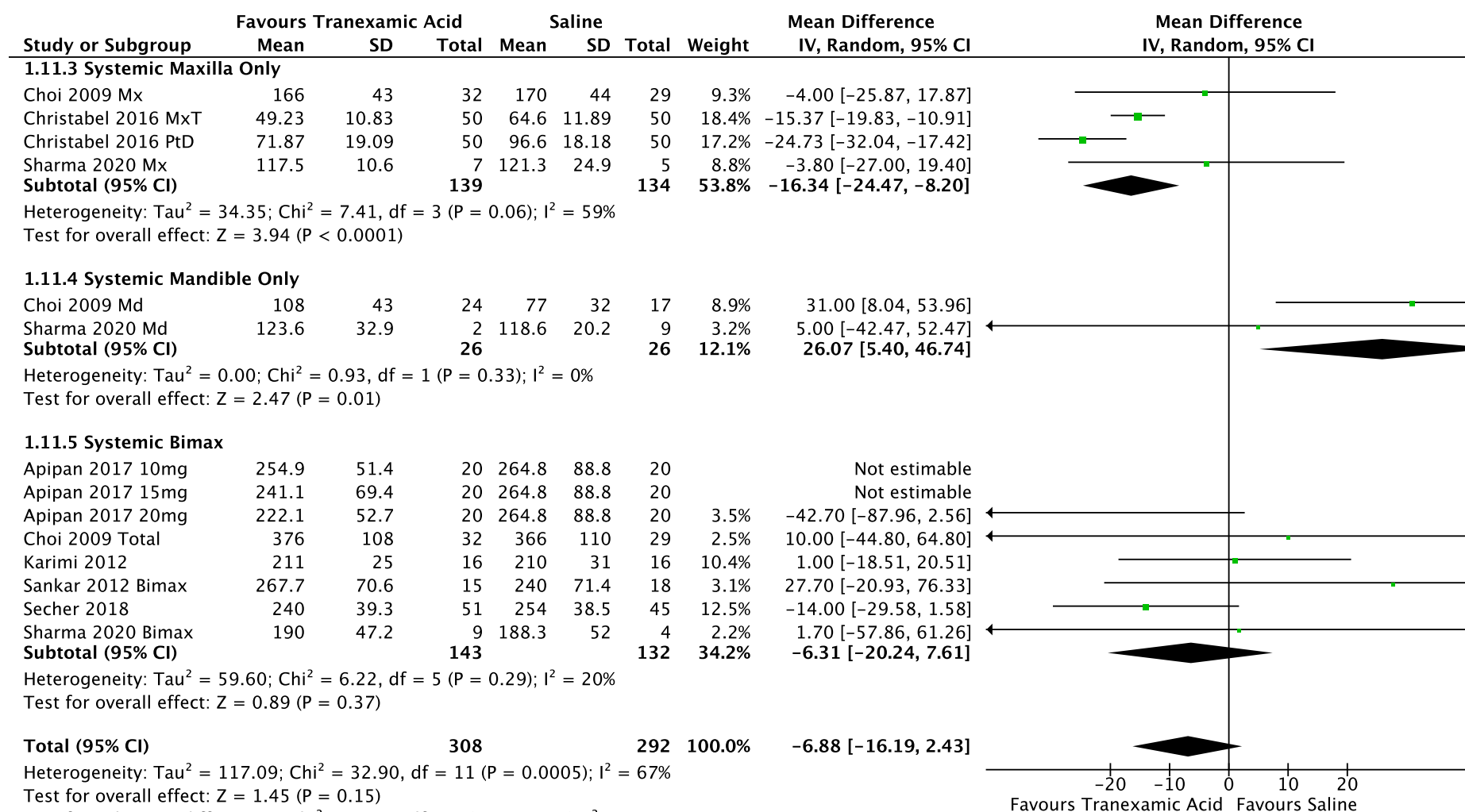


Figure 12. Forest plot for operative time – various surgery types

Operation time sensitivity analysis

Sensitivity analysis by exclusion of the less-than-ideal risk of bias score did not significantly change the results.

Length of stay

Length of stay was reported in four studies (13, 14, 16, 70), accounting for 180 experimental and 138 control participants (Figure 13 – all Apipan, Rummasak and Narainthonsaene data is presented, but only one set was included in meta-analysis). However, meta-analysis was only possible for 52 experimental and 49 controls from two studies (13, 14). The mean difference between length of stay was 0.3 days (95% CI -0.9, 0.3). This analysis was not statistically significant ($p > 0.05$), with no heterogeneity (I^2 of 0%).

Length of stay sensitivity analysis

Sensitivity analysis by exclusion of the less-than-ideal risk of bias score was not possible due to the small number of pooled studies.

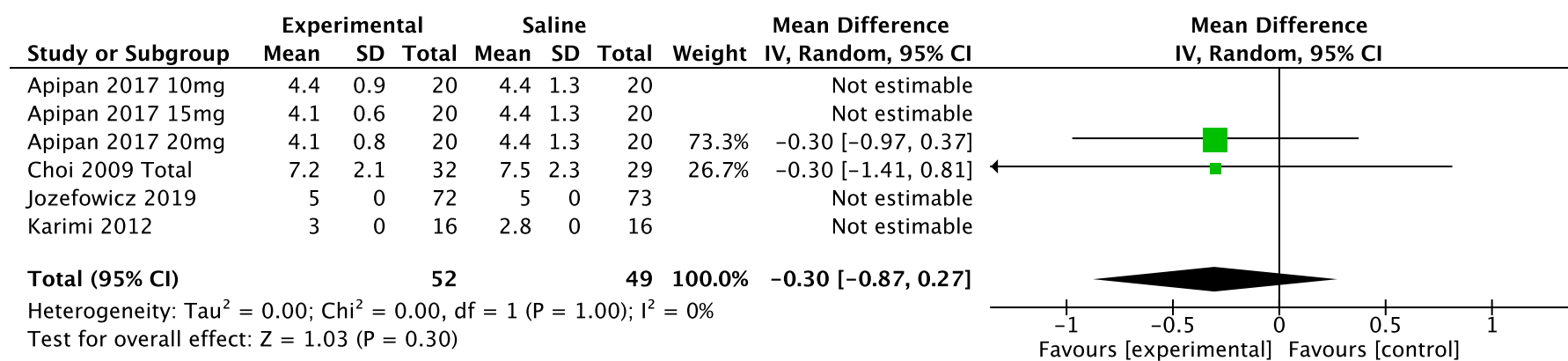


Figure 13. Forest plot for length of stay – systemic route

Adverse effects

Finally, the incidence of adverse effects was reported in all studies. No studies reported any adverse outcomes attributable to TXA use.

Publication bias

Where there were more than 10 included studies, publication bias was measured and demonstrated via funnel plots. The funnel plots for intraoperative blood loss and operative time are included below (Figures 14 and 15). However, due to the limited availability of data, no strong conclusions can be drawn from these graphs.

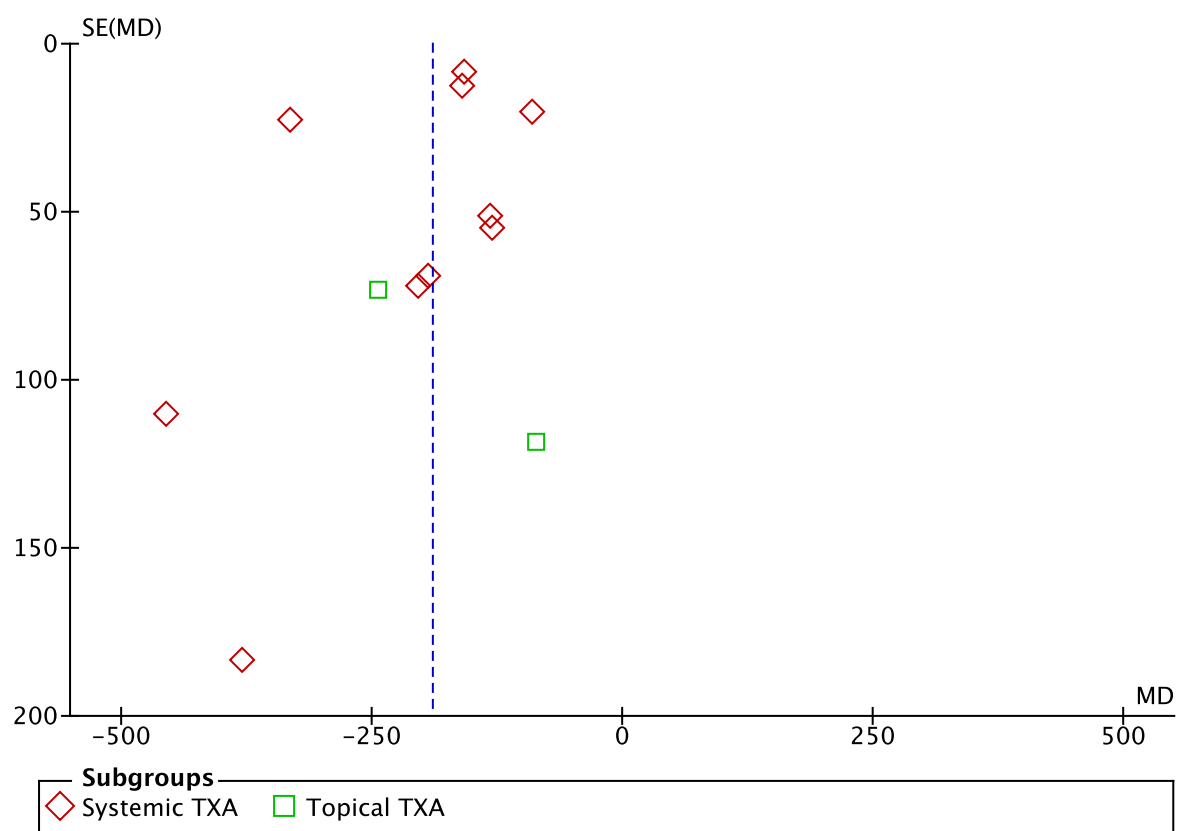


Figure 14. Funnel plot for intraoperative blood loss – systemic or topical route

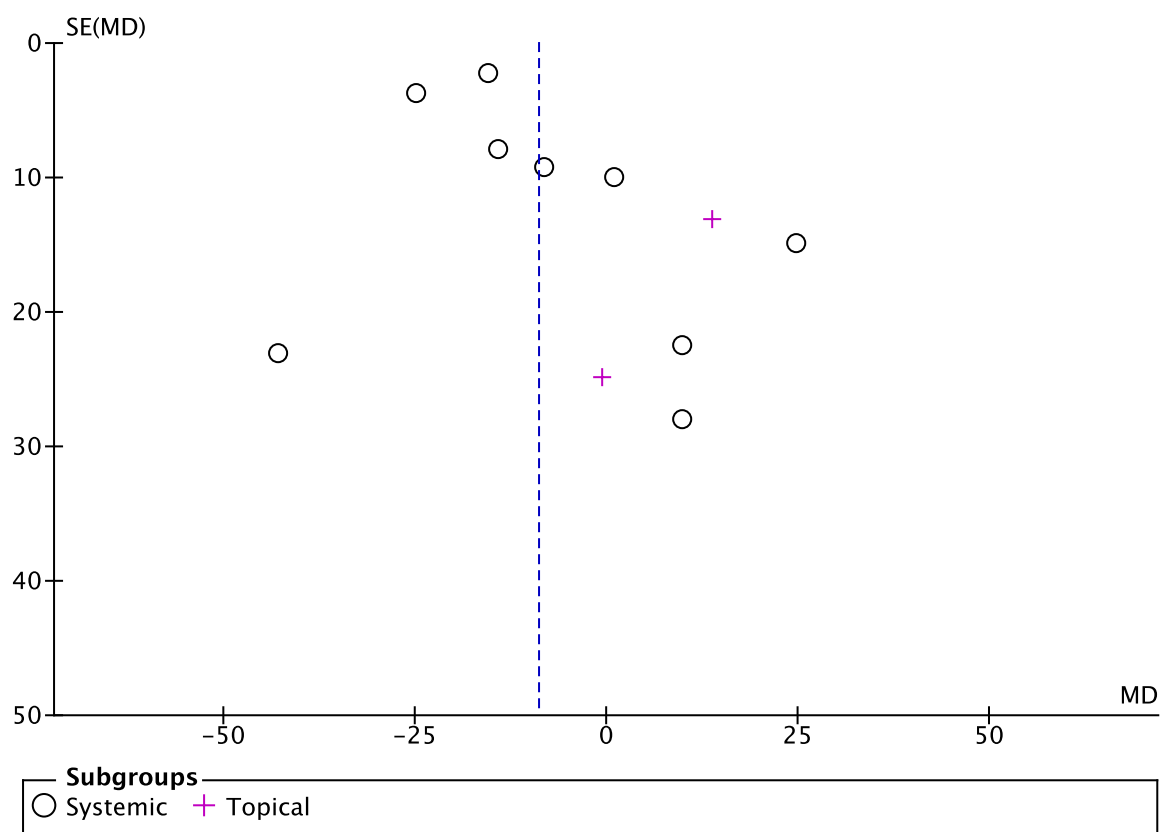


Figure 15. Funnel plot for operative times – systemic or topical route

GRADE Summary of Findings

A GRADE Summary of Findings table was formed (Table 2). While there were many outcomes of interest, seven of the outcomes of greatest clinical importance were reported. Intraoperative blood loss and systemic TXA at any dosage received a high certainty due to low risk of bias, inconsistency, indirectness or imprecision. The certainty of this outcome was enhanced by the dose-response gradient seen in the study by Apipan, Rummasak and Narainthonsaene (13). Certainty of intraoperative blood loss when using 20mg/kg TXA dosage was reduced to moderate because more than half of the included studies had 'some concerns' with risk of bias. Transfusion rates in studies using systemic TXA of any dosage received a high certainty. Operative time in systemic TXA of any dosage was downgraded to moderate certainty because of issues with imprecision. A difference of operating time greater than five minutes has been selected as the threshold of clinical significance. Given that the 95% confidence interval of the mean difference in this outcome crossed this threshold (95% CI = 19.97 – 2.93 mins), the imprecision domain of this outcome was downgraded. This was not an issue in the operating time in maxilla-only surgery, which received a high certainty. In the operating time for systemic TXA of any dosage in mandible-only surgery, the certainty was downgraded due to suboptimal risk of bias. It should be noted that there were only two randomised controlled trials that reported on this outcome. Finally, the presence of adverse reactions or outcomes from TXA use was reported with high certainty. The full GRADE summary of findings is included in the Appendix 6. The inter-rater agreement (kappa) value for the assessment of the quality of the evidence was 1.0, suggesting perfect agreement between the reviewers.

Table 2. GRADE Summary of Findings

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic Acid	Placebo	Relative (95% CI)	Absolute (95% CI)	
Intraoperative blood loss - systemic TXA											
9	randomised trials	not serious	not serious	not serious	not serious	none	358	350	-	MD 189.9 lower (240.62 lower to 139.19 lower)	⊕⊕⊕⊕ High
Intraoperative blood loss - systemic TXA 20mg/kg											
4	randomised trials	serious ^a	not serious	not serious	not serious	none	92	89	-	MD 318.94 lower (402.01 lower to 235.87 lower)	⊕⊕⊕○ Moderate
Transfusion rate random effect - systemic TXA											
6	randomised trials	not serious	not serious	not serious	serious ^b	none	4/267 (1.5%)	15/263 (5.7%)	57 fewer per 1000	30 fewer per 1,000 (from 70 fewer to 10 more)	⊕⊕⊕○ Moderate
Operating time - systemic TXA											
8	randomised trials	not serious	not serious	not serious	serious ^c	none	334	326	-	MD 11.45 lower (19.97 lower to 2.93 lower)	⊕⊕⊕○ Moderate
Operating time - systemic maxilla-only											
3	randomised trials	not serious	not serious	not serious	not serious	none	139	134	-	MD 16.34 lower (24.47 lower to 8.2 lower)	⊕⊕⊕⊕ High
Operating time - systemic mandible-only											
2	randomised trials	serious ^a	not serious	not serious	serious ^b	none	26	26	-	MD 26.07 higher (5.4 higher to 46.74 higher)	⊕⊕○○ Low
Adverse reaction											
8	randomised trials	not serious	not serious	not serious	not serious	none	0/301 (0.0%)	0/300 (0.0%)	not pooled	not pooled	⊕⊕⊕⊕ High

CI: confidence interval; MD: mean difference; OR: odds ratio; TXA: tranexamic acid

Explanations

a. More than half of the studies did not have low risk of bias.

Domain 1, Randomisation [Eftekharian (66)]

Domain 3, Missing outcome data [Choi, Irwin and Samman (14), Secher (17)]

Domain 4, Measurement of the outcome [Mortazavi (71), Sharma (74)]

Domain 5, Selection of reported results [Jozefowicz (16)]

b. Due to wide confidence intervals and low number of participants

c. Five minutes is used as a threshold of importance. The 95% CI cross the threshold and thus the comparison is imprecise.

Summary of results

There were 11 randomised controlled trials included in this review, accounting for up to 406 participants from the experimental group and 398 controls. The results of the primary outcomes demonstrated that the use of TXA led to reduced intraoperative blood loss reduced postoperative drop in haematocrit and haemoglobin, and reduced the need for postoperative blood transfusions. The use of TXA was most strongly supported when it was given systemically, at a dosage of 20mg/kg when undergoing at least a maxillary osteotomy. The secondary outcomes measured also supported the use of TXA in reducing the overall operative time and length of hospital stay without increasing the risk of adverse effects. The operative time was decreased in cases of maxilla-only or bimaxillary surgery, but increased in mandible-only surgery.

CHAPTER 4: DISCUSSION AND CONCLUSIONS

Intraoperative blood loss

The results of this review suggest that the use of prophylactic TXA results in a statistically significant reduction of intraoperative blood loss, irrespective of route administered. When used systemically, dosages of 10 and 20 mg/kg and 1.0 gram resulted in a statistically significant reduction in blood loss volume in maxilla-only and bimaxillary surgery. While a mean reduction of 270 ml (as seen in the bimaxillary subgroup) may not appear significant, it should be noted that it would equate to a 33% reduction when analysing data from Thongmalai (6). Nevertheless, Schwaiger et al. suggest that accepted clinical measurements of blood loss – volumetric and gravimetric calculations – provide an underestimate of total blood loss (75). They reported that calculating the total blood loss based on changes in haematocrit/haemoglobin revealed an additional mean of 287-346ml (additional 32-62%) volume of blood loss from bimaxillary or BSSO surgery. They attributed this hidden volume to haemorrhage into tissue spaces and maxillary sinuses, and ingested blood. This suggests that the level of absolute blood loss in this review are likely to be underestimated.

In connection, bleeding into tissue spaces postoperatively can lead to development of haematomas that can lead to airway compromise or postoperative infections (76, 77). Although haematoma formation was not an outcome measure of this review, reduction of bleeding intraoperatively using a systemic agent is likely to reduce bleeding postoperatively while the TXA is still active. As such, the risk of haematoma formation and subsequent infection of such haematomas is likely to be reduced. This notion has not been investigated in this review and the role of *postoperative* systemic TXA could be the focus of future research.

Haematocrit

The results of this review suggest that the use of prophylactic TXA, irrespective of route, results in a statistically significant reduction in the degree of haematocrit drop. While there were close to 300 participants for the systemic subgroup, there was only a single study with 40 participants being given topical TXA. While most studies clearly defined the timing of the

postoperative data collection (24 hours), one study did not provide details of the specific timing of the postoperative blood test (6).

Haemoglobin

The results of this review suggest that the use of prophylactic TXA, irrespective of dosage, results in a statistically significant reduction of haemoglobin drop. Once again, the specific timing of the postoperative haemoglobin measurement was not clear in two studies (16, 71).

Rate of transfusion

The results of this review suggest that the rate of postoperative blood transfusion in orthognathic surgery is low. Based on the pooled data on almost 300 experimental group participants and 300 controls, blood transfusion was only reported in four cases in the experimental groups and 15 in the control groups. Given the rarity of these cases, it is possible that the sample sizes were too small to show statistically significant results. Nevertheless, where blood transfusions did take place, there was a trend towards having undergone maxilla-only or bimaxillary surgery. This supports limiting the use of TXA in cases involving maxillary osteotomies.

Operation time

The results of this review suggest that the use of prophylactic TXA, irrespective of route, results in a statistically significant reduction in the operative time. The efficiency of surgery was increased when the TXA was used systemically and where maxillary osteotomies were involved. Interestingly, the use of systemic TXA in mandible-only surgery appeared to *prolong* the operative time, however this is likely due to the small sample sizes (only 26 participants in each arm) and the surgical difference between the two groups..

Nevertheless, reduction of operative time may be attributed to the reduced bleeding and need to halt operative progress to establish haemostasis, as well as the improved visibility and overall 'quality' of the surgical field. In fact, two of the included studies measured and reported the quality of surgical field as an outcome. Both Sharma (42) and Sanker (30)

independently reported significant improvements in the surgeon's satisfaction with the surgical field when TXA was used.

Length of stay

The final outcome of duration of hospital stay was not routinely reported in the included studies. Where meta-analysis was possible, the comparison was not statistically significant. Once again, Apipan, Rummasak and Narainthonsaene (13) demonstrated a dose-dependent relationship. Similarly, Choi, Irwin and Samman reported that increased length of stay was associated with blood transfusion taking place. Anecdotally, this is a common clinic occurrence where post-transfusion monitoring and blood tests can prolong the duration of hospital stay. Nevertheless, Andersen et al. showed in their retrospective review of 335 patients that operative time and relative blood loss were predictive of prolonged length of stay (46).

Overall completeness and applicability of evidence

This review assessed the role of prophylactic TXA in reducing blood loss in orthognathic surgery in healthy patients. While blood loss was measured both directly and indirectly, many of the included studies did not assess all of the included outcomes. Where statistically and clinically appropriate, results were compiled across studies in the meta-analysis. Occasionally the data was presented in part, and certain aspects (e.g. standard deviations) were missing. Attempts to contact authors for further data often proved unfruitful, and therefore led to exclusion of this data from further meta-analysis. Occasionally, there was adequate data presented to enable calculation or estimation of figures based on the advice contains within the Cochrane Handbook. Resultantly, given the scarcity of the evidence, it is difficult to make confident recommendations about the ideal dosage of TXA.

In terms of applicability of the results of this review, the included trials were pragmatic and surgeries reflected common surgical practice. Their inclusion and exclusion criteria were reasonable and populations involved closely resembled those presenting to orthognathic surgeons. When considering the applicability of the interventions in the real world, the regime of one-off systemic TXA dosage at the time of induction, with concurrent use of local

anaesthetic, reverse Trendelenburg head position, hypotensive anaesthesia and conventional oscillating saws for osteotomies, is reasonably easy to implement. Tranexamic acid is readily available and allergy to it is rare. The cost of intravenous TXA administration is relatively low [USD\$5-50 (78)] compared with costs associated with further serology monitoring, prolonged surgery or prolonged hospital stay. In Australia, the cost of running an operating theatre is estimated at \$AUD 42 per *minute* (79). Finally, systemic TXA use is relatively easy (and convenient) to implement as patients would already have intravenous access as part of surgery.

Strengths and limitations of this review

Study inclusion and search strategy

One of the strengths of this review is the very comprehensive search strategy. This review used a wide inclusion criterion to capture the relevant literature. By setting no publication date and language limitations, including three of the most relevant databases, cross-referencing any published trial registries, and finally screening reference lists of included studies, the risk of missing any relevant peer-reviewed publications was minimised. To ensure the contemporaneity of the review, the search was repeated at a later time to capture any literature published while this thesis was being written. To enhance the transparency and reproducibility of this review, the protocol was peer-reviewed, published and made publicly available to minimise deviations from the protocol. Nevertheless, there were a few limitations within the search strategy that need to be discussed.

While the search strategy would have in theory picked up all non-English studies, in practice, non-English studies that did not use any English key terms would not have been captured by the search. For a study to be captured, it must have had at least one of the English key-terms in its title, abstract or key-terms section. While it would be rare for a non-English study to not use the terms 'TXA' or 'tranexamic acid' in its title or abstract, it is not impossible that TXA may have been referred to by other terms or names in different languages.

Study design

Another strength of this review is the clear inclusion and exclusion criteria. By limiting the inclusion criteria to randomised controlled trials, the highest quality of primary data was utilised. Nevertheless, this strict inclusion criteria may have contributed to the limited the amount of pooled data. If the inclusion criteria had been broadened to non-clinical trials, there would have been three additional studies that would have met the selection criteria. As part of comprehensiveness of this review, they are summarised below under 'Context within the literature'.

Heterogeneity

While this review attempted to minimise its effect, heterogeneity between studies is a limitation that can never be completely eradicated. Potential clinical heterogeneity existed at participant, procedure and surgeon levels. There were subtle physiological and anatomical differences in participants in each study, there were nuanced differences in surgical techniques used by each surgeon within each trial, and different surgical teams would have varying levels of surgical experience and associated skills that affected surgical efficiency, tissue handling and iatrogenic trauma.

Methodological heterogeneity mainly consisted of differences in the timing of TXA administration. Although broadly grouped into intraoperative systemic administration of TXA, the procedure ranged from a bolus being given at the time of induction to being given as a slow infusion over 30 minutes after induction of anaesthesia. Similarly, there was heterogeneity in the way outcomes were measured across the studies. For instance, some studies used gravimetric and volumetric means of assessing intraoperative blood loss, while others estimated blood loss by comparing the pre- and postoperative haematocrit/haemoglobin. Furthermore, the timing of postoperative haematocrit/haemoglobin varied across studies and to allow for some form of comparison, the measurement taken closest to 24 hours was accepted as the postoperative measurement. Finally, there was methodological heterogeneity as seen in the varying risk of bias assessment. All of these variations are evident in the I^2 values for heterogeneity among the studies.

Publication bias

This review attempted to minimise publication bias by not using a language limit in its inclusion criteria. As a result, one previously uncaptured randomised controlled trial from Iran was discovered, which had been published in Farsi (71). Similarly, all articles that fulfilled the criteria at title and abstract screening were retrieved and assessed. Cost and paywalls did not limit access. The selection of databases for searching were the most appropriate to include the relevant publications. In an ideal world with unlimited resources, this review could have included a greater breadth of databases, however inclusion of further databases would lead to a greater lag time between the search phase and the publication of the review, ultimately resulting in an out-of-date review. Nonetheless, there is always an element of publication bias within each study which usually forms the basis for measurement and reporting of outcomes in scientific literature; that is, typically studies that have positive or very negative results get published while those with less 'impressive' results may not eventuate to peer-reviewed publications.

Data extraction

This review implemented several controls against data extraction errors. This was principally by using two independent investigators. The data extraction template was prepared by lead investigator (HB), trialled on multiple studies, incorporated into Covidence, and the data extraction was done independently. Each investigator had their own version of the full-text reports to prevent any annotations on the document undermining the independent extraction of data. The extracted data in Covidence was cross referenced by the software and any discrepancies discussed and resolved. The majority of discrepancies were around grammar or syntax and were easily resolved. The finalised data was exported and used by the lead investigator to develop the study characteristics table. While this step was not duplicated independently, the co-investigator reviewed the table to ensure its accuracy.

One limitation that arose was around importing the Covidence data into RevMan. The exported data could not be directly imported into RevMan for analysis. As such, the lead investigator had to manually import the raw data into RevMan. In order to save time, raw data was retrieved from Covidence (raw data that was *independently* extracted into

Covidence). However, again, a duplicate independent RevMan data base was not set up, and instead the co-reviewer was requested to cross-reference the RevMan data against Covidence. Despite this, the manual input of data into RevMan increased the risk of human error in the analysis.

Finally, as part of including publications in all languages, both reviewers had to rely on the translation of two of the studies. While each reviewer had independently interpreted, reviewed and extracted data from each English study, for non-English studies both reviewers had to rely on the accuracy of the translations. Although the translators were proficient in both languages and had extensive medical and research-based training, in each case, the manuscript was translated by a single person, and it is possible that some of nuances of the studies could have been lost during translation.

Data analysis

Data analysis was performed by the lead investigator and the database was made available to the entire team for review. There were multiple instances of missing data which reduced the quality of the analysis. In particular, Kaewpradub et al. (69) had reported baseline and 24-hour postoperative haematocrit, however they had not calculated or presented the mean difference between the two. Based on guidelines from the Cochrane Handbook (9.4.5.2 Meta-analysis of Change Scores) (37), the final haematocrit values were used for analysis. Use of final haematocrit values did not account for the baseline variability between the two cohorts. This reduced the precision of the analysis and as such was given a smaller weight in the meta-analysis. Similarly, to enable the analysis to be undertaken, an *unstandardised* mean difference model was used.

Similarly, Karimi et al. (70) did not report standard deviation results for some of their outcomes. This had to be calculated using guidelines from the Cochrane Handbook (Obtaining Standard Deviations from Standard Errors, Confidence Intervals, T Values and P Values for Differences in Means) (37).

Context within the literature

The findings of this review were in keeping with those of previous reviews conducted by Fu et al. (40) and Zhao et al. (41) discussed in Chapter 1. While this review was limited to randomised controlled trials, the search strategy revealed four relevant studies (6, 7, 56, 57) with other study designs. These studies are summarised here for completeness.

- Akbas (56) and team conducted a study (unclear if it was retro- or prospective study, or a case control or cohort study; there was no information about randomisation or definition of outcomes, nor responses from the authors) in Turkey in 2014, involving 17 quasi-experimental and 17 control participants who underwent a modified LeFort I maxillary osteotomy (plus midline sagittal split) for rapid maxillary expansion in healthy patients. A dosage of 10mg/kg of TXA was used as an IV bolus preoperatively. They reported a statistically significant difference in the mean intraoperative blood loss volume: 52.65 (SD 17.51) in the TXA group compared to 219.71 (SD 72.96) ($P < 0.05$).
- Ichikawa et al. (7) had registered a randomised controlled trial in 2015 (64) and published the results in 2018. This study was written in Japanese with the abstract in English. In their abstract, the authors referred to their study as a 'prospective randomised controlled trial', however their patient recruitment was undertaken from April 2006 to March 2017. Assessing their results sections, they had four arms in the study: group 1 BSSO + TXA ($n=52$), group 2 BSSO without TXA ($n=119$), group 3 bimaxillary surgery with TXA ($n=53$) (further split into 36 participants receiving 20mg/Kg of TXA at start of maxillary and 17 participants receiving 10mg/Kg of TXA at start of maxillary osteotomy and 10mg/Kg before the mandibular osteotomy) and group 4 bimaxillary surgery without TXA ($n=46$). While three of the four groups had roughly 50 participants, group 2 which was composed of those receiving BSSO without TXA contained close to 120 participants. Nevertheless, this study was translated into English and reviewing the full text failed to clarify the methods any further. Multiple attempts were made to contact the lead author via emails in both English and Japanese neither of which received a response. The reviewers believed that many of the BSSO controls for this study were derived retrospectively. This is because the ethics approval of the study was dated 2015. Furthermore the trial was registered in

2015 (64). Finally the number of participants in group 2 which included the conventional treatment of BSSO without TXA was double that of the other groups. These all indicated that the authors had included many retrospective BSSO controls from 2006-2015. While variables such as surgical technique, use of hypotensive anaesthesia etc. *may* have been accounted for, the difference in the level of surgical experience when performing the first case in 2007 and those performed in 2015 onwards cannot be ignored. As such, this study was excluded for not following a randomised controlled trial definition. Nevertheless, they reported reduced blood loss in the TXA groups in both mandible-only (BSSO with 20mg/kg IV TXA resulting in 93.4 ml [SD=56.9] versus BSSO without TXA 95.6 [SD=68.3]) and bimaxillary surgery (bimaxillary with 20mg/kg TXA resulting in a mean of 220.5 ml [SD=127.3] versus without TXA resulting in a mean of 328.1 [SD=252.6]).

- Thongmalai (6) and team conducted a retrospective cohort study of healthy patients undergone bimaxillary osteotomy in 2016-2019 at their institution in Thailand. They included 14 experimental and 14 control participants further matched by the operation they received (BSSO and segmental LeFort I osteotomy versus BSSO and non-segmental LeFort I osteotomy). They reported intraoperative blood loss volume, change to haematocrit at day one and the operative time in hours. The intraoperative blood loss was reported as 664.29 (SD 213.42) in the TXA group and 850.00 (SD 356.26) in the controls. Operative time was 6.12 (SD 1.2) in the TXA group and 6.16 (SD 1.67) in the controls. Changes in pre- and 24-hour haematocrit levels were 3.9 (SD 3.93) for the TXA group and 6.29 (SD 3.82) in the controls. None of the abovementioned results were statistically significant.
- Yoshida et al. (57) published a retrospective cohort trial in 2021 including 20 experimental and 20 control participants. The experimental group received 1g of TXA at the time of induction and the control group received the same *after* the surgery. They reported statistically significant reduction in intraoperative blood loss in the TXA group was 161.7 (SD 45.3ml) versus 270.2 (SD 24ml) as well as operative time of 141.3 (SD 16.8min) versus 166.8 (SD 24.9min).

While all four studies supported the prophylactic use of TXA in orthognathic surgery, they were excluded to ensure the quality of data and improve the homogeneity of the meta-analysis.

Implications for practice

The result of this review recommends the use of prophylactic TXA, at a dosage of 10-20mg/kg or 1g, given intravenously at the time of induction, to healthy patients undergoing orthognathic surgery that involves a LeFort I osteotomy. This protocol reduces operative blood loss and reduces the operative time without any increased risk of thromboembolic events. This is in combination of other adjuncts discussed elsewhere in the literature, such as use of vasoconstrictors in local anaesthetic, deliberate hypotensive, 15-degree reverse Trendelenburg head position and preoperative anaemia optimisation.

There was limited data about the frequency of maintenance dosages. In other settings, an eight-hourly maintenance dosage has been recommended (80), however this may not be necessary in prophylactic use in orthognathic surgery where the largest risk of blood loss occurs during the preparation of osteotomies.

Implications for research

Based on the review of the current literature, it would be prudent for future trials to investigate and report more clinically important outcomes such as length of stay, need for transfusion and operative time. While intraoperative blood loss is a direct and easy outcome to measure, it may not be a patient specific outcome. Length of stay, need for transfusion and operative time are important patient, surgeon and economic outcomes. Nonetheless, given the indirect and infrequent nature of these outcomes, future studies will likely need larger sample sizes to allow adequate strength for assessing them. While data from multiple smaller studies can be pooled in meta-analyses to overcome sample size issues, heterogeneity amongst studies consequently becomes a significant barrier. As such, when designing a trial protocol, it is crucial to comprehensively assess the literature to ensure a clear, robust and standardised method of defining, measuring and reporting outcomes. Finally, while some

journals may implement word limits for their physical publications, most would be happy to include supplemental resources online. Making these e-resources available at the time of publication is undoubtedly easier than trying to go back to the data after receiving a correspondence from a researcher many years down the track. Since the start of this review, there have been two additional randomised controlled trial protocols (72, 73) registered that may be of significance to this topic. While both studies appear to be based in India, neither one has started recruiting participants.

Conclusion

Orthognathic surgery refers to a group of elective procedures involving osteotomy of the mandible and/or maxilla, with fixation into a functionally and cosmetically ideal position. Given the extensive blood supply in these structures and the invasive nature of such surgeries, these procedures are associated with significant blood loss. This review assessed the role of prophylactic TXA use in healthy patients undergoing orthognathic surgery and found its use beneficial in reducing: intraoperative blood loss, postoperative haematocrit and haemoglobin drop, the need for blood transfusions, and operative time and length of hospital stay, without increasing the risk of thromboembolic events. The results most widely support the use of TXA via the intravenous route and at a single dosage of 20mg/kg for surgeries including LeFort 1 osteotomy.

REFERENCES

1. Zaghi S, Holty JE, Certal V, Abdullatif J, Guilleminault C, Powell NB, et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2016;142(1):58-66.
2. Michael Miloro GEG, Peter E. Larsen, Peter Waite. *Peterson's Principles of Oral and Maxillofacial Surgery*. 4 ed 2022.
3. Bagheri SC, Bell RB, Khan HA. *Current therapy in oral and maxillofacial surgery*. Philadelphia: Elsevier Saunders; 2012.
4. Santos Junior JF, Abrahao M, Gregorio LC, Zonato AI, Gumieiro EH. Genioplasty for genioglossus muscle advancement in patients with obstructive sleep apnea-hypopnea syndrome and mandibular retrognathia. *Braz J Otorhinolaryngol*. 2007;73(4):480-6.
5. Samman N, Cheung LK, Tong AC, Tideman H. Blood loss and transfusion requirements in orthognathic surgery. *J Oral Maxillofac Surg* 1996;54(1):21-4; discussion 5-6.
6. Thongmalai N, Supatraviwat P, Vongvatcharanon S. The efficacy of low dose intravenous tranexamic acid on intraoperative blood loss in bimaxillary surgery. *J Oral Maxillofac Surg Med Pathol*. 2021;33(1):13-7.
7. Ichikawa H, Kakuya T, Yagisawa J, Ito AKI, Tanaka J-I. The Effect of Tranexamic Acid on the Reduction of Bleeding in Orthognathic Surgery. *The Japanese Journal of Jaw Deformities*. 2018;28(4):269-75.
8. AbuKarakly A, Al Mousa M, Samara OA, Baqain ZH. Pseudoaneurysm in the inferior alveolar artery following a bad split in bilateral sagittal split osteotomy. *Int J Oral Maxillofac Surg*. 2021;50(6):798-800.
9. Dal Pont G. Retromolar osteotomy for the correction of prognathism. *J Oral Surg Anesth Hosp Dent Serv*. 1961;19:42-7.
10. Hunsuck EE. A modified intraoral sagittal splitting technic for correction of mandibular prognathism. *J Oral Surg*. 1968;26(4):250-3.
11. Epker BN. Modifications in the sagittal osteotomy of the mandible. *J Oral Surg*. 1977;35(2):157-9.

12. Alrefai M, Daboul A, Fleischhacker B, Landes C. Piezoelectric versus conventional techniques for orthognathic surgery: Systematic review and meta-analysis. *J Stomatol Oral Maxillofac Surg*. 2022;123(5):e273-e8.
13. Apipan B. The effect of different dosage regimens of tranexamic acid on blood loss in bimaxillary osteotomy: a randomized, double-blind, placebo-controlled study. *Int J Oral Maxillofac Surg*. 2018;47(11):1504-5.
14. Choi WS, Irwin MG, Samman N. The effect of tranexamic acid on blood loss during orthognathic surgery: a randomized controlled trial. *J Oral Maxillofac Surg*. 2009;67(1):125-33.
15. Christabel A, Anantanarayanan P, Subash P, Soh CL, Ramanathan M, Muthusekhar MR, et al. Comparison of pterygomaxillary dysjunction with tuberosity separation in isolated Le Fort I osteotomies: a prospective, multi-centre, triple-blind, randomized controlled trial. *Int J Oral Maxillofac Surg*. 2016;45(2):180-5.
16. Jozefowicz E, Sabourdin N, Lambelin V, Lejeune V, Delassus R, Tavernier B. The effect of tranexamic acid on blood loss in orthognathic surgery: a randomized, placebo-controlled, equivalence study. *Int J Oral Maxillofac Surg*. 2022;51(5):637-42.
17. Secher JJ, Sidelmann JJ, Ingerslev J, Thorn JJ, Pinholt EM. The Effect of Tranexamic Acid and Gender on Intraoperative Bleeding in Orthognathic Surgery-A Randomized Controlled Trial. *J Oral Maxillofac Surg*. 2018;76(6):1327-33.
18. Koc EK, Besir A, Tugcugil E, Livaoğlu M. The effects of 5-degree, 10-degree and 20-degree reverse Trendelenburg positions on intraoperative bleeding and postoperative Edemea and ecchymosis around the eye in open rhinoplasty. *Am J Otolaryngol*. 2022;43(2):103311.
19. Ozkose M, Baykan H, Coşkuner İ. The Effect of Patient Positioning on Amount of Intraoperative Bleeding in Rhinoplasty: A Randomized Controlled Trial. *Aesthetic Plast Surg*. 2016;40(4):453-7.
20. Reed MR, Woolley LT. Uses of tranexamic acid. *Cont Educ Anaesth Crit Care Pain*. 2015;15(1):32-7.
21. Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. *Br J Surg*. 2013;100(10):1271-9.

22. Perel P, Ker K, Morales Uribe CH, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. *Cochrane Database Syst Rev.* 2013;2013(1):CD010245.
23. Dakir A, Ramalingam B, Ebenezer V, Dhanavelu P. Efficacy of Tranexamic Acid in Reducing Blood Loss during Maxillofacial Trauma Surgery-A Pilot Study. *J Clin Diagn Res.* 2014;8(5):ZC06-8.
24. McNicol ED, Tzortzopoulou A, Schumann R, Carr DB, Kalra A. Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. *Cochrane Database Syst Rev.* 2016;9(9):CD006883.
25. Samieirad S, Tohidi H, Eshghpour M, Hashemipour MA. An Unusual Case of Deep Vein Thrombosis After Orthognathic Surgery: A Case Report and Review of the Literature. *J Oral Maxillofac Surg.* 2018;76(12):2649 e1- e9.
26. Sundstrom A, Seaman H, Kieler H, Alfredsson L. The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: a case-control study using the General Practice Research Database. *BJOG.* 2009;116(1):91-7.
27. Taeuber I, Weibel S, Herrmann E, Neef V, Schlesinger T, Kranke P, et al. Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA Surg.* 2021; 156(6)::e210884.
28. Alimian M, Mohseni M. The effect of intravenous tranexamic acid on blood loss and surgical field quality during endoscopic sinus surgery: a placebo-controlled clinical trial. *J Clin Anesth.* 2011;23(8):611-5.
29. Abu Dakir BR, Vijay Ebenezer, Prakash Dhanavelu. Efficacy of Tranexamic Acid in Reducing Blood Loss during Maxillofacial Trauma Surgery–A Pilot Study. *J Clin Diagn Res.* 2014;8(5):ZC06-ZC8.
30. Sankar D, Krishnan R, Veerabahu M, Vikraman B. Evaluation of the efficacy of tranexamic acid on blood loss in orthognathic surgery. A prospective, randomized clinical study. *Int J Oral Maxillofac Surg.* 2012;41(6):713-7.
31. Nuhi S, Goljanian Tabrizi A, Zarkhah L, Rashedi Ashrafi B. Impact of Intravenous Tranexamic Acid on Hemorrhage During Endoscopic Sinus Surgery. *Iran J Otorhinolaryngol.* 2015;27(82):349-54.
32. Jordan Z, Lockwood C, Munn Z, Aromataris E. The updated Joanna Briggs Institute Model of Evidence-Based Healthcare. *Int J Evid Based Healthc.* 2019;17(1):58-71.

33. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? *PLoS Med.* 2010;7(9):e1000326.
34. Aromataris E, Munn Z (Editors). *JB I Manual for Evidence Synthesis*. JBI, 2020. [internet; cited: 14/05/2022] Available from <https://synthesismanual.jbi.global>.
35. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
36. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c332.
37. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 Cochrane; 2019.
38. Pearson A, Wiechula R, Court A, Lockwood C. The JBI model of evidence-based healthcare. *Int J Evid Based Healthc.* 2005;3(8):207-15.
39. Baghaie H, Shukla K, Stone J, Breik O, Munn Z. Effectiveness of prophylactic tranexamic acid versus placebo or no intervention for reducing blood loss in healthy patients undergoing orthognathic surgery: a systematic review protocol. *JB I Evid Synth.* 2023;21(2):430-40.
40. Fu R, Liu C, Yan Y, Suo L, Xie Y, Li Q, et al. Tranexamic Acid in Craniomaxillofacial Surgery: A Meta-Analysis and Systematic Review. *Facial Plast Surg Aesthet Med.* 2021;23(6):422-9.
41. Zhao H, Liu S, Wu Z, Zhao H, Ma C. Comprehensive assessment of tranexamic acid during orthognathic surgery: A systematic review and meta-analysis of randomized, controlled trials. *J Craniomaxillofac Surg.* 2019;47(4):592-601.
42. Sharma H, Arora S, Bhatia N, Rattan V, Sethi S. Tranexamic Acid Is Associated With Improved Operative Field in Orthognathic Surgery. *J Oral Maxillofac Surg.* 2020;78(9):1509-17.
43. van Galen KP, Engelen ET, Mauser-Bunschoten EP, van Es RJ, Schutgens RE. Antifibrinolytic therapy for preventing oral bleeding in patients with haemophilia or Von Willebrand disease undergoing minor oral surgery or dental extractions. *Cochrane Database Syst Rev.* 2019;4(4):CD011385.
44. Engelen ET, Schutgens RE, Mauser-Bunschoten EP, van Es RJ, van Galen KP. Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing minor oral surgery or dental extractions. *Cochrane Database Syst Rev.* 2018;7(7):CD012293.

45. Walker HK, Hall WD, Hurst JW. Clinical methods : the history, physical, and laboratory examinations. 3rd ed. Boston: Butterworths; 1990.
46. Andersen K, Thastum M, Norholt SE, Blomlof J. Relative blood loss and operative time can predict length of stay following orthognathic surgery. *International journal of oral and maxillofacial surgery*. 2016;45(10):1209-12.
47. Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M, et al. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Chapter 4: Searching for and selecting studies. 2021. [internet; cited 14/10/2022] Available from: www.training.cochrane.org/handbook.
48. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc*. 2015;13(3):196-207.
49. Brown S, Yao A, Taub PJ. Antifibrinolytic Agents in Plastic Surgery: Current Practices and Future Directions. *Plast Reconstr Surg*. 2018;141(6):937e-49e.
50. Choi WS. The value of tranexamic acid in orthognathic surgery. *Int J Oral Maxillofac Surg*. 2015;44(suppl 1):e3-.
51. Espahbod C, Veitz-Keenan A. Tranexamic acid reduces intraoperative blood loss in orthognathic surgery. *Evid Based Dent*. 2014;15(2):63.
52. Fathimani K, Perenack J, Christensen BJ. The Use of Tranexamic Acid in Facial Cosmetic Surgery Procedures: A Technical Note. *J Oral Maxillofac Surg*. 2021;79(11):2334-8.
53. Kurian A, Ward-Booth P. Blood transfusion and orthognathic surgery--a thing of the past? *Br J Oral Maxillofac Surg*. 2004;42(4):369-70.
54. O'Connor MK, Emanuelli E, Garg RK. Le Fort I maxillary osteotomy in a Jehovah's Witness patient: strategies for minimizing blood loss and maximizing safety. *Maxillofac Plast Reconstr Surg*. 2022;44(1):10.
55. Tabrizi R. Should we use prophylactic tranexamic acid in orthognathic surgery to decrease blood loss? *Int J Oral Maxillofac Surg*. 2018;47(11):1504.
56. Akbas E, Cebi Z, Cansiz E, Isler SC, Cakarar S. Does intravenous tranexamic acid reduce blood loss during surgically assisted rapid palatal expansion? *J Istanb Univ Fac Dent*. 2017;51(3):32-7.

57. Yoshida M, Ono S, Shimizu Y, Oue K, Mukai A, Doi M, et al. Usefulness of Tranexamic Acid Administration During Sagittal Split Ramus Osteotomy. *J Craniofac Surg.* 2021;32(1):273-6.
58. Arantes GC, Pereira RMR, de Melo DB, Alonso N, Duarte M. Effectiveness of tranexamic acid for reducing intraoperative bleeding in palatoplasties: A randomized clinical trial. *J Craniomaxillofac Surg.* 2017;45(5):642-8.
59. Nishat M, Iqbal S, Ahmed A, Younas S, Deokah LA, Rashid Z. Clinical study of Evaluation of the Effect of Tranexamic Acid in Primary Cleft Palate Surgery in Children. *Pak J Med. Health Sci..* 2021;15(10):2708-10.
60. Christabel A, Muthusekhar MR, Narayanan V, Ashok Y, Soh CL, Ilangoan M, et al. Effectiveness of tranexamic acid on intraoperative blood loss in isolated Le Fort I osteotomies- a prospective, triple blinded randomized clinical trial. *J Craniomaxillofac Surg.* 2014;42(7):1221-4.
61. Zellin G, Rasmusson L, Palsson J, Kahnberg KE. Evaluation of hemorrhage depressors on blood loss during orthognathic surgery: a retrospective study. *J Oral Maxillofac Surg.* 2004;62(6):662-6.
62. Sidelmann JJ, Gram JB, Godtfredsen ACM, Thorn JJ, Ingerslev J, Pinholt EM. Orthognathic Surgery-Induced Fibrinolytic Shutdown Is Amplified by Tranexamic Acid. *J Oral Maxillofac Surg.* 2020;78(7):1183-9.
63. Eftekharian H. Local use of "Tranxamic Acid" as an irrigation solution in orthognathic surgery. [Internet; cited: 10/08/2022]. 2012. Available from: <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01835391/full>.
64. Ichikawa H. The effect of tranexamic acid on blood loss in bimaxillary orthognathic surgery. [Internet; cited: 11/08/2022]. 2015. Available from: <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01880104/full>.
65. Olsen JJ. Prevention of Intraoperative Bleeding and Postoperative Swelling in Orthognathic Surgery Through the Use of Tranexamic Acid. [Internet; cited: 11/08/2022]. 2014. Available from: <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01548399/full>.
66. Eftekharian H, Vahedi R, Karagah T, Tabrizi R. Effect of tranexamic acid irrigation on perioperative blood loss during orthognathic surgery: a double-blind, randomized controlled clinical trial. *J Oral Maxillofac Surg.* 2015;73(1):129-33.

67. Emanuele N. The Effects of Tranexamic Acid on Blood Loss During Orthognathic Surgery. [Internet; cited: 10/08/2022]. 2018. Available from: <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01593704/full>.
68. Ito A. The effect of tranexamic acid on blood loss in orthognathic surgery. [Internet; cited: 10/08/2022]. 2013. Available from: <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01802851/full>.
69. Kaewpradub P, Apipan B, Rummasak D. Does tranexamic acid in an irrigating fluid reduce intraoperative blood loss in orthognathic surgery? A double-blind, andomized clinical trial. *J Oral Maxillofac Surg*. 2011;69(6):e186-9.
70. Karimi A, Mohammadi SS, Hasheminasab M. Efficacy of tranexamic acid on blood loss during bimaxillary osteotomy: A randomized double blind clinical trial. *Saudi J Anaesth*. 2012;6(1):41-5.
71. Mortazavi SH, Hamdzadeh H, Afsharinia S. The effect of tranexamic acid on the blood loss volumes in the patients underwent orthognathic surgeries. *J Kerman Univ Medical Sci*.. 2016;23(1):137-44.
72. Abdul Wahab PU. Evaluation of synergistic effect of Tranexamic acid and Haemocoagulase on intra-operative blood loss during Orthognathic Surgery. [Internet; cited: 02/02/2023]. 2022. Available from: <https://trialssearch.who.int/Trial2.aspx?TrialID=CTRI/2022/04/041767>.
73. Senthilnathan Periasamy. Comparing the effectiveness of intravenous clonidine and tranexamic acid on intraoperative blood loss and quality of surgical field during orthognathic surgery-a randomised clinical trial. [Internet; cited: 02/02/2023]. 2022. Available from: <https://trialssearch.who.int/Trial2.aspx?TrialID=CTRI/2022/06/043194>.
74. Sharma H, Arora S, Bhatia N, Rattan V, Sethi S. Tranexamic Acid Is Associated With Improved Operative Field in Orthognathic Surgery. *J Oral Maxillofac Surg* .. 2020;78(9):1509-17.
75. Schwaiger M, Wallner J, Edmondson SJ, Mischak I, Rabensteiner J, Gary T, et al. Is there a hidden blood loss in orthognathic surgery and should it be considered? Results of a prospective cohort study. *J Craniomaxillofac Surg*. 2021;49(7):545-55.
76. Mantzikos K, Segelnick SL, Schoor R. Hematoma following periodontal surgery with a torus reduction: a case report. *J Contemp Dent Pract*. 2007;8(3):72-80.

77. Bertossi D, Malchiodi L, Shideh E, Albanese M, Portelli M, Lucchese A, et al. Delayed progressive haematoma after Le Fort I osteotomy: A possible severe complication in orthognatic surgery. *Dent Res J (Isfahan)*. 2012;9(Suppl 2):S246-50.
78. Aziz S, Rossiter S, Homer CSE, Wilson AN, Comrie-Thomson L, Scott N, et al. The cost-effectiveness of tranexamic acid for treatment of postpartum hemorrhage: A systematic review. *Int J Gynaecol Obstet*. 2021;155(3):331-44.
79. Mizumoto R, Cristaudo AT, Hendaheewa R. A surgeon-led model to improve operating theatre change-over time and overall efficiency: A randomised controlled trial. *Int J Surg*. 2016;30:83-9.
80. de Vasconcellos SJ, de Santana Santos T, Reinheimer DM, Faria ESAL, de Melo MF, Martins-Filho PR. Topical application of tranexamic acid in anticoagulated patients undergoing minor oral surgery: A systematic review and meta-analysis of randomized clinical trials. *J Craniomaxillofac Surg*. 2017;45(1):20-6.

APPENDICES

Appendix 1: Initial search terms

PubMed:

Search term: **bleeding AND orthognathic surgery AND tranexamic acid**

("bleedings"[All Fields] OR "hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleed"[All Fields] OR "bleeding"[All Fields] OR "bleeds"[All Fields]) AND ("orthognathic surgical procedures"[MeSH Terms] OR ("orthognathic"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "orthognathic surgical procedures"[All Fields] OR ("orthognathic"[All Fields] AND "surgery"[All Fields]) OR "orthognathic surgery"[All Fields] OR "orthognathic surgery"[MeSH Terms] OR ("orthognathic"[All Fields] AND "surgery"[All Fields])) AND ("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields])

Restrictions: No date or language restrictions

Results: 27 records found (19/02/2022)

Appendix 2: PubMed search strategy example

Key Words:	Results
"Orthognathic Surgery"[MeSH Terms] OR "Orthognathic Surgical Procedures"[MeSH Terms] OR ("orthognathic surgical procedure"[All Fields] OR ("procedure"[All Fields] AND "orthognathic surgical"[All Fields]) OR (((("surgical procedures, operative"[MeSH Terms] OR ("Surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "Surgical"[All Fields] OR "surgically"[All Fields] OR "surgicals"[All Fields]) AND "procedure"[All Fields]) AND "Orthognathic"[All Fields]) OR "jaw surger"[All Fields] OR ("surger"[All Fields] AND "Jaw"[All Fields]) OR "maxillo mandibular surger"[All Fields] OR "maxillo mandibular surger"[All Fields] OR ("surger"[All Fields] AND "Maxillo-Mandibular"[All Fields]) OR ("surger"[All Fields] AND "Maxillo-Mandibular"[All Fields]) OR "maxillofacial"[All Fields] OR (((("Orthognathic"[All Fields] OR "orthognathics"[All Fields]) AND "surger"[All Fields]) AND "Maxillofacial"[All Fields]) OR ("surger"[All Fields] AND "maxillofacial orthognathic"[All Fields]) OR "Orthognathic"[All Fields] OR "maxillary osteotom"[All Fields] OR "mandibular osteotom"[All Fields] OR "lefort osteotom"[All Fields] OR "orthognathic surger"[All Fields] OR ("surger"[All Fields] AND "Orthognathic"[All Fields]))	1# 126,162
"Blood Transfusion"[MeSH Terms] OR "Operative Time"[MeSH Terms] OR "Hospitalization"[MeSH Terms] OR ("blood loss, surgical"[MeSH Terms] OR "Hemorrhage"[MeSH Terms] OR ("bleed"[All Fields] OR "hemorrhag"[All Fields] OR "haemorrhag"[All Fields] OR "blood"[All Fields]))	2# 4,848,665
("Tranexamic Acid"[MeSH Terms] OR "Antifibrinolytic Agents"[MeSH Terms]) OR (((((((("amstat"[All Fields] OR ("cl"[All Fields] AND "65336"[All Fields])) OR "cyclokapron"[All Fields]) OR "AMCA"[All Fields] OR "AMCA"[All Fields] OR "AMCHA"[All Fields] OR "amikapron"[All Fields] OR	3# 116,649

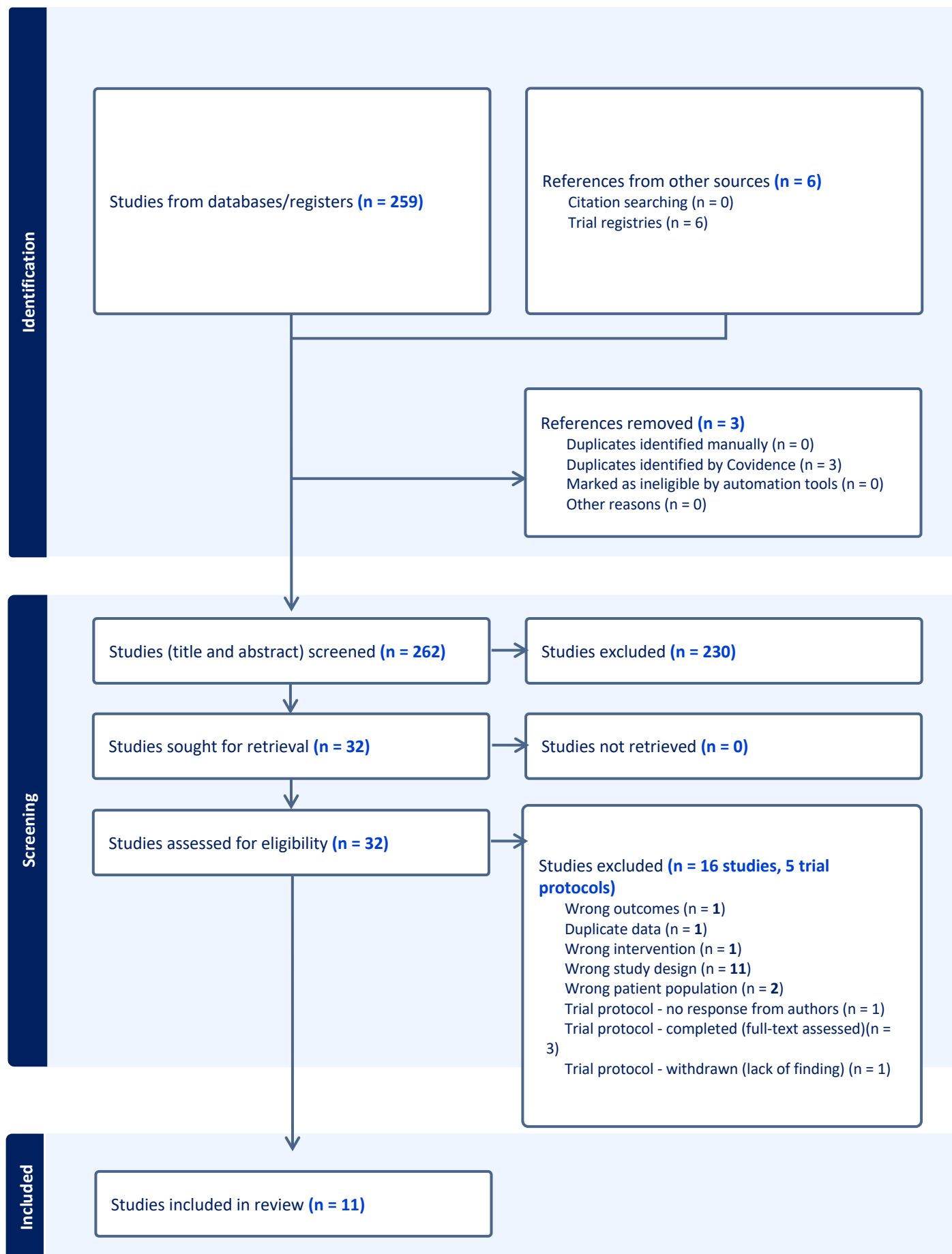
"aminomethyl"[All Fields] OR "anvitoff"[All Fields] OR "cyclocapron"[All Fields] OR "cyklocapron"[All Fields] OR "exacyl"[All Fields] OR "frenolyse"[All Fields] OR "kabi 2161"[All Fields] OR "t-AMCHA"[All Fields] OR "tranex*" [All Fields] OR "trans 4"[All Fields]) AND ("aminomethyl"[All Fields] OR "aminomethylated"[All Fields] OR "aminomethylation"[All Fields])) AND "cyclohexanecarboxylic acid"[All Fields]) OR "transamin*" [All Fields] OR "ugurool"[All Fields] OR ("methylcyclohexane"[All Fields] AND "carboxylate"[All Fields]) OR "antifibrinolysin*" [All Fields] OR "antifibrinolytic*" [All Fields] OR "antifibrinolytic agent"[All Fields] OR ("agent*" [All Fields] AND "Antifibrinolytic"[All Fields]) OR "plasmin inhibitor*" [All Fields] OR ("inhibitor*" [All Fields] AND "Plasmin"[All Fields]) OR "antiplasmin*" [All Fields] OR "plasmin inhibitor*" [All Fields] OR ("inhibitor*" [All Fields] AND ("fibrinolysin"[MeSH Terms] OR "fibrinolysin"[All Fields] OR "Plasmin"[All Fields] OR "plasmin s"[All Fields] OR "plasmine"[All Fields] OR "plasmins"[All Fields]))))	
#1 AND #2 AND #3	115

No date restrictions

No language restrictions

Conducted on 06/04/2022

Appendix 3: PRISMA flowchart of study selection process



Appendix 4: Excluded full text studies

Akbas, E., et al. (2017). "Does intravenous tranexamic acid reduce blood loss during surgically assisted rapid palatal expansion?" J Istanbul Univ Fac Dent 51(3): 32-37.

Wrong study design – unclear if retrospective or prospective cohort study

Arantes, G. C., R. M. R. Pereira, D. B. de Melo, N. Alonso and M. Duarte (2017). "Effectiveness of tranexamic acid for reducing intraoperative bleeding in palatoplasties: A randomized clinical trial." J Craniomaxillofac Surg 45(5): 642-648.

Wrong patient population – craniofacial/syndromal

Brown, S., A. Yao and P. J. Taub (2018). "Antifibrinolytic Agents in Plastic Surgery: Current Practices and Future Directions." Plast Reconstr Surg 141(6): 937e-949e.

Wrong study design – commentary

Choi, W. S. (2015). "The value of tranexamic acid in orthognathic surgery." J Oral Maxillofac Surg 44: e3-.

Wrong study design – conference presentation

Christabel, A., Muthusekhar, M. R., Narayanan, V. Ashok, Y., Soh, C. L., Ilango M., and Krishnan, N. (2014). "Effectiveness of tranexamic acid on intraoperative blood loss in isolated Le Fort I osteotomies--a prospective, triple blinded randomized clinical trial." J Craniomaxillofac Surg 42(7): 1221-1224.

Duplicate data

Espahbod, C. and A. Veitz-Keenan (2014). "Tranexamic acid reduces intraoperative blood loss in orthognathic surgery." Evid Based Dent 15(2): 63.

Wrong study design – review

Fathimani, K., J. Perenack and B. J. Christensen (2021). "The Use of Tranexamic Acid in Facial Cosmetic Surgery Procedures: A Technical Note." J Oral Maxillofac Surg 79(11): 2334-2338.

Wrong study design – commentry

Ichikawa, H., T. Kakuya, J. Yagisawa, A. K. I. Ito and J.-I. Tanaka (2018). "The Effect of Tranexamic Acid on the Reduction of Bleeding in Orthognathic Surgery." The Japanese Journal of Jaw Deformities 28(4): 269-275.

Wrong Study design – unclear if retrospective or prospective (the method discrepancy was evident in the originally English abstract, and the translation of the study into English did not clarify the methods. Emails to authors for clarification did not yield a reply)

Kurian, A. and P. Ward-Booth (2004). "Blood transfusion and orthognathic surgery--a thing of the past?" Br J Oral Maxillofac Surg 42(4): 369-370.

Wrong study design – Letter to the editor

Nishat, M., S. Iqbal, A. Ahmed, S. Younas, L. A. Deokah and Z. Rashid (2021). "Clinical study of Evaluation of the Effect of Tranexamic Acid in Primary Cleft Palate Surgery in Children." Pakistan J Medical Health Sci 15(10): 2708-2710.

Wrong patient population – Craniofacial/syndromal

O'Connor, M. K., E. Emanuelli and R. K. Garg (2022). "Le Fort I maxillary osteotomy in a Jehovah's Witness patient: strategies for minimizing blood loss and maximizing safety." Maxillofac Plast Reconstr Surg 44(1): 10.

Wrong study design – Case report

Sidelmann, J. J., J. B. Gram, A. C. M. Godtfredsen, J. J. Thorn, J. Ingerslev and E. M. Pinholt (2020). "Orthognathic Surgery-Induced Fibrinolytic Shutdown Is Amplified by Tranexamic Acid." J Oral Maxillofac Surg 78(7): 1183-1189.

Wrong outcomes

Tabrizi, R. (2018). "Should we use prophylactic tranexamic acid in orthognathic surgery to decrease blood loss?" Int J Oral Maxillofac Surg 47(11): 1504.

Wrong study design – letter to the editor

Thongmalai, N., P. Supatraviwat, and S. Vongvatcharanon (2020), "The efficacy of low dose intravenous tranexamic acid on intraoperative blood loss in bimaxillary surgery". J Oral Maxillofac Surg, Med & Path 33.

Wrong study design – retrospective cohort

Yoshida, M., S. Ono, Y. Shimizu, K. Oue, A. Mukai, M. Doi and M. Irifune (2021). "Usefulness of Tranexamic Acid Administration During Sagittal Split Ramus Osteotomy." J Craniofac Surg 32(1): 273-276.

Wrong study design – retrospective cohort

Zellin, G., L. Rasmusson, J. Palsson and K. E. Kahnberg (2004). "Evaluation of hemorrhage depressors on blood loss during orthognathic surgery: a retrospective study." J Oral Maxillofac Surg 62(6): 662-666.

Wrong comparators – Hypotensive anaesthesia vs Hypotensive anaesthesia AND TXA AND DDAVP

Appendix 5: Breakdown of risk of bias analysis

Unique ID	HB	Study ID	Apipan 2018	Assessor	
Experimental	IV TXA 10, 15, 20 mg/kg	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Assigned randomly to one of four groups by a computer-generated random number.	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY	No clear mention of timing of concealment, however the experimental drug was concealed from surgeon and anaesthetist.	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	Table 1 - subjectively numbers are similar, objectively P-values are all above 0.05	
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		PN	The medication was given intraoperatively once the patient was asleep. Given steps were taken to blind the surgeon and anaesthetist, it is likely that the participants would have also been blinded.	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA		
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA		

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Results from all 80 recruited participants are presented.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for intraoperative blood loss, length of stay, changes in haematocrit.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups. The examiners were not aware of group allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The only person aware of the assignment appears to be an "independent anaesthetics nurse"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	There was no change in the group allocations.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Only a single analysis was reported.
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	HB	Study ID	Choi 2009	Assessor	
Experimental	IV TXA 20 mg/kg	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response		Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Randomisation by computer-generated random number. Sealed envelopes were used and kept by clerical staff not involved in the study. All members of the surgical team, nursing staff, and the anaesthetist were unaware of the allocation. The	

	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	medication was given to the participant after the induction of anaesthetic.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	Table 1 - subjectively numbers are similar. The authors have also noted there is no significant difference in demographic data and baseline hemodynamic data.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	The medication was given intraoperatively once the patient was asleep.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN	There were 6/39 experimental participants and 3/39 of the control participants were excluded due to incomplete data collection
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Some concerns	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for intraoperative blood loss, length of stay, changes in haematocrit.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The only person aware of the assignment appears to be an "independent anaesthetics nurse"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	There was no change in the group allocations.

	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Only a single analysis was reported.
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

Unique ID	HB	Study ID	Christabel 2016	Assessor	
Experimental	IV TXA 10 mg/kg	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response		Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Randomisation was done by block method to ensure unbiased case selection by equal distribution. The test solution was supplied by someone who was independent of the trial. Investigator, anaesthetic team, and surgical team were unaware of the allocation.	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	Table 2 - subjectively numbers are similar.	

	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	The medication was given intraoperatively once the patient was asleep.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Yes. 50/50/50/50 and the ones excluded seem befitting (ASA II, CLAP, high MAP)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	

	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for intraoperative blood loss, length of stay, changes in haematocrit.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Triple blinded.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	There was no change in the group allocations.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Only a single analysis was reported.
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	HB	Study ID	Eftekharian 2015	Assessor	
Experimental	Topical TXA 1mg/ml	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		PY	States as randomised, but unclear about the method of randomisation. The surgeon and patient is blinded, the nursing staff may not have been?	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	Table 1 - limited data present about demographics (gender, age, weight) but they appear to be similar with a non-significant p value.	
	Risk of bias judgement		Some concerns		
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		PN	The medication was given intraoperatively once the patient was asleep. The surgeon and patient were blinded to the intervention and the outcomes measured are objective enough to not be affected by unblinding.	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	56 participants, and while mentioned that power analysis has been done to determine the sample size, it is not explicitly noted.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for intraoperative blood loss, length of surgery.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	The only person aware of the assignment appears to be the scrub nurse.

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	There was no change in the group allocations.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Only a single analysis was reported.
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

Unique ID	HB	Study ID	Jozefowicz 2019	Assessor	
Experimental	IV TXA 2g	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response		Comments

Bias arising from the randomisation process	1.1 Was the allocation sequence random?	Y	"...patients were randomly allocated in a one-to-one ratio to receive either TA or placebo. The randomisation sequence was provided by an independent statistician (who did not take part in assessing the patients at any point in the study) using computer-generated random numbers with block sizes of six." Double blinded (patient and anaesthetic team were blinded)
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	The medication was given intraoperatively once the patient was asleep. The surgeon and patient were blinded to the intervention and the outcomes measured are objective enough to not be affected by unblinding.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to	NA	

	analyse participants in the group to which they were randomised?		
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	56 participants, and while mentioned that power analysis has been done to determine the sample size, it is not explicitly noted.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for blood loss, length of surgery and Hb change.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	There were several cases that were unblinded due to safety concerns, and if they belonged to the control group, they received the experimental treatment. However the data is presented as PP and ITT.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	

	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Y	ITT and PP results are both given.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	Y	ITT and PP results are both given.
	Risk of bias judgement	Some concerns	
Overall bias	Risk of bias judgement	Low	

Unique ID	HB	Study ID	Kaewpradub 2011	Assessor	
Experimental	Topical TXA 0.05%	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response		Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	"Patients assigned randomly to 2 groups by drawing lots"	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		

	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	Subjectively in table 1 and objectively in lack of statistical significance.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	The medication was given intraoperatively once the patient was asleep. The surgeon and patient were blinded to the intervention and the outcomes measured are objective enough to not be affected by unblinding.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	20 controls and 20 experimental participants.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for blood loss, length of surgery and Hb change.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Unclear as who recorded the intraoperative data
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	All measurements are objective.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	No changes to the groups.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	Low	

Overall bias	Risk of bias judgement	Low	
---------------------	-------------------------------	------------	--

Unique ID	HB	Study ID	Karimi 2012	Assessor	
Experimental	IV TXA 20mg/kg	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Computer generated codes. Sealed envelopes, opened by an external member, experiment drug or placebo prepared and given to anaesthetic team, the allocation resealed and kept hidden until end of study.	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	Subjectively in the description of the groups (age, weight etc.) but also objectively with lack of statistical significance.	
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		N	The medication was given intraoperatively once the patient was asleep. The surgeon, anaesthetist and patient were blinded to the	

	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	intervention and the outcomes measured are objective enough to not be affected by unblinding.
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	16 controls and 16 experimental participants. None lost to follow up.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for Hb, Hct and estimate of IOL.

Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	No changes to the groups.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	HB	Study ID	Mortazavi 2015	Assessor	
------------------	----	-----------------	----------------	-----------------	--

Experimental	IV TXA 20mg/kg	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		NI	Used a coding system' but unclear how they assigned to each group	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	Subjectively in the description of the groups (age, weight etc.) but also objectively with lack of statistical significance.	
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		PN	The medication was given intraoperatively once the patient was asleep. The surgeon and patient were blinded to the intervention and the outcomes measured are objective enough to not be affected by unblinding.	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA		
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y		

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	24 controls and 24 experimental participants. No mention of loss to follow up.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Appropriate measurement method for Hb and Hct, however it is unclear why they did not measure intraoperative blood loss and chose to calculate it. IOBL is routinely recorded at the end of the operation and forms part of the basic surgical record. Especially as some of the other studies referenced had measured this outcome before.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	Surgeon prepared the medication, anaesthetic team delivered, but unclear if surgeon was blinded or not.

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	No changes to the groups.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	High	

Unique ID	HB	Study ID	Sankar 2012	Assessor	
Experimental	IV TXA 10mg/kg bolus and 1mg/kg infusion	Comparator	Saline	Source	Journal article(s)

Domain	Signalling question	Response	Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?	Y	Computer generated codes. Experiment drug or placebo prepared preoperatively, unlabelled, placed in envelope, and the envelope is attached to each participant. None of the surgical, nursing, or anaesthetic teams were aware of the allocation.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	Subjectively in the description of the groups (age, weight etc.) but also objectively with lack of statistical significance.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	N	The medication was given intraoperatively once the patient was asleep. The surgeon, anaesthetist and patient were blinded to the intervention and the outcomes measured are objective enough to not be affected by unblinding.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	

	2.7 If N/PN/Ni to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	25 controls and 25 experimental participants. None lost to follow up.
	3.2 If N/PN/Ni to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/Ni to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for Hb, Hct and estimate of intraoperative blood loss.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/Ni to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/Ni to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	No changes to the groups.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	HB	Study ID	Secher 2018	Assessor	
Experimental	IV TXA 1g	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response		Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		PY	Block randomisation was used. Experiment drug or placebo prepared by pharmacist, unlabelled, and delivered by the anaesthetist. None of the surgical, nursing, or anaesthetic teams were aware of the allocation.	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		

	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	Subjectively in the description of the groups (age, weight etc.) but also objectively with lack of statistical significance.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	N	The medication was given intraoperatively once the patient was asleep. The surgeon, anaesthetist and patient were blinded to the intervention and the outcomes measured are objective enough to not be affected by unblinding.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	52 controls and 52 experiments were allocated. there was some drop out (predominantly in control group... due to logistical difficulties.) This brings about some concern, however I appreciate that the researchers were blinded about which group they belonged to and as such excluded all such patients.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Some concerns	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for Hb, Hct and estimate of intraoperative blood loss.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was	PY	No changes to the groups.

the reported result	finalized before unblinded outcome data were available for analysis?		
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented are universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

Unique ID	HB	Study ID	Sharma 2020	Assessor	
Experimental	15mg/kg IV TXA	Comparator	Saline	Source	Journal article(s); Trial protocol
Domain	Signalling question		Response		Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Computer generated random numbers were used. The envelopes were kept sealed until 30 minutes prior to general anaesthetic. The patient, anaesthesia provider reporting intraoperative data, and operating surgeon were kept unaware of the group allocation.	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		

	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	Subjectively in the description of the groups (age, weight etc.) but also objectively with lack of statistical significance.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	N	"The medication was given intraoperatively once the patient was asleep. The surgeon, anaesthetist and patient were blinded to the intervention and the outcomes measured are objective enough to not be affected by unblinding.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	18 controls and 18 experiments were allocated; there was no drop out.

Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement method for Hb, Hct and estimate of intraoperative blood loss. Same issue as Mortazavi, unclear why they did not report the IOBL directly.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same method was used in different groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Surgical and anaesthetic team blinded.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	No changes to the groups.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.

	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	KS	Study ID	Apipan 2018	Assessor	
Experimental	10/15/20 mg/kg TXA	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Computer generated randomisation to 1 of 4 groups Unclear concealment, however surgeon and anaesthesiologist were both blinded to study drug	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	Mostly non-statistically significant ($p>0.05$) demographic parameters	
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		N	Intervention administered after induction of anaesthesia	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PN		
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA		
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y		
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to		NA		

	analyse participants in the group to which they were randomised?		
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	80 patients completed the study, with no loss to follow up
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement of IOBL, LOS, Hct change
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Only 2x independent anaesthetics nurses were aware of allocation
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was	Y	No changes to groups, analysed with 'intention to treat'

the reported result	finalized before unblinded outcome data were available for analysis?		
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis reported
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	KS	Study ID	Choi 2009	Assessor	
Experimental	20mg/kg TXA	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response		Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y		Computer generated randomisation to receive 20ml/kg TXA or 0.9% saline Sealed envelopes kept regarding the allocations, handled by clerical staff not involved in study. Treating surgeon, nurses and anaesthetic team all blinded

	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	No statistically significant difference noted in baseline demographic and haemodynamic data between treatment groups
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	N	Intervention administered after induction of anaesthesia
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	PN	73 patients initially enrolled, 12 patients excluded (9 due to incomplete data collection, and 3 due to post-op reintubation). Final analysis completed for 61 participants
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Some concerns	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement of IOBL, LOS, Hb, Hct change
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Treating team blinded to allocations. Allocation information kept in sealed envelopes by clerical staff (not involved in study)
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was	Y	No changes to groups, analysed with 'intention to treat'

the reported result	finalized before unblinded outcome data were available for analysis?		
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis reported
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

Unique ID	KS	Study ID	Christabel 2016	Assessor	
Experimental	10mg/kg TXA	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response		Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Randomised by block method (drawing lots)	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	No statistically significant difference noted in demographic data between treatment groups (P>0.05)	
	Risk of bias judgement		Low		

Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	PN	Intervention administered after induction of anaesthesia Test solution provided by an independent person (not part of trial)
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	49 patients underwent analysis, nil loss to follow up
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	

Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement of IOBL, Hb, operating time
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Triple blinded. Surgeon, anaesthetist, and investigator blinded. Independent person prepared test drug
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	No changes to groups, analysed with 'intention to treat'
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis reported
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	KS	Study ID	Eftekharian 2015	Assessor	
Experimental	1000 mg TXA	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		PY	Randomisation method not described Irrigation fluid provided by a nurse just before the operation	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	No statistically significant difference noted in demographic data between treatment groups ($P>0.05$)	
	Risk of bias judgement		Some concerns		
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?		PN	Intervention likely administered after induction of anaesthesia All surgeons and patients were blinded to the randomisation (however no mention of anaesthetics/nursing/theatre staff blinding)	
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA		
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y		

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	PY	56 patients analysed, nil mention of loss to follow up
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Appropriate measurement of IOBL, operating time, however postoperative Hb and Hct not measured
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	Surgeon and patient blinded A nurse provided the solution before the operation (however unclear whether they were aware of the allocation, or any other parties were aware (anaesthetics, theatre staff))
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	No changes to groups, analysed with 'intention to treat'
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis reported
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

Unique ID	KS	Study ID	Jozefowicz 2019	Assessor	
Experimental	2x 1000 mg TXA	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response		Comments
Bias arising from the	1.1 Was the allocation sequence random?		Y		

randomisation process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Computer generated randomisation (block sizes of 6) independent statistician Patient and anaesthetic team in charge were blinded
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN	No p value provided
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	Intervention administered after induction of anaesthesia Anaesthetic team and patients were blinded to the randomisation
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	PY	147 participants included in analysis PP and ITT analysis data available
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Appropriate measurement of IOBL, operating time, Hb, transfusion, LOS
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	2 patients unblinded from experimental group, 5 patients unblinded from placebo group. Unblinding protocol only followed where there were concerns about excess blood loss and patient safety. Placebo group then received treatment with TXA
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	Data presented as ITT and PP
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Some changes to groups during study following an unblinding protocol, however, final data analysed by 'intention to treat' and 'per protocol'
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.

	5.3 ... multiple eligible analyses of the data?	Y	ITT and PP analysis provided
	Risk of bias judgement	Some concerns	
Overall bias	Risk of bias judgement	Low	

Unique ID	KS	Study ID	Kaewpradub 2011	Assessor	
Experimental	500mg TXA	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Randomisation into 2 groups by drawing lots Surgical and anaesthetic teams were blinded	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	No statistically significant difference noted in demographic data (p>0.05)	
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		PN	Intervention administered after induction of anaesthesia Anaesthetic and surgical teams blinded to randomisation	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		

	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	40 participants included in analysis, no loss to follow up
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement of IOBL, operating time, Hct, transfusion
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	IOBL calculated by anaesthesiologist, who was blinded to allocation

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	No changes to groups, analysed with 'intention to treat'
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis reported
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	KS	Study ID	Karimi 2012	Assessor	
Experimental	20mg/kg TXA	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response		Comments

Bias arising from the randomisation process	1.1 Was the allocation sequence random?	Y	Computer generated randomisation Allocations kept in sealed envelopes by staff who were not in the study, allocation provided to independent anaesthetic team member who prepared drug and gave it to blinded anaesthetist
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	No statistically significant difference noted in demographic data ($p>0.05$), limited demographic data available
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	N	Intervention administered after induction of anaesthesia Anaesthetic, nursing and surgical teams blinded to randomisation
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	

	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	32 patients completed the study, nil loss to follow up
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement of IOBL, operating time, Hb, Hct, LOS, transfusion
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Surgical, anaesthetic team and nursing team all blinded to allocations, allocations known to independent staff member and anaesthetist, allocations sealed in envelopes after drug prepared by independent anaesthetist
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	No changes to groups, analysed with 'intention to treat'
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis reported
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	KS	Study ID	Mortazavi 2016	Assessor	
Experimental	20mg/kg TXA	Comparator	Saline	Source	Journal article(s); Trial protocol
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		PY	No description of randomisation process - however mentioned specific coding system	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	No significant difference noted between groups (p = 0.770)	

	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	N	Surgical team and patient were blinded to the injected drug The drug was prepared by a surgeon and given to anaesthetist for injection, unclear whether they were involved in the surgery
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	48 patients completed the study, with no loss to follow up
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	

	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Appropriate measurement of IOBL using change in Hb or Hct
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	Surgeon prepared drug to give to anaesthetist for injection, however unclear whether they were part of the "surgical team"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	High	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	No mention of unblinding, changes to groups or adverse events
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis only
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	High	

Unique ID	KS	Study ID	Sankar 2012	Assessor	
Experimental	10mg/kg TXA bolus, 1mg/kg maintenance	Comparator	Saline	Source	Journal article(s)
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Computer generated randomisation Theatre nurse provided with allocation Nursing staff, anaesthetic team and surgical team blinded	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	No statistically significant difference noted in demographic data (p>0.05)	
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		N	Intervention administered after induction of anaesthesia Anaesthetic, nursing and surgical teams blinded to randomisation	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA		

	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	50 patients completed the study, nil loss to follow up
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement of IOBL, Operating time, Transfusion
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Surgical, anaesthetic team and nursing team all blinded to allocations; allocations only known to theatre nurse who administered medication
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	No changes to groups, analysed with 'intention to treat'
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis reported
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	KS	Study ID	Secher 2018	Assessor	
Experimental	1000mg TXA	Comparator	Saline	Source	Journal article(s); Trial protocol
Domain	Signalling question		Response		Comments
Bias arising from the	1.1 Was the allocation sequence random?		Y	Block randomisation Patient, anaesthetic team and surgical team blinded	

randomisation process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	Hospital pharmacy aware of allocation, responsible for preparing drug, administered by blinded anaesthetist
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	No statistically significant difference noted in demographic data ($p>0.05$)
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	N	Intervention administered after induction of anaesthesia Patient, Anaesthetic and surgical team blinded to randomisation Medication prepared by pharmacy and administered by anaesthetist (blinded)
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	PN	104 patients included in study, 1 dropped out in intervention, 7 dropped out in control (from logistical difficulties)

	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY	Patients, surgical and anaesthetic team were blinded to allocations
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Some concerns	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement of IOBL, Operating time, Hb, Hct
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Surgical and anaesthetic team blinded
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	No changes to groups, analysed with 'intention to treat'
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis reported

	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

Unique ID	KS	Study ID	Sharma 2020	Assessor	
Experimental	15mg/kg TXA + 0.25- 0.7ug/kg DT	Comparator	Saline + Dexmedetomidine (DT)	Source	Journal article(s); Trial protocol
Domain	Signalling question		Response	Comments	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?		Y	Computer generated randomisation Patient, anaesthetic operator recording, and surgeon was blinded Allocations concealed in opaque sealed envelopes until patient enrolment	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?		N	No statistically significant difference noted in demographic data (p>0.05)	
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?		N	Intervention administered after induction of anaesthesia Patient, anaesthetic team and surgical team blinded to randomisation	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y	18 patients in study, nil loss to follow up
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Appropriate measurement of IOBL, operating time
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement consistent across treatment arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Surgical and anaesthetic team blinded
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	No changes to groups, analysed with 'intention to treat'
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The information assessed and presented is universally accepted.
	5.3 ... multiple eligible analyses of the data?	N	Single analysis reported
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Appendix 6: Extended GRADE assessment of quality of evidence and strength of recommendations

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic acid	Placebo	Relative (95% CI)	Absolute (95% CI)	
Intraoperative blood loss - systemic TXA											
9	randomised trials	not serious	not serious	not serious	not serious	none	358	350	-	MD 189.9 lower (240.62 lower to 139.19 lower)	⊕⊕⊕⊕ High
Intraoperative blood loss - topical TXA											
2	randomised trials	not serious	not serious	not serious	serious ^a	none	48	48	-	MD 191.11 lower (336.33 lower to 45.89 lower)	⊕⊕⊕⊕ High
Intraoperative blood loss - systemic TXA 20mg/kg											
4	randomised trials	serious ^b	not serious	not serious	not serious	none	92	89	-	MD 318.94 lower (402.01 lower to 235.87 lower)	⊕⊕⊕⊖ Moderate
Intraoperative blood loss - systemic TXA Single 1g dose											
2	randomised trials	serious ^b	not serious	not serious	serious ^a	none	123	118	-	MD 153.96 lower (234.83 lower to 73.08 lower)	⊕⊕⊕⊖ Moderate
Intraoperative blood loss - systemic TXA maxilla-only											
2	randomised trials	serious ^b	not serious	not serious	not serious	none	132	129	-	MD 158.69 lower (172.34 lower to 145.04 lower)	⊕⊕⊕⊖ Moderate
Intraoperative blood loss - systemic TXA bimaxillary surgery											
5	randomised trials	not serious	not serious	not serious	not serious	none	107	107	-	MD 269.45 lower (424.27 lower to 114.62 lower)	⊕⊕⊕⊕ High
Postoperative haematocrit change - systemic TXA											
3	randomised trials	not serious	serious ^c	not serious	not serious	none	152	149	-	MD 1.86 lower (2.86 lower to 0.85 lower)	⊕⊕⊕⊖ Moderate
Postoperative haemoglobin change - systemic TXA											

Certainty assessment							No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic acid	Placebo	Relative (95% CI)	Absolute (95% CI)	
4	randomised trials	serious ^b	serious ^c	not serious	not serious	none	244	242	-	MD 6.88 lower (9.57 lower to 4.19 lower)	⊕⊕○○ Low

Transfusion rate random effect - systemic TXA

6	randomised trials	not serious	not serious	not serious	serious ^a	none	4/267 (1.5%)	15/263 (5.7%)	57 fewer per 1000	30 fewer per 1,000 (from 70 fewer to 10 more)	⊕⊕⊕○ Moderate
---	-------------------	-------------	-------------	-------------	----------------------	------	--------------	---------------	-------------------	---	------------------

Operating time - systemic TXA

8	randomised trials	not serious	not serious	not serious	serious ^{a,b}	none	334	326	-	MD 11.45 lower (19.97 lower to 2.93 lower)	⊕⊕⊕○ Moderate
---	-------------------	-------------	-------------	-------------	------------------------	------	-----	-----	---	--	------------------

Operating time - systemic maxilla-only

3	randomised trials	not serious	not serious	not serious	not serious	none	139	134	-	MD 16.34 lower (24.47 lower to 8.2 lower)	⊕⊕⊕⊕ High
---	-------------------	-------------	-------------	-------------	-------------	------	-----	-----	---	---	--------------

Operating time - systemic mandible-only

2	randomised trials	serious ^b	not serious	not serious	serious ^a	none	26	26	-	MD 26.07 higher (5.4 higher to 46.74 higher)	⊕⊕○○ Low
---	-------------------	----------------------	-------------	-------------	----------------------	------	----	----	---	--	-------------

Operating time - systemic bimaxillary surgery

6	randomised trials	not serious	not serious	not serious	very serious ^{d,e}	none	143	132	-	MD 6.31 lower (20.24 lower to 7.61 higher)	⊕⊕○○ Low
---	-------------------	-------------	-------------	-------------	-----------------------------	------	-----	-----	---	--	-------------

Length of stay

2	randomised trials	serious ^b	not serious	not serious	not serious	none	52	49	-	MD 0.3 lower (0.87 lower to 0.27 higher)	⊕⊕⊕○ Moderate
---	-------------------	----------------------	-------------	-------------	-------------	------	----	----	---	--	------------------

Adverse reaction

8	randomised trials	not serious	not serious	not serious	not serious	none	0/301 (0.0%)	0/300 (0.0%)	not pooled	see comment	⊕⊕⊕⊕ High
---	-------------------	-------------	-------------	-------------	-------------	------	--------------	--------------	------------	-------------	--------------

CI: confidence interval; MD: mean difference; OR: odds ratio; TXA: tranexamic acid

Explanations

a. Wide confidence intervals indicating imprecise outcome.

b. More than half of the studies did not have low risk of bias.

Domain 1, Randomisation [Eftekharian (66)]

Domain 3, Missing outcome data [Choi, Irwin and Samman(14), Secher (17)]

Domain 4, Measurement of the outcome [Mortazavi (71), Sharma(74)]

Domain 5, Selection of reported results [Jozefowicz (16)]

c. The timing of postoperative haemoglobin and haematocrit varied among studies (ranging from four to 24 hours). Given that these values change overtime, there is potential for inconsistency.

d. Five minutes is used as a threshold of importance. The 95% CI cross the threshold and thus the comparison is imprecise.

e. The 95% CI crosses zero and thus the comparison is very imprecise.