# Lysine Analogue Use and Thromboembolic Risks: An Evidence Based Analysis

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## Synopsis

Allogenic blood transfusions, although potentially life-saving, are associated with increased risk of infection, fluid overload, thrombosis, and death. Minimizing exposure to blood products is important for patients and the healthcare system. Antifibrinolytic lysine analogues are effective antihaemorrhagic agents used for the reduction of blood loss and subsequent need for transfusion. However, the pharmacologic mechanism of decreased clot breakdown would suggest the medications should increase the risk of venous thromboembolic adverse events. Trials of lysine analogue administration are often underpowered to detect the effect of these medications on thrombotic events. As lysine analogue use increases for blood loss reduction, there is an important need for research dedicated to the safety of lysine analogues, especially in patients who are at highest risk of venous thromboembolism.

Through systematic review and meta-analyses, we investigated the use of lysine analogues in cancer patients, where VTE is particularly prevalent. We identified that only a small number of trials have been performed in cancer patients. Among available data, similar reduction of transfusion was observed in cancer patients treated with lysine analogues compared to non-cancer patients. However, we also found that existing data was grossly underpowered to determine the effect of lysine analogues on risk of VTE (Peto odds ratio (OR) 0.60; 95% CI 0.28-1.30).

By administering lysine analogues topically, as opposed to intravenously, systemic absorption of the drug may be limited, and the occurrence of unwanted side-effects may be minimized. We also reviewed the published literature to determine if there was sufficient evidence to support topical application of tranexamic acid. Topically applied tranexamic acid effectively reduces both transfusion risk and blood loss and no increased risk of VTE events was observed (pooled OR=0.78, 95% CI 0.47 to 1.29). However, none of these studies included cancer patients and the vast majority of the trials were in orthopedic surgery.

Lastly, we sought to determine the extent to which lysine analogues are currently used at a large tertiary care academic institution. In addition, we explored which factors influenced lysine analogue use, and areas of informational or study need. Surgeons reported low lysine analogue use, and the timing of administration varied considerably. Many surgeons (66%) believed a clinical trial was needed to demonstrate the efficacy of lysine analogues in their respective surgical field, and 59% felt a trial was needed to demonstrate that the medication was safe in their patient population.

We confirmed that there are only a few studies evaluating the effect of lysine analogues in cancer patients and that many surgeons are concerned about the safety profile of these medications. Surgeons may feel more comfortable administering these agents topically as opposed to intravenously, and while this may be a safer option, there has been limited evaluation of this approach outside of orthopedic procedures.

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# Table of Contents

## Glossary

1. DVT……..Deep vein thrombosis
2. EACA……Epsilon aminocaproic acid
3. GRADE……..Grading of Recommendations Assessment, Development, and Evaluation
4. MI……..…Myocardial infarction
5. NSQIP……National Surgical Quality Improvement Program
6. OR……..Odds ratio
7. PE……..Pulmonary embolism
8. PRESS……..Peer reviewed electronic search strategy
9. PRISMA……..Preferred reporting items for systematic reviews and meta-analysis
10. RBC……..…Red blood cell
11. RCT……..…Randomized controlled trial
12. ROB……..Risk of bias
13. RR……Relative risk
14. SMD……..Standardized mean difference
15. TDF……..Theoretical Domains Framework
16. TOH……..The Ottawa Hospital
17. TXA……..Tranexamic acid
18. VTE……..Venous thromboembolic
19. WMD……..Weighted mean difference

# Table Index

## Chapter 3



## Chapter 5



## Chapter 7



## Chapter 8



# Figure Index

## Chapter 3



## Chapter 5

# Chapter 1

# Thesis Introduction and Overview

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### 1.1 The Problem

Peri-operative bleeding is a common and often severe side-effect of surgical procedures and is a significant cause of both morbidity and mortality in the operative setting(1,2). Major bleeding related to surgery presents significant peri-operative challenges for the both the surgeon and the surgical team. Although mortality rates are low for many routine surgical procedures, severe and unexpected surgical bleeding can increase these rates substantially(3,4). In cases of severe peri-operative bleeding, blood transfusions are often administered, with an estimated 60-70% of red blood cell (RBC) transfusions being used in the surgical setting(5,6). Allogenic blood transfusions are often a life-saving intervention, but transfusion also exposes patients to other risks(7,8).

Effective methods to minimize blood loss and subsequent transfusions are of great interest to the medical community. Antifibrinolytic lysine analogues are pharmacologic haemostatic agents, which have been shown to be incredibly effective at reducing blood loss and RBC transfusion requirements(9–14). Due to the mechanism of action of lysine analogues, a theoretical increased risk of developing venous thromboembolic (VTE) complications is introduced(15). However there have only been sporadic, isolated reports of venous or arterial thrombosis or embolism associated with lysine analogue use(16–18). Lysine analogues are considered to have generally strong safety profiles, although some concerns remain due to the lack of comparative trials with safety endpoints, such as VTE, as primary outcomes.

Despite all of the existing evidence supporting the efficacy of lysine analogues, the physician uptake of these drugs in certain areas of medicine has been slow or even non-existent(19,20). It is argued that the foremost issue concerning lysine analogues is the lack of comparative clinical trials addressing safety, outside of cardiac surgery. The rarity of VTE makes properly powering a trial to detect differences between groups very difficult. Until a trial of such nature is performed, the safety profile of lysine analogues may remain in question in patients at higher risk for VTE events.

## 1.2 Purpose & Rationale

There is an important need for further research into the relationship between lysine analogue administration and VTE risk in patient populations where VTE is already prevalent. We sought to develop a foundation of research and evidence that would help facilitate a study of lysine analogue administration, properly designed and powered to detect differences in adverse events. To do so, we conducted various studies to fill important evidence and knowledge gaps in the current literature. Understanding how these agents are currently used at our institution is also key to the planning of a potential trial.

The overarching purpose of my thesis was to investigate the efficacy and safety of lysine analogues in cancer patients in an attempt to fill important gaps in the literature and potentially improve physician uptake of these drugs. We aimed to address these gaps by investigating the use of topically administered lysine analogues, as well as exploring the use of lysine analogues in patients with cancer. The end goal of this thesis was to determine if a randomized controlled trial involving lysine analogues in cancer patients was required prior to routine use of these medications.

## 1.3 Objectives

We will address three specific objectives that are explored within separate but related manuscripts in chapters 3, 5, and 7.

1. The first objective of this thesis was to evaluate the safety and efficacy of lysine analogue administration in cancer patients through systematic review of the existing literature (Chapter 3).
2. The second objective of this thesis was to evaluate the efficacy and safety of topically administered lysine analogues compared to control in all populations (Chapter 5).

3. The third objective of this thesis was to evaluate the extent of lysine analogue use at TOH, the reasons for non-use, and finally, we wished to explore surgeon interest in participation in a clinical trial (Chapter 7).

## 1.4 Overview of Submitted Thesis & Manuscripts

This thesis was developed in order to fill existing gaps in current literature and to aid in the development of a potential clinical trial involving lysine analogues, properly designed and powered to detect differences in safety outcomes. Outlined below are the stages of research of this thesis, coupled with the relevant chapters.

- Chapter 2 *"Background Evidence"* was the first stage, which involved the creation of a solid foundation of background evidence and knowledge. This chapter provides information needed by the reader to comprehend the issues surrounding blood loss and transfusion, the specific safety concerns surrounding lysine analogues in cancer patients, as well as the concerns regarding the method of administration of lysine analogues.
- Chapter 3 *"The safety and efficacy of lysine analogues in cancer patients: A systematic review and meta-analysis"*, presents a published systematic review and meta-analysis and provides the reader in-depth results regarding the safety and efficacy of lysine analogues in the oncology population.
- Chapter 4 "*The topical application of tranexamic acid, is it effective?"* introduces the issue of the most optimal route of administration of lysine analogues. This chapter provides the reader with the context needed to proceed to the following chapter.
- Chapter 5 "*The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis",* presents a manuscript and related appendices which provides the reader all available evidence and in-depth analyses regarding the use of topically administered tranexamic acid.

- Chapter 6 "*Surgeon usage of lysine analogues at The Ottawa Hospital"*, summarizes the results from the reviews from chapters 3 and 5 and provides context for the proceeding survey of physicians.
- Chapter 7 "*Lysine analogue use in high risk surgery: A single institution survey"* explores the extent to which lysine analogues are currently used at The Ottawa Hospital in surgical procedures which are associated with a high risk of blood transfusion. The manuscript and its related appendices provide the reader with results of a survey of surgeons at our institution, detailing their lysine analogues use patterns, as well as trial interest.
- Chapter 8 "*Discussion"* summarizes the findings of the thesis, reviews the presented evidence, highlights the strengths and limitations of the conducted studies, and provides an overall overview, as well as future directions and next steps for research in this area.

# Chapter 2

# Background Evidence

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## 2.1 Transfusion & Lysine Analogues

Thousands of Canadians undergo major surgery each year(21). Excessive bleeding is one of the most common complications of surgery and often results in the receipt of an allogenic blood transfusion for the patient(1). Transfusions are often necessary and can be potentially life-saving, although they are also associated with an increased risk of infection and immune reactions and are a major source of both morbidity and mortality for recipients(7,8). Methods for reducing peri-operative bleeding and resulting RBC transfusions are numerous, ranging from specific surgical techniques, to pharmacologic haemostatic agents(22,23).

Antifibrinolytic lysine analogues have been shown to be highly effective in reducing blood loss associated with surgery, trauma, and non-surgical diseases such as haemorrhaging related to cancer(9–14). Lysine analogues are synthetic derivatives of the essential amino acid lysine. They work by blocking lysine binding sites on plasminogen and thus inhibit plasmin formation and the subsequent breakdown of blood clots(15). Lysine analogues tranexamic acid (TXA) and ε-aminocaproic acid (EACA) are the two most common agents, with TXA being more potent than EACA and therefore more widely used(24). Considering all of the existing evidence supporting the efficacy of lysine analogues, coupled with the relatively cheap cost of the drug, it is curious that the physician uptake of these drugs in certain areas of medicine has been slow or even non-existent(19,20).

## 2.2 Safety Concerns

Despite the proven efficacy of these drugs, there exists legitimate concerns which could explain their limited use in practice(25). Safety concerns linger due to their method of action introducing a theoretical increased risk of developing venous thromboembolic (VTE) complications such as deep venous thrombosis (DVT) or pulmonary embolism (PE)(26). Despite the intuitive and theoretical risk of an increase in thrombotic events, there have only been isolated reports of venous or arterial thrombosis or embolism associated with the use of lysine analogues(16–18). The CRASH-2 trial (Clinical Randomisation

of an Antifibrinolytic in Significant Hemorrhage), assessed the efficacy of TXA in over 20,000 adult trauma patients, with no increased risk of thromboembolic events being reported. However, the precision of the estimate was low and therefore a potential for increased risk was not ruled out(11). In a systematic review and meta-analysis of 129 randomized controlled trials involving a total of 10,488 patients treated with TXA, Ker *at al*. reported a 30% reduction in the need for transfusion, however the effect of TXA on the occurrence of thromboembolic events remained uncertain(27). Many other systematic reviews and meta-analyses have failed to demonstrate an association between lysine analogue administration and an increased rate of thromboembolic events(10)(12–14). Due in most part to the rarity of VTE events, no placebo controlled clinical trials properly powered to evaluate safety concerns with lysine analogues have been performed, making it difficult to establish a definitive relationship.

Adding to the concerns about safety is a lack of standardized dosing protocols for the administration of lysine analogues(28,29), with doses varying wildly in the literature(24,30) and some evidence suggesting that high levels are TXA are associated with seizures(31–34). Tranexamic acid is often given intravenously at a dose of 10-15 mg/kg pre-operatively, followed by 1mg/kg/hr during surgery, with EACA being given at ten times that dose(35–37). However, the optimal dosing regimen of both TXA and EACA remain unknown. TXA has a half-life of roughly 80 minutes and reaches peak plasma concentration within one hour of the injection(38). Many institutions do not administer the drug in a weight adjusted fashion(39,40), and the timing of administration also varies within the literature. The lack of a standard dosing regimen for lysine analogues is one potential reason why the physician uptake of this drug has been slow. Because of these concerns, some physicians are hesitant to administer these drugs to certain populations, with one of those populations being oncology patients(19).

### 2.3 VTE and Cancer

Cancer patients often undergo major surgeries as part of their treatment and can also be susceptible to haemorrhage depending on the type of cancer(41). The risk of blood loss combined with frequent pre-operative anemia results in cancer patients often requiring blood transfusions during or after surgery. Receipt of a perioperative blood transfusion has been associated with decreased survival in a number of malignancies(42–44) yet other studies have shown no association (45–47). Whether or not the receipt of a perioperative blood transfusion is associated with cancer recurrence or survival is still unknown, however, reducing perioperative blood loss and subsequent transfusions is important to patients and their surgeons.

Oncology patients are ideal candidates for lysine analogue administration given the extensive and complicated surgical procedures they often undergo. However, VTE is a common complication in cancer patients and a leading cause of non-cancer related death(48). The estimated annual incidence of VTE in the cancer population is 0.5% compared with 0.1% in the general population(49). The risk following major surgery is much higher. The reasons for the association between cancer and VTE are not well understood. In 1996, Seto and Dunlap published a short, informal narrative review detailing the use of TXA in oncology(50). This paper concluded that a large, controlled clinical trial was needed before a recommendation for the routine use of tranexamic acid in the oncology population can be made. Since 1996, a number of trials of lysine analogues in cancer patients have been conducted. A systematic review and meta-analysis of lysine analogue use in cancer patients is necessary and timely.

### 2.4 Topical Administration

Because of the highlighted potential safety concerns associated with systemic lysine analogue use, interest has been increasing in the topical administration of these drugs(51,52). It is believed that topical administration will result in less systemic absorption of the drug and therefore a decreased risk of systemic adverse events such as VTE. Indeed, topical TXA results in plasma concentrations less than one tenth of the level seen after intravenous administration(53,54). In 2013, Ker *et al* published a systematic

review and meta-analysis examining the efficacy of topically applied TXA (30). The review contained 29 RCTs and over 2,600 patients and saw a 45% reduction in the risk of receiving a blood transfusion. This risk reduction was in fact larger than that seen for intravenous TXA use in a review that same group(24). However, as with intravenously administered TXA, the effect of topical TXA on thromboembolic events remained uncertain. Similarly to intravenous TXA, the optimal dosing strategy for topical TXA has not been established, and varies wildly in the literature

### 2.5 Summary

In summary, lysine analogues such as TXA are highly effective haemostatic agents. They appear to have generally strong safety profiles, however concerns remain due to the lack of comparative trials with safety endpoints as primary outcomes. They are used across a variety of surgical specialties, but may be underused in others where they could be of great benefit. Limiting blood loss and reducing the rate of blood transfusions in any surgery is of great importance, and the introduction of routine lysine analogue use during surgical procedures at risk for transfusion could provide an opportunity to greatly improve patient care. The foremost issue is that no comparative clinical trials properly designed and powered to evaluate safety concerns surrounding these drugs have been performed, making it difficult to establish a definitive relationship between lysine analogue administration and VTE risk. Before a trial of this nature can be planned and carried out, some existing evidence and knowledge gaps in the literature need to be addressed.

# CHAPTER 3

# The safety and efficacy of lysine analogues in cancer patients: A systematic review and meta-analysis

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**Author Contributions**

Dr. Rodney Breau is the primary thesis supervisor and contributed to the conception and design of the study, as well as the analysis and the drafting of the manuscript. Dr. Brian Hutton (thesis co-supervisor) and Dr. Dean Fergusson (TAC member) both contributed to the design and analysis of the study, as well as the drafting of the manuscript. Dr. Luke Lavallée, Dr. Chris Morash, Dr. Ilias Cagiannos and Sonya Cnossen contributed to the drafting and revision of the manuscript. Nicholas Fergusson contributed to the analysis of the project and was the second reviewer during all stages of the review.

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## Abstract

Lysine analogues are effective agents used for the reduction of blood loss and transfusion. However, the safety of lysine analogues in cancer patients remains in question due to a potential risk of venous thromboembolism (VTE). The objective of our review is to investigate safety and efficacy of lysine analogue administration in the patients with cancer. Medline, Embase, and The Cochrane Library were searched from inception to June, 2016. Reference lists of retrieved studies were searched to identify additional publications. We included randomized clinical trials in adult cancer patients for which a lysine analogue was administered for the purpose of blood loss reduction. Abstract and full-text selection as well as data extraction and risk of bias assessment was done by two independent reviewers. The primary outcome was venous thromboembolic events. Secondary outcomes were other adverse events, blood transfusion, and blood loss. Overall, eleven studies involving 1,177 patients evaluated at least one of the primary or secondary outcomes. Nine studies evaluated the effects of tranexamic acid, one study evaluated the effects of aminocaproic acid and one study examined both agents. No increased risk of venous thromboembolism was observed for patients who received lysine analogues compared to control (Peto OR 0.60; 95% CI 0.28-1.30). The administration of a lysine analogue significantly decreased both transfusion risk (pooled RR 0.52, 95% CI 0.34-0.80) and blood loss (SMD -1.57, 95% CI -2.21 to -0.92). Among three eligible studies, no increased risk was observed for mortality (Peto OR 1.01; 95% CI 0.14-7.18) or infection (OR 0.58; 95% CI 0.27-1.27). The safety of lysine analogues in cancer patients has not been extensively studied. Based on the available literature, lysine analogue use has not been associated with increased risk of venous thromboembolism or other adverse events, while being effective in reducing blood loss and subsequent transfusion.

**Keywords:** Cancer; Venous thromboembolism; Lysine analogue; Surgery; Blood transfusion

## Background & Rationale

Blood transfusion, although potentially life-saving, has been associated with an increased risk of infection and other morbidities(7,8). These potential risks, in conjunction with the high cost of transfusion have led to an increased use of haemostatic agents to reduce blood loss and transfusion need(55). Antifibrinolytic lysine analogues such as tranexamic acid (TXA) and ε-aminocaproic acid (EACA) are effective for reducing blood loss during surgery, trauma, and non-surgical diseases(9–11). Lysine analogue drugs are synthetic derivatives of the amino acid lysine that block binding sites on plasminogen and therefore inhibit plasmin formation and the breakdown of blood clots(15). TXA is more potent than EACA and is more widely used(56). TXA has been demonstrated to be efficacious and has a strong safety profile in cardiac, orthopedic, pelvic, and spinal surgeries, among others(10,12–14,56) and is listed on the World Health Organization's List of Essential Medicines(57).

Due to the mechanism of action of lysine analogues, there exists the potential risk of venous thromboembolism (VTE). Despite this risk, there have only been isolated reports of venous thrombosis or embolism associated with the use of lysine analogues(16–18). Recent systematic reviews and meta-analyses that have focused on the safety of TXA have not demonstrated an association with TXA use and VTE(12,58). Importantly, the established clinical benefits of TXA have consistently been deemed to outweigh the risks(14).

Cancer patients often receive major surgery as part of their treatment and frequently experience major bleeding requiring blood transfusion(41). Use of lysine analogues during cancer surgery could potentially reduce transfusion requirements for many patients. On the other hand, VTE is more common in cancer patients and a leading cause of non-cancer death(48). Patients with malignant disease have an increased risk of VTE, and necropsy studies document an increased prevalence of thrombosis among patients with visceral cancers(59,60). The estimated annual incidence of VTE in the cancer population is 0.5%

compared with 0.1% in the general population(49). The causal pathway between cancer and thrombosis is poorly understood(48) but given the association between cancer and VTE, cancer patients may be at a higher risk than non-cancer patients for adverse events if they are exposed to lysine analogues. Thus, the safety of lysine analogues in cancer patients warrants specific evaluation.

The safety and efficacy of lysine analogues has been the subject of systematic reviews and meta-analyses in liver transplantation(61), orthopedic surgery(13), spinal surgery(14), cardiac surgery(12), pelvic surgery(10), pediatric surgeries(62), and many others(63,64). Small, niche reviews have been done in patients with malignancies such as haematological, cervical and ovarian. These reviews are small and results are inconclusive. However, no review exists on the safety and efficacy of lysine analogue drugs in the oncology population as a whole. In 1996, Seto and Dunlap published a brief, non-systematic narrative review detailing the use of tranexamic acid in oncology(50). This paper concluded that a large, controlled clinical trial was needed before use of tranexamic acid in cancer patients can be made. In the two decades since this publication, clinical trials of lysine analogue administration in cancer patients have been conducted, but none were performed with VTE as the primary outcome.

The aim of this systematic review and meta-analysis was to examine the safety and efficacy of lysine analogue administration (TXA or EACA) in cancer patients. Specifically, we evaluated whether lysine analogue administration (TXA or EACA) increases the incidence of thromboembolic events in cancer patients when compared to placebo or an active control.

## Methods

This review was registered in full on Prospero, the international prospective register of systematic reviews (no. CRD42016035902) in February of 2016.

### *Eligibility Criteria*

We included randomized controlled trials (RCTs) that compared a lysine analogue to either placebo or an active control. Studies compared to a no treatment arm (i.e. standard of care) were also included. Studies examining surgical or non-surgical cancer patients 18 years of age and older were included. All studies were included, regardless of dose, route of administration, or timing of administration.

### *Outcomes*

The primary outcome was venous thromboembolic complications (defined as pulmonary embolism, deep venous thrombosis). Our secondary outcomes included blood transfusion, estimated blood loss, and any other adverse events reported in the trials. Where endpoint definitions varied across studies, these were captured and described.

### *Literature Search Strategy*

A comprehensive literature search of indexed databases was conducted to identify all relevant studies in collaboration with an information specialist and a clinical expert in the field. The following databases were searched: MEDLINE, Embase, and The Cochrane Library. Due to funding constraints, we limited the search to English and French articles only. No date restrictions were imposed. The search was last conducted on June 4$^{th}$, 2016. The literature search strategy used in MEDLINE is provided online (Appendix 1). Clinicaltrials.gov was searched in order to identify ongoing trials in the area of interest.

### *Study Selection Process*

Upon completion of the literature search, all duplicate studies were removed. Titles and abstracts were screened for inclusion by two independent reviewers (JM and NF). Titles and abstracts deemed potentially relevant were recorded and the full text articles obtained. Two independent reviewers screened the full articles for final eligibility, with disagreements settled by consultation of a third party (RB) to achieve consensus. The study selection process was documented and reported using a flow diagram as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Figure 1)(65).

### *Data Extraction and Risk of Bias Assessment*

Two reviewers extracted relevant data from the included studies using a standardized data extraction form that was pilot-tested by both reviewers. Each reviewer independently documented publication traits (year of publication, journal, authorship list), study populations (e.g, eligibility criteria, age, race, gender, comorbidities), intervention types (type of lysine analogue, dose, route and timing of administration), study designs (methods, setting, sample size, number of centres), clinical endpoints (gathering numbers of events and number randomized per group), and risk of bias details. The risk of bias was assessed using the Cochrane risk of bias tool)(66).

### *Data Analysis*

Data for our dichotomous primary outcome (incidence of thromboembolic events) was analyzed via fixed effects meta-analyses using Peto odds ratios. An odds ratio less than one indicates fewer events in the lysine analogue group compared to the control. Peto's method was used due to the rarity of events. In this method, a correction factor of 0.5 is added to each cell where zero events occurred. Study level odds ratios with 95% confidence intervals were calculated and presented. A sensitivity analysis was performed including only trials which had an event in either arm and an odds ratio with accompanying 95% confidence intervals was calculated via random-effects meta-analysis. For the dichotomous outcome of blood transfusion a risk ratio with accompanying 95% confidence intervals was calculated via random effects meta-analysis. For the continuous outcome of blood loss, the standardized mean difference (SMD) and 95% confidence intervals were calculated via random effects meta-analysis. Statistical heterogeneity was assessed for all outcomes using the $I^2$ statistic, as well as the $Chi^2$ test or the Cochrane Q test, depending on the analysis method. An $I^2$ value of >50% was considered to indicate substantial heterogeneity(67). For the $Chi^2$ test and the Cochrane Q test, a P-value of <0.10 was deemed to indicate substantial heterogeneity. Publication bias was assessed via funnel plots. There were notable differences in the types of non-VTE adverse events reported across studies and therefore data regarding

the occurrence of any adverse event were not formally pooled using meta-analysis. However, mortality and infection were reported across multiple studies and an accompanying meta-analysis was performed for each of these adverse events individually. Pooling of data was carried out using RevMan 5.3 (Cochrane Collaboration, Oxford, United Kingdom) and Open Meta-Analyst for Windows 8 (http://www.cebm.brown.edu/openmeta/). We carried out a GRADE assessment to assess the strength of evidence obtained from included trials(68).

## Results

A total of 5,578 titles and abstracts were identified by the electronic search, of which 5,497 were excluded during the review of titles and abstracts based on irrelevancy to our study question. Of 81 full text articles reviewed, 70 did not to meet eligibility criteria and were excluded. Eleven full text articles met eligibility and were included in analyses (Figure 1) (35–37,39,40,69–74).

### *Characteristics of Included Trials*

Included articles were published between 1972 and 2016 from eight different countries (Table 1). Study sample sizes ranged from 12 patients to 219 patients. The types of cancer under investigation included leukemia (n=2)(70,74), musculoskeletal neoplasms (n=1)(69), cervical (n=2)(71,73), liver (n=1)(39), prostate (n=1)(40), ovarian (n=1)(35), brain (n=1)(36), and head and neck (n=2)(37,72). One leukemia trial divided participants into 2 groups, those undergoing induction treatment, and those undergoing consolidation treatment (Table 1)(74).

Nine trials evaluated TXA(35–37,39,40,70,72–74), one evaluated EACA(69), and one evaluated both(71). The study drug was given intravenously in ten studies(35–37,39,40,69–72,74) and orally in one(73). The dosage was weight adjusted in six studies with dose ranging from 10-20mg/kg for TXA and 100-150 mg/kg for EACA(35–37,69,71,72). The dosage was not weight adjusted in four studies, with dosage

varying from 500-2000mg of TXA(39,40,70,74). Four and a half grams per day was given orally for 12 days in one study(73). All trials used a placebo as a comparator (Table 1).

The method of thrombotic complication detection and classification was not reported in three studies(39,70,74). Two studies clinically monitored patients until discharge for symptomatic VTE(36,37). One study followed up with patients by phone at 1 and 6 months post-randomization(40). Radiologic methods of thrombotic complication diagnosis such as ultrasound and pulmonary scintigraphy were used in three studies(35,69,71). Two studies did not specify if thrombotic complications were evaluated(72,73).

### *Study Quality and Risk of Bias*

The risk of bias assessed in duplicate using the Cochrane risk of bias tool (Figure 2). The majority of studies had an unclear risk of bias for at least one methodological criterion. One study was deemed to have a low risk of bias across all six domains. Less than half of the included studies adequately described their random sequence generation procedure or their allocation concealment technique and were found to be at an unclear risk of selection bias. The majority of studies were deemed to have adequately blinded their participants and personnel, as well as their outcome assessment for thrombotic event detection and were therefore at a low risk for both performance bias and detection bias. The majority of studies had complete data or had adequately described their reasons for missing data. Few studies were found to be at low risk of reporting bias, as not many studies were registered on clinicaltrials.gov or had an available study protocol. One study was deemed to be at a high risk of other biases due to a lack of a clearly defined inclusion/exclusion criteria.

### *Venous Thromboembolic Events*

Nine studies involving 1,075 patients reported on the incidence of VTE events. Six of the nine studies reported 0 thromboembolic events in both arms. One of the studies stratified their population into 2 cohorts, patients undergoing either the consolidation or induction phase of leukemia treatment and therefore appears as two separate entries in the meta-analysis. Our pooled estimate suggests no increase in the risk of VTE events for lysine analogues compared to control (Peto OR 0.60; 95% CI 0.28-1.30) (Figure 3). There was no evidence of statistical heterogeneity in the findings (Cochrane's Q=1.13, df=9, P=0.999). Publication bias was assessed via funnel plot, with no clear asymmetry present (appendix 2). In our sensitivity analysis including only trials with an event in either arm, similar results were seen (OR 0.49; 95% CI 0.19-1.28; $I^2$=0%) (appendix 3).

### *Blood Transfusion*

Seven studies involving 955 patients reported data on the rate of blood transfusion. The administration of a lysine analogue reduced the risk of receiving a blood transfusion by 48% (pooled RR 0.52, 95% CI 0.34-0.80; P = 0.003) (Figure 4). We found substantial statistical heterogeneity between trials ($Chi^2$ = 18.20, df = 6 (P = 0.006); $I^2$ = 67%). Publication bias was assessed via funnel plot, with some small asymmetry present (appendix 2). In our sensitivity analysis removing extreme values, similar results were seen (pooled RR 0.68, 95% CI 0.54-0.86; P = 0.001), while heterogeneity was eliminated ($Chi^2$ = 1.93, df = 4 (P = 0.75); $I^2$ = 0%) (appendix 3).

### *Blood Loss*

Nine studies involving 1,109 patients reported data on blood loss. The administration of a lysine analogue significantly reduced the blood loss experienced by cancer patients (SMD -1.57, 95% CI -2.21 to -0.92; P <0.00001) (Figure 5). We found substantial statistical heterogeneity between trials ($Chi^2$ = 198.92, df = 9 (P < 0.00001); $I^2$ = 95%). The two studies involving leukemia patients reported data on blood loss which was not suitable for inclusion in the meta-analysis. Avvisati *et a*l(70), noted a significant

decrease in the haemorrhagic score in the lysine analogue group compared to the control group (P=0.0045). Shpliberg *et* al(74), noted a significantly decreased cumulative bleeding score ($p<0.05$) in the lysine analogue group compared to the control in patients undergoing consolidation treatment, but no difference in those undergoing induction treatment. Publication bias was assessed via funnel plot, with some small asymmetry present (appendix 2). In our sensitivity analysis removing extreme values, statistical benefits were still observed (SMD -0.50, 95% CI -0.69 to -0.31; $P < 0.00001$), while heterogeneity was minimized ($Chi^2 = 5.82$, df = 4 ($P = 0.21$); $I^2 = 31\%$) (appendix 3).

### *Non-VTE Adverse Events*

Three studies reported on death, with one death occurring in each group (Peto OR 1.01; 95% CI 0.14-7.18). Three studies reported on infection, slightly favouring the lysine analogue group, however, results did not reach statistical significance (OR 0.58; 95% CI 0.27-1.27). Four studies reported on the incidence of other adverse events encountered. Other adverse events reported were unique to each study and therefore were not pooled for meta-analysis. No individual study reporting an increase in adverse events in their respective lysine analogue group, with the exception of one study reporting a higher re-admission rate in patients treated with tranexamic acid(35). Data for all other adverse events is reported online in Appendix 4.

### *Strength of evidence*

The GRADE evidence profile is presented in Table 2. We found the strength of evidence for our three clinical outcomes to be low. When making our decision, we considered: the impact of the risk of bias of included studies, inconsistency or heterogeneity, the indirectness of the evidence, the precision of the effect estimate, as well as selective reporting and publication biases.

## Discussion

There is a plethora of evidence that prove lysine analogues are safe and effective in patients with benign disease. However, due to lingering safety concerns, these drugs may be underused or overused in

cancer patients. This systematic review and meta-analysis indicates that the safety of lysine analogues has not been extensively studied in cancer patients. This is a notable finding given the increased risk of VTE observed in cancer patients and the increased interest in these drugs for cancer patients(49,55). Indeed, of the 11 studies included in this review, 5 have been published since 2010 and there are at least 9 additional ongoing trials in cancer patients (clinicaltrials.gov; NCT01655927, NCT02153593, NCT01869413, NCT01655641, NCT01980355, NCT02627560, NCT01651182, NCT00308880, and NCT02650791) none of these ongoing trials are powered to detect a clinically significant differences in VTE. Clearly, an ongoing and rigorous evaluation of lysine analogue safety in cancer patients is warranted.

Reassuringly, despite the small number of trials, this review suggests that lysine analogues in cancer patients have a similar safety profile to what has been observed in non-cancer patients(13,14,58). The pooled risk of VTE in this review is slightly lower than estimates in the literature(10,13,61,75,76). However our confidence intervals are very wide, and in our sensitivity analysis including only trials with an event in either arm, the point estimate is slightly higher and more in line with other published literature. In a large systematic review and meta-analysis of over 10,000 trial patients, the relative risk of developing a DVT or a PE was 0.86 (0.53-1.39) and 0.68 (0.25-1.47), respectively(27). We also observed that lysine analogues in cancer patients reduces blood loss and blood transfusion. This strength and direction of effect observed in this review is consistent to what has been observed in non-cancer patients(10–12). Through a detailed GRADE assessment of our outcomes, we found the strength of evidence to be low across all outcomes.

None of the studies in this review were designed to detect differences in the incidence of VTE events. This is an issue surrounding these drugs and the rarity of VTE events makes it difficult to properly power trials to detect such differences. Because of this, individual studies were underpowered to detect an effect on VTE, and in addition the methods of surveillance and detection of VTE events were rarely

adequately described. Of the nine studies that reported VTE events, only four detailed how surveillance for VTE was conducted**.** The duration of follow-up also dramatically varied between studies, potentially affecting VTE detection across studies. The differences in surveillance and detection methods, or lack thereof, may account for some of the trials reporting zero events. These factors also introduce clinical heterogeneity in our review. Furthermore, only two studies detailed if VTE prophylaxis was used(35,69).

Although no statistical heterogeneity was found during the meta-analysis of our primary outcome of VTE events, this may be biased with so many trials reporting zero events and thus being unable to contribute effectively to the meta-analysis. A potential source of heterogeneity could arise from the populations in the included trials. With the exception of leukemia (n=2), and head and neck cancers (n=2) all of the included trials were examining different types of cancer surgery. These cancers, and associated procedures, vary in complexity and have varying risks of bleeding and VTE. Each procedure is associated with its own inherent risk, some higher than others. This is demonstrated by the substantial heterogeneity found in the analysis of our secondary outcomes of transfusion risk and blood loss. Blood loss can be a difficult outcome to accurately measure, and measurement techniques vary across surgical teams and specialties. In addition, transfusion triggers vary across healthcare systems and surgical specialties. This leads to clinical heterogeneity and is a potential explanation for the statistical heterogeneity. We investigated the effects of statistical heterogeneity with sensitivity analyses. We removed extreme values to limit the heterogeneity in our analysis and the beneficial effects of lysine analogues were still observed.

There are additional potential limitations to this review. We were limited by the quality of the published studies, many of which were found to be at an unclear risk of bias as they did not report some methodological details of their trial. By limiting our search to English articles and French articles only, we opened our review to the potential for some slight language biases. The slight asymmetry seen in the funnel plots of both transfusion risk and blood loss could suggest the presence of a small degree of

publication bias, however asymmetry was very small and difficult to assess due to the small number of studies present. Another limitation of our review was the small number of studies included in the final analysis. Many of the included studies were of small sample size and reported zero events in each arm, making an accurate estimation of the odds ratio difficult. There is no agreed upon standard approach to this analytic problem(77,78). To be conservative in our estimate, a correction factor of 0.5 was applied to each zero cell to generate a Peto odds ratio(79). Some of the included trials had a small sample size, potentially biasing the association toward the null hypothesis. Finally, harms are often not collected or underreported in randomized controlled trials(80–82).

High-quality randomized controlled trials designed and powered to detect differences in VTE risk are difficult to carry out due to the baseline risk of developing a VTE being very low. We have calculated potential sample sizes needed for a trial powered to detect differences in VTE risk based on baseline risks of developing a VTE of both 2.5% and 5%. We considered a 50% relative difference to be considered a large effect and a 25% relative difference to be considered a moderate effect. At a baseline risk of 2.5%, 3,041 patients are needed in each of the two arms to detect a large effect and 10,984 patients are needed in each of the two arms to detect a moderate effect. At a baseline risk of 5%, 1,471 patients are needed in each of the two arms to detect a large effect and 5,333 patients are needed in each of the two arms to detect a moderate effect. The resources required for trials of this magnitude are substantial, however the exact nature of the relationship between lysine analogues and VTE risk cannot be determined until such trials are performed.

## Conclusion

The safety of lysine analogues in cancer patients has not been extensively studied. Based on the available literature, lysine analogue use has not been associated with increased risk of venous thromboembolism or other adverse events, while being effective in reducing blood loss and subsequent transfusion. Despite the limitations of the available literature, this review provides physicians with the

most complete, up to date information on the safety of lysine analogues in patients with cancer. Before definitive conclusions can be made regarding the safety of lysine analogue administration in cancer patients, high-quality randomized controlled trials designed and powered to detect differences in adverse events are needed.

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**Conflict of Interest Statement: The authors have no conflicts of interest to declare.**

***Table 1 Characteristics of Included studies***

| Author (year) | Host country(ies) | Sample size (n) | Type of cancer | Procedure | Treatment | Dose | Thrombosis detection method |
|---|---|---|---|---|---|---|---|
| **Rybo (1972)**(73) | Sweden | 45 | Cervical | Conization of the cervix | TXA | 4500mg/day for 12 days post-op | N/A |
| **Avvisati (1989)**(70) | Italy, Netherlands | 12 | Leukemia | Reduction of haemorrhage | TXA | 2000mg every 8 hours for 6 days | N.R. |
| **Shpilberg (1995)**(74) | Israel | 38 | Leukemia | Reduction of haemorrhage | TXA | 1000mg every 6 hours | N.R. |
| **Amar (2003)**(69) | USA | 69 | musculoskeletal neoplasms | Orthopedic surgery | EACA | 150mg/kg for 30 minutes pre-op, then 15/mg/kg intra-op | Daily clinical exam and Doppler ultrasonography performed once between post-op days 4 and 6. Spiral computed tomography and/or ventilation/perfusion lung scans for PE |
| **Celebi (2006)**(71) | Turkey | 105 | Cervical | Hysterectomy | TXA & EACA | 10mg/kg (TXA)<br>100 mg/kg (EACA) | Pre-op as well as 12 and 24 hours post-op evaluations. Signs of PE were evaluated using pulmonary scintigraphy |
| **Wu (2006)**(39) | Taiwan | 214 | Liver | Liver resection | TXA | 500mg pre-op, then 250 mg every 6 hours for 3 days | N.R. |
| **Crescenti (2011)**(40) | Italy | 200 | Prostate | Prostatectomy | TXA | 500mg 20 minutes pre-op, then 250mg/hr until end of surgery | Telephone follow-up at 1 and 6 months post-randomization |
| **Lundin (2014)**(35) | Sweden | 100 | Ovarian | Laparotomy | TXA | 15mg/kg | 5 week post-op interview. Optional referral to lower extremity duplex ultrasound regardless of symptoms |
| **Das (2015)**(72) | India | 80 | Head and neck | Various neck dissections | TXA | 20mg/kg | N/A |
| **Vel (2015)**(36) | India | 100 | Brain | Craniotomy | TXA | 10mg/kg for 10 minutes, then 1/mg/kg/hr intra-op | Monitored until discharge |
| **Kulkarni (2016)**(37) | India | 219 | Head and neck | Head & neck surgery | TXA | 10mg/kg pre-op, repeated every 3 hours | Monitored until discharge |

**Table 2. GRADE evidence profile**

| Outcome | Quality assessment | | | | | | | No of patients | | Effect Estimate (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Lysine analogue** | **Control** | | |
| **Thromboembolic events** | | | | | | | | | | | |
| **All included trials** | 9 | RCT | Serious[1] | No serious inconsistency | No serious indirectness | serious imprecision[3] | Selective reporting[4] | 523 | 529 | Peto OR 0.60 (0.28-1.30) | Low |
| **Blood transfusion** | | | | | | | | | | | |
| **All included trials** | 7 | RCT | Serious[1] | Serious inconsistency[2] | No serious indirectness | No serious imprecision | Publication bias[5] | 478 | 477 | RR 0.52 (0.34-0.80) | Low |
| **Blood loss** | | | | | | | | | | | |
| **All included trials** | 9 | RCT | Serious[1] | Serious inconsistency[2] | No serious indirectness | No serious imprecision | Publication bias[5] | 553 | 556 | SMD -1.57 (-2.21 to -0.92) | Low |

[1] Majority of trials at unclear risk of bias across at least one domain

[2] Substantial statistical heterogeneity

[3] Few events

[4] Few trials adequately assessing outcome

[5] Observed asymmetry in funnel plot

## Figure Legends

***Figure 1.*** Selection flow diagram

**Figure 2.** Risk of bias assessment

***Figure 3.*** Peto odds ratios (95% CI) and pooled estimates for the incidence of venous thromboembolic events

***Figure 4.*** Risk ratio (95% CI) and pooled estimates for risk of blood transfusion

***Figure 5.*** Standardized mean difference (95% CI) for estimated blood loss

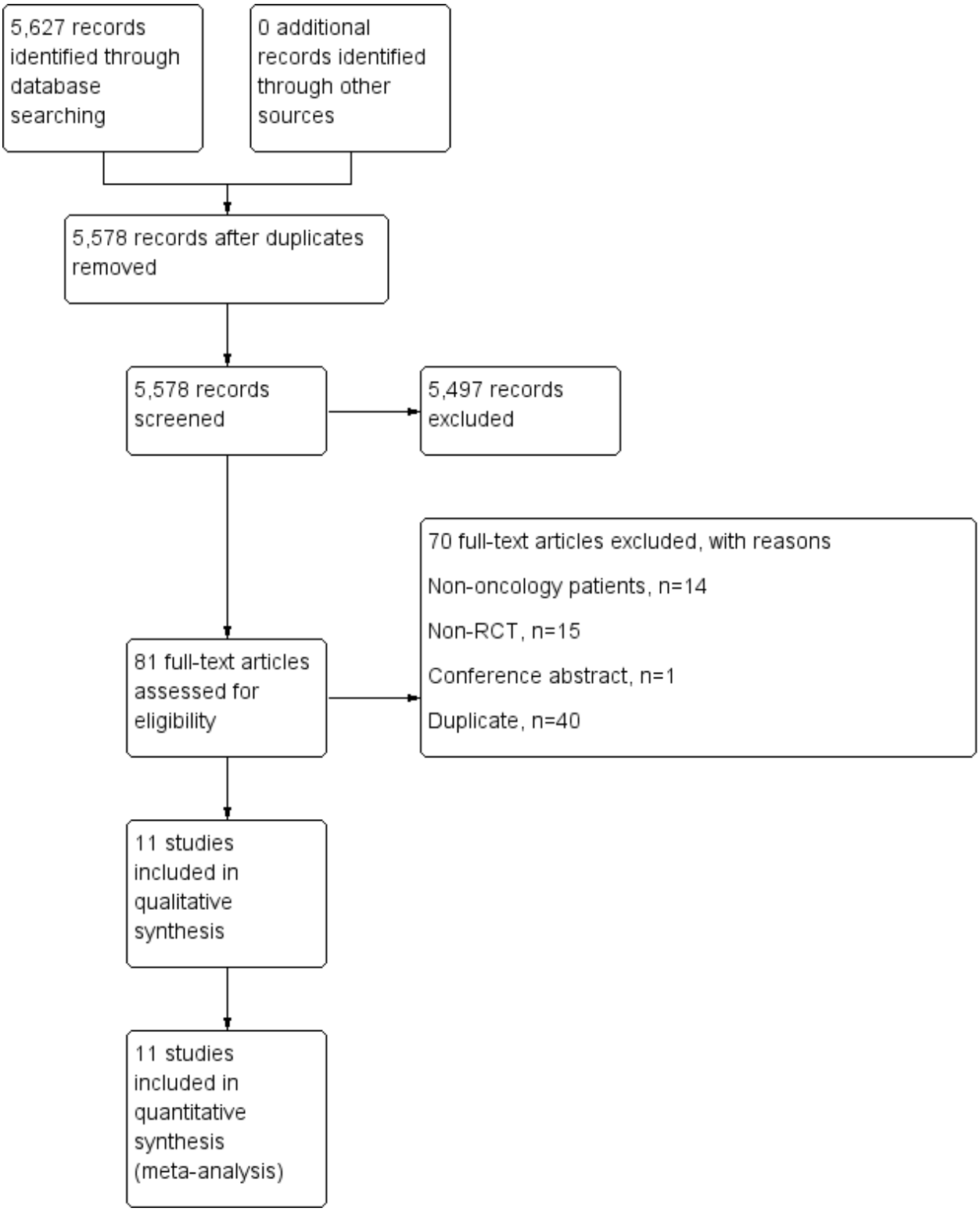



***Figure 1.*** Selection flow diagram

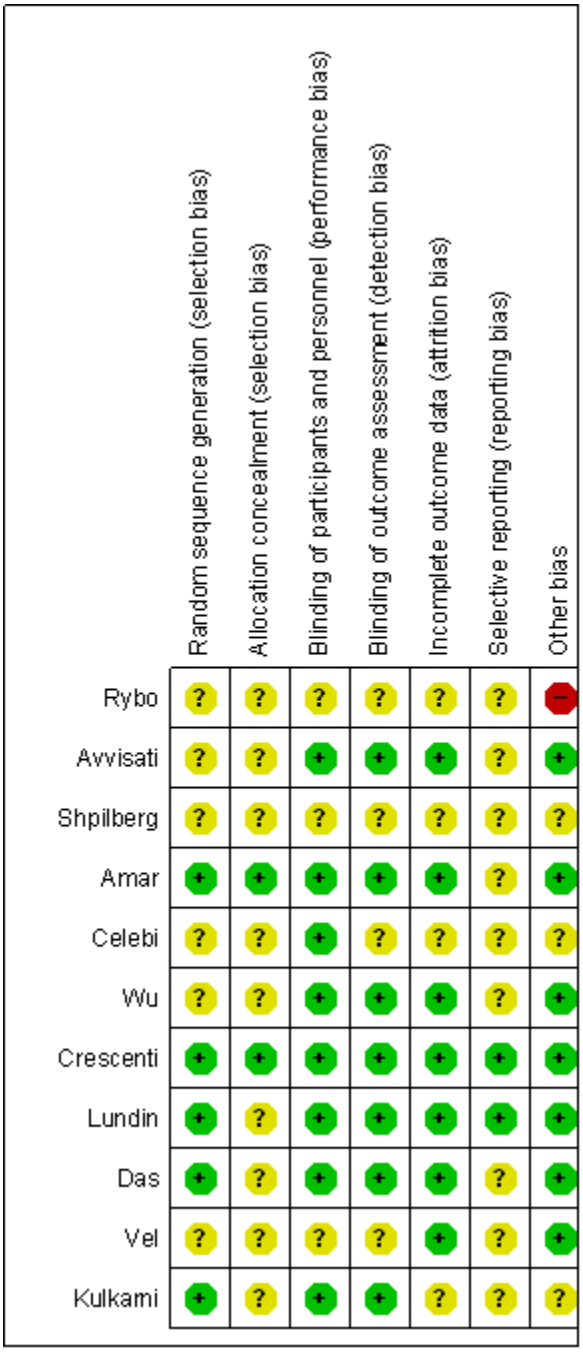



**Figure 2.** Risk of bias assessment

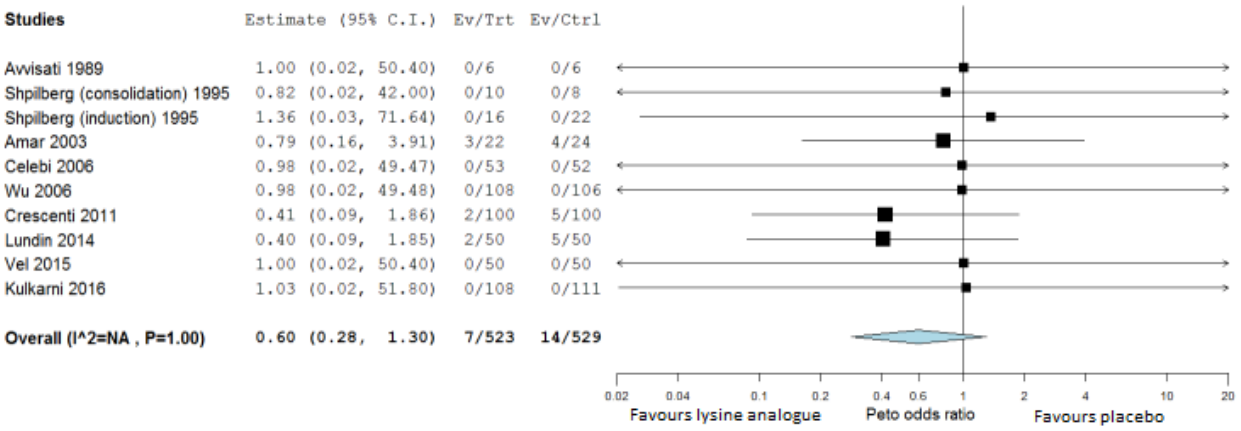



***Figure 3.*** Peto odds ratios (95% CI) and pooled estimates for the incidence of venous thromboembolic events

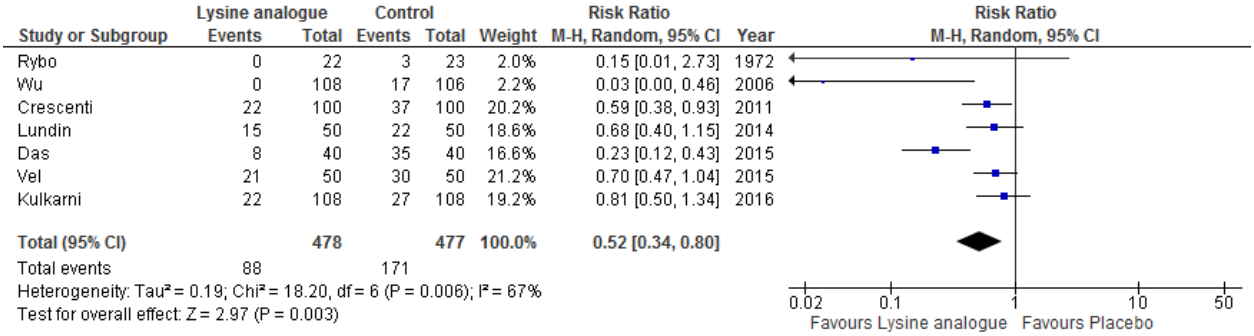



***Figure 4.*** Risk ratio (95% CI) and pooled estimates for risk of blood transfusion

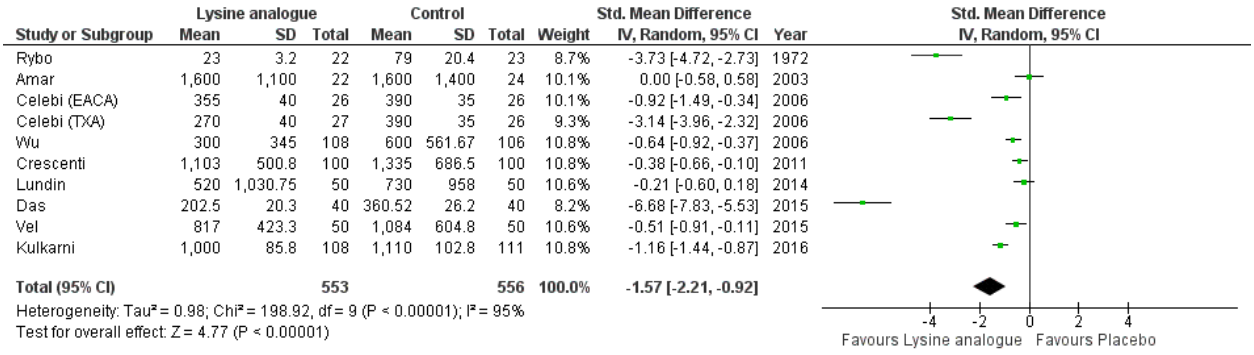



***Figure 5.*** Standardized mean difference (95% CI) for estimated blood loss

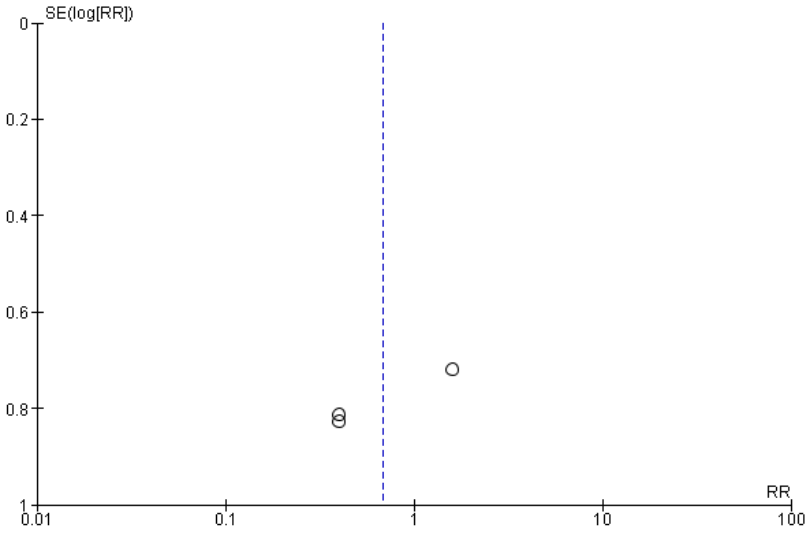
## Supplemental Material

### Appendix 1: Literature search strategy for MEDLINE

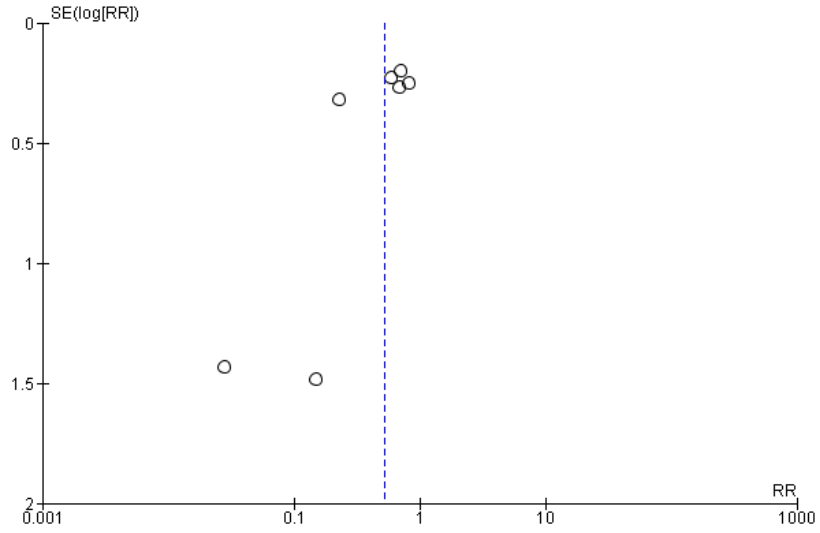
1. exp Antifibrinolytic Agents/
2. (antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).mp.
3. ((aminocaproic adj2 acid*) or (amino?caproic adj2 acid*) or (aminohexanoic adj2 acid*) or (amino?hexanoic adj2 acid*) or (epsilon-aminocaproic adj2 acid*) or (E-aminocaproic adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177 or neocaprol or nsc?26154 or tachostyptan).mp.
4. (tranexamic or cyclohexanecarboxylic or methylamine or amcha or amca or kabi or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol or aminomethylcyclo-hexane or aminomethylcyclohexanecarbonic or aminomethylcyclohexanecarboxylic or AMCHA or amchafibrin or amicar or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA or Lysteda or transcam).mp.
5. lysine analog*.tw.
6. (lysine adj3 analog$).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Neoplasms/
9. Neoplasm*.tw.
10. Cancer*.tw.
11. tumo?r*.tw.
12. neoplasia.tw.
13. exp Medical Oncology/
14. oncolog*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
15. 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 7 AND 15

## Appendix 2: Assessment of publication bias

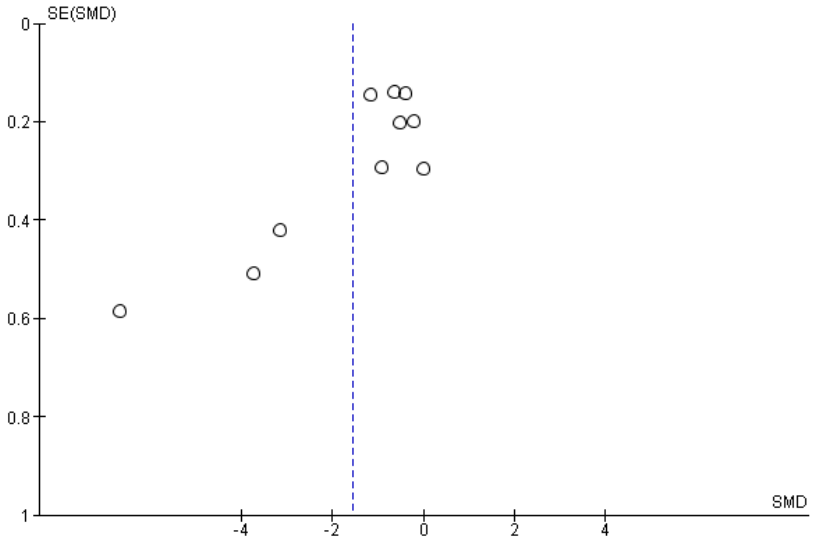
**A2 a) Funnel plot VTE**




**A2 b) Funnel plot transfusion risk**



**A2 c) Funnel plot blood loss**

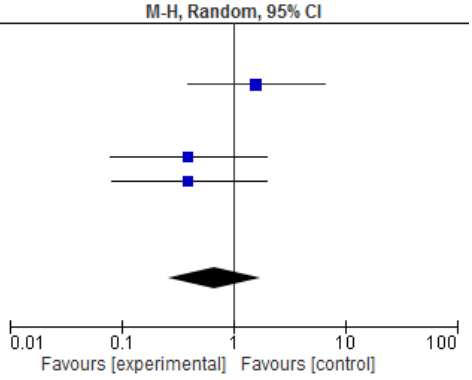



## Appendix 3: Sensitivity analyses

**A3a)** Odds ratios (95% CI) and pooled estimates for the incidence of venous thromboembolic events removing zero event trials

| Study or Subgroup | Lysine analog Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Awisati | 0 | 6 | 0 | 6 | | Not estimable | 1989 |
| Shpilberg | 0 | 26 | 0 | 30 | | Not estimable | 1995 |
| Amar | 3 | 22 | 4 | 47 | 38.5% | 1.60 [0.39, 6.55] | 2003 |
| Wu | 0 | 108 | 0 | 106 | | Not estimable | 2006 |
| Celebi | 0 | 53 | 0 | 52 | | Not estimable | 2006 |
| Crescenti | 2 | 100 | 5 | 100 | 30.3% | 0.40 [0.08, 2.01] | 2011 |
| Lundin | 2 | 50 | 5 | 50 | 31.1% | 0.40 [0.08, 1.97] | 2014 |
| Vel | 0 | 50 | 0 | 50 | | Not estimable | 2015 |
| Kulkarni | 0 | 108 | 0 | 111 | | Not estimable | 2016 |
| **Total (95% CI)** | | **523** | | **552** | **100.0%** | **0.68 [0.27, 1.76]** | |
| Total events | 7 | | 14 | | | | |

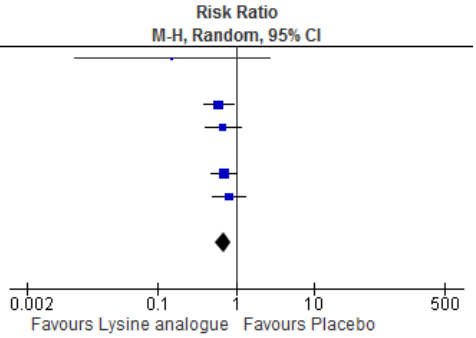
Heterogeneity: Tau² = 0.09; Chi² = 2.28, df = 2 (P = 0.32); I² = 12%
Test for overall effect: Z = 0.79 (P = 0.43)




**A3b)** Risk ratio (95% CI) and pooled estimates for risk of blood transfusion removing extreme values

| Study or Subgroup | Lysine analogue Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Rybo | 0 | 22 | 3 | 23 | 0.6% | 0.15 [0.01, 2.73] | 1972 |
| Wu | 0 | 108 | 17 | 106 | 0.0% | 0.03 [0.00, 0.46] | 2006 |
| Crescenti | 22 | 100 | 37 | 100 | 26.0% | 0.59 [0.38, 0.93] | 2011 |
| Lundin | 15 | 50 | 22 | 50 | 18.9% | 0.68 [0.40, 1.15] | 2014 |
| Das | 8 | 40 | 35 | 40 | 0.0% | 0.23 [0.12, 0.43] | 2015 |
| Vel | 21 | 50 | 30 | 50 | 33.3% | 0.70 [0.47, 1.04] | 2015 |
| Kulkarni | 22 | 108 | 27 | 108 | 21.3% | 0.81 [0.50, 1.34] | 2016 |
| **Total (95% CI)** | | **330** | | **331** | **100.0%** | **0.68 [0.54, 0.86]** | |
| Total events | 80 | | 119 | | | | |

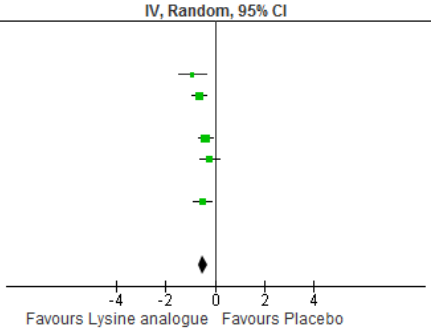
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 4 (P = 0.75); I² = 0%
Test for overall effect: Z = 3.27 (P = 0.001)



**A3c)** Standardized mean difference (95% CI) for estimated blood loss removing extreme values

| Study or Subgroup | Lysine analogue Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Rybo | 23 | 3.2 | 22 | 79 | 20.4 | 23 | 0.0% | -3.73 [-4.72, -2.73] | 1972 |
| Amar | 1,600 | 1,100 | 22 | 1,600 | 1,400 | 24 | 0.0% | 0.00 [-0.58, 0.58] | 2003 |
| Celebi | 355 | 40 | 26 | 390 | 35 | 26 | 9.7% | -0.92 [-1.49, -0.34] | 2006 |
| Wu | 300 | 345 | 108 | 600 | 561.67 | 106 | 28.0% | -0.64 [-0.92, -0.37] | 2006 |
| Celebi | 270 | 40 | 27 | 390 | 35 | 26 | 0.0% | -3.14 [-3.96, -2.32] | 2006 |
| Crescenti | 1,103 | 500.8 | 100 | 1,335 | 686.5 | 100 | 27.5% | -0.38 [-0.66, -0.10] | 2011 |
| Lundin | 520 | 1,030.75 | 50 | 730 | 958 | 50 | 17.6% | -0.21 [-0.60, 0.18] | 2014 |
| Das | 202.5 | 20.3 | 40 | 360.52 | 26.2 | 40 | 0.0% | -6.68 [-7.83, -5.53] | 2015 |
| Vel | 817 | 423.3 | 50 | 1,084 | 604.8 | 50 | 17.3% | -0.51 [-0.91, -0.11] | 2015 |
| Kulkarni | 1,000 | 85.8 | 108 | 1,110 | 102.8 | 111 | 0.0% | -1.16 [-1.44, -0.87] | 2016 |
| **Total (95% CI)** | | | **334** | | | **332** | **100.0%** | **-0.50 [-0.69, -0.31]** | |

Heterogeneity: Tau² = 0.02; Chi² = 5.82, df = 4 (P = 0.21); I² = 31%
Test for overall effect: Z = 5.06 (P < 0.00001)




## Appendix 4: Other adverse events recorded

| Author (year) | Adverse event(s) reported | Treatment group (n) | Control group (n) |
|---|---|---|---|
| **Amar (2003)**(69) | Thrombocytopenia | 0 (0%) | 1 (4.2%) |
| | Respiratory failure | 1 (4.5%) | 0 |
| **Wu (2006)**(39) | Ascites | 5 (4.6%) | 5(4.7%) |
| | Intra-abdominal abscess | 6 (5.6%) | 8 (7.5%) |
| | Bile leak | 4 (3.7%) | 6 (5.7%) |
| | Colon perforation | 1 (0.9%) | 0 (0%) |
| | Pleural effusion | 1 (0.9%) | 2 (1.9%) |
| **Lundin (2014)**(35) | Re-admission* | 11 (22%) | 4 (8%) |
| | Re-operation | 5 (10%) | 6 (12%) |
| **Kulkarni (2016)**(37) | Skin flap necrosis | 2 (1.9%) | 2 (1.8%) |
| | >50% necrosis of reconstruction flap | 3 (2.8%) | 3 (2.7%) |
| | Re-exploration of wound for bleeding | 2 (1.9%) | 1 (0.9%) |
| | Oro-fistula | 0 (0%) | 3 (2.7%) |

** = p-value<0.05*

# CHAPTER 4

## The topical application of tranexamic acid, is it effective?

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In chapter 3, we investigated the safety of lysine analogues in cancer patients. Although the evidence suggests no increase in VTE events in cancer patients who had been given a lysine analogue, establishing a definitive relationship between lysine analogue administration and VTE remains difficult due to the low statistical power of the trials, leading to imprecise effect estimates and wide confidence intervals. While the evidence presented may be enough to ease concerns of some surgeons and physicians, some may remain skeptical due to the lack of high quality evidence surrounding this potential relationship. With that in mind, methods to potentially improve the safety profile of lysine analogues and ease lingering concerns remain of great interest. Improving the safety profile of lysine analogues has the added benefit of potentially leading to an increased interest among surgeons and physicians in participation in a clinical trial, such as the one described earlier. As noted in chapter 2, the answer to improving the safety profile of lysine analogue may lie in the route of administration. By administering these agents topically as opposed to intravenously, systemic absorption of the drug may be limited, thereby minimizing the risk of unwanted side-effects. In the following chapter, we address the second objective of this thesis, to evaluate the efficacy and safety of the topical administration of lysine analogues. In order to address this objective, we present data from a systematic review and meta-analysis focusing on the efficacy and safety of topically administered tranexamic acid.

In the proceeding chapter, we provide full details of the methodological process by which this review was performed, as well as additional background information regarding the topical administration of lysine analogues. We discuss the results of the review in detail, including appropriate subgroup and sensitivity analyses, as well as provide study quality and risk of bias assessments. Finally, we discuss how the findings from this review fill gaps in current literature, direct future research efforts and impact potential clinical trials.

# Chapter 5

# The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis

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**Author Contributions**

Dr. Rodney Breau is the primary thesis supervisor and contributed to the conception and design of the study, as well as the analysis and the drafting of the manuscript. Dr. Brian Hutton (thesis co-supervisor), Dr. Dean Fergusson (TAC member) and Dr. Alan Tinmouth (TAC member) all contributed to the design and analysis of the study, as well as the drafting of the manuscript. Dr. Cheng provided input on the analytic approach, as well as the drafting of the manuscript. Dr. Preveshen Moodley contributed to the analysis of the project and was the second reviewer during all stages of the review.

**Additional Information**

This manuscript has been submitted to *Transfusion Medicine Reviews* for publication. Appendices included in the publication are found at the end of the manuscript, while additional appendices not included in the initial publication are found in the appendices section at the end of the thesis (page 109).

## Abstract

Tranexamic acid (TXA) is an effective haemostatic agent used for the reduction of blood loss and transfusion, however, the safety profile of TXA remains in question due to a potential risk of venous thromboembolism. By applying TXA topically as opposed to intravenously, systemic absorption may be reduced and unwanted side-effects mitigated. The objective of our review is to investigate the efficacy and safety of topically applied tranexamic acid. Cochrane Central Register of Controlled Trials, MEDLINE, Embase, ISI Web of Science, PubMed, and Clinicaltrials.gov were searched from inception to November, 2016. We included randomized controlled trials (RCTs) that compared topical tranexamic acid to placebo (or standard care) in adult patients. Surgical and non-surgical trials were included. Abstract, full-text selection, data extraction and risk of bias assessment were all performed in duplicate. Our primary outcome was the risk of blood transfusion defined as the proportion of patients requiring at least one unit of red blood cells transfused. Our secondary outcomes included blood loss and adverse events (mortality, myocardial infarction (MI), stroke, venous thromboembolic events). In total, 53 studies involving 4,503 patients met inclusion criteria and were included in our review. The administration of topical TXA significantly reduced the odds of receiving a blood transfusion (pooled OR 0.28, 95% CI 0.20 to 0.38; $P < 0.001$) and significantly reduced mean blood loss (WMD -276.6, 95% CI -327.8 to -225.4; $P < 0.0001$). There was no difference in the odds of developing a venous thromboembolic complication, stroke, or MI between the topical TXA and control groups (pooled OR=0.78, 95% CI 0.47 to 1.29; P=0.33). The topical application of TXA effectively reduces both transfusion risk and blood loss. Our review suggests the lack of a relationship between topical TXA administration and an increased risk of venous thromboembolic events, although more high-quality evidence from trials designed and powered to detect differences in safety outcomes are needed before definitive conclusions can be drawn.

## Background & Rationale

Allogenic blood transfusions, although potentially life-saving, may be associated with an increased risk of infection and immune reactions, which may be a major source of morbidity for patients (7,8). A number of strategies are available that limit surgical blood loss and transfusions. Use of haemostatic agents has increased over the last decade (55) with antifibrinolytics emerging as popular agents in both medical and surgical practice. Antifibrinolytic lysine analogues have been shown to be effective in reducing blood loss during surgery and trauma as well as non-surgical diseases such as anemia related to cancer(9–11). Tranexamic acid (TXA) is a lysine analogue and is a widely used antifibrinolytic. Systemic use of TXA has been shown in meta-analyses to be safe and effective at reducing blood loss in cardiac (12), orthopedic(13), pelvic(10), and spinal surgeries(14), among others, and is listed on the World Health Organization's List of Essentials Medicines.

Due to the mechanism of action of lysine analogues, there exists a theoretical increased risk of developing venous thromboembolic (VTE) complications such as deep venous thrombosis (DVT) or pulmonary embolism (PE)(26). In one of the largest trauma trials to date, the CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage), the efficacy and safety of TXA was assessed in over 20,000 adult trauma patients and no increase in thromboembolic events was reported. However the precision of the safety estimate was low and therefore a potential for increased risk of VTE was not ruled out (11). Many systematic reviews have examined the relationship between lysine analogues and VTE risk, with point estimates remaining imprecise and thus unable to rule out a potential increased risk of VTE(10,27,30,83). Because the theoretical risk of VTE, lysine analogues have not been adopted as part of routine practice for most major surgeries except perhaps in cardiac procedures (19,20,84).

There remains a need to assess safety and efficacy of different modes of TXA delivery that may maintain the benefits of systemic administration while reducing the risk of VTE (51,52). The plasma concentration

of topically applied TXA has been shown to be approximately 90% less than when the medication is administered intravenously (53,54). Conversely, it is possible that high local tissue drug concentrations from topical application may increase the risk of adverse events.

A previous systematic review showed that local TXA was effective, but safety could not definitively established (30). In recent years, there has been an influx of data, with numerous trials assessing topical TXA. Given the need for safe and effective haemostatic interventions, we performed a systematic review and meta-analysis to evaluate the efficacy and safety of topically administered tranexamic acid.

## Methods

Our review was registered on Prospero (no. CRD42016035902). A review protocol was prepared according to the PRISMA-P checklist (85) and is available upon request. The final report was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)(65).

### *Eligibility Criteria*

We included randomized controlled trials (RCTs) that compared topical tranexamic acid to placebo (or standard care) in adult patients. Surgical and non-surgical trials were included. We did not restrict inclusion by drug dose or timing of administration. Our primary outcome was the risk of blood transfusion defined as the number of patients requiring at least one unit of red blood cells transfused. Our secondary outcomes included blood loss and adverse events (mortality, myocardial infarction (MI), stroke, venous thromboembolic events). We did not impose any language restrictions.

### *Literature Search Strategy*

A comprehensive literature search of indexed databases was conducted to identify all relevant studies in collaboration with an information specialist and a clinical expert in the field. We had a separate information specialist review the search strategy to check for consistency according to the PRESS framework(86). The following databases were searched: Cochrane Central Register of Controlled Trials,

MEDLINE, Embase, ISI Web of Science, PubMed, and Clinicaltrials.gov. Grey literature was searched via Google using the same search terms. We searched from database inception to September 10th 2016 (Appendix 1).

### *Study Selection Process*

Citations from the literature search were collated and duplicate studies removed. Titles and abstracts were screened for inclusion by two independent reviewers (JM and PM). Titles and abstracts deemed potentially relevant were recorded and the full text articles obtained. The same reviewers screened the full text articles for final eligibility, with disagreements settled by consultation of a third party (RB) to achieve consensus. The study selection process was documented and reported using a PRISMA flow diagram (figure 1)(65).

### *Data Extraction and Risk of Bias Assessment*

Two reviewers (JM and PM) extracted all relevant data from the included studies using a standardized and piloted data extraction form in Microsoft Excel (version 15.0, Microsoft Corporation, Seattle, Washington, USA). We collected information related to publication traits (year of publication, journal, authorship list), study population (e.g, eligibility criteria, age, gender, comorbidities), the interventions compared (type of comparator, dose, and timing), study design (methods, setting, sample size, number of centres), clinical endpoints (transfusion, blood loss, death, stroke, myocardial infarction, and venous thromboembolic events; endpoint definitions were also abstracted), and risk of bias details. The risk of bias was assessed by two independent reviewers using the Cochrane Risk of Bias tool(66).

### *Data Analysis*

Studies were pooled using Cochrane Review Manager, version 5.3 (Cochrane Collaboration, Oxford, United Kingdom) and Open Meta-Analyst for Windows 8 (http://www.cebm.brown.edu/open_meta). For dichotomous outcomes, odds ratios were calculated using a random effects frequentist analysis based on the Der-Simonian Laird model and presented with accompanying 95% confidence intervals.

This method allows for the inclusion of continuity corrections of 0.5 for all zero cells across outcomes, allowing us to estimate odds ratios for studies reporting no events. For outcomes with zero events, a sensitivity analysis was also performed with a fixed effects meta-analysis using Peto odds ratios. For continuous outcomes, a mean difference and 95% confidence intervals are presented. Pooled mean differences were calculated using random effects inverse variance meta-analysis.

Statistical heterogeneity was assessed using the $I^2$ statistic, as well as the $Chi^2$ test or the Cochrane Q test, depending on the analysis method. An $I^2$ value of >50% was considered to indicate important heterogeneity requiring additional exploration. For the $Chi^2$ test and the Cochrane Q test, a P-value of <0.1 was deemed to indicate heterogeneity requiring additional exploration. The presence of publication bias was assessed using funnel plots if more than 6 studies were identified. We conducted subgroup analyses to determine whether the effect of topical TXA on blood transfusion and blood loss varied by the type of surgical procedure, as well as the baseline rate of transfusion. A sensitivity analysis was performed on outcomes with sufficient data, to determine if the effect of topical TXA varied when analyses were restricted to trials with adequate allocation concealment. A random-effects meta-regression was performed to determine if the association between topical TXA and blood transfusion rate was affected by the dose of topical TXA used in the trial.

## Results

The electronic search identified 1,167 titles and abstracts after the removal of duplicates, of which 1,087 were excluded based on irrelevancy to our study question. Of 80 full-text articles reviewed, 27 did not meet eligibility criteria and were excluded. Fifty-three trials met eligibility representing 4,503 patients(87–137) (138,139)(figure 1). Nine of the 53 articles did not report sufficient for inclusion in our meta-analyses(87–91,97,105,106,124).

### *Characteristics of Included Studies*

Included articles were published between 1979 and 2016 from 24 different countries (Table 1). Study sample sizes ranged from 30 patients to 333 patients (median = 84). Fifty-two of the studies assessed the efficacy of topical TXA in surgical patients. Twenty-one trials involved knee arthroplasty(93,99,101,103,105,107,108,110,111,113,118,121,124,127,128,130–135), eight hip arthroplasty(109,114,115,119,120,129,136,138), eight cardiac surgery(92,95,98,99,103,113,117,123), four dental surgery(87–89,91), two otolaryngological surgery(96,97), two spinal surgery(82,137), and two orthognathic surgery(101,126), one transurethral prostate resection(105), one reduction mammoplasty(124), one pulmonary resection(107), one hip and knee arthroplasty(118), and one shoulder arthroplasty(127). The sole study which assessed non-surgical patients studied the efficacy of topical TXA in epistaxis patients(90). Two trials consisted of two distinct topical TXA arms (different doses, administration techniques)(114,119) and therefore were included twice in analysis for which they contributed data. For these trials, the control group size and events were split in half.

In 25 of the 52 surgical trials, topical TXA was either poured (wound irrigation) or sprayed directly onto the operative site. In 16 trials involving hip or knee arthroplasty, topical TXA was administered via an intra-articular injection. Two trials involving hip arthroplasty used a combination of these two techniques(120,121). Another trial assessed both these techniques in two separate groups of patients(119). In two of the dental surgery trials, the wound was irrigated and the patients were given a mouthwash to use for a number of days post-operatively(88,89). Post-operative mouthwash alone was given in one dental surgery trial(91). In the last dental surgery trial, TXA soaked cones were applied to each tooth socket(87). Two trials were vague in their method of topical TXA application describing it their technique as “administered topically”(96) and “infiltration of TXA”(106). Two trials did not report their technique(130,134). In the one non-surgical trial, TXA gel was applied to the nasal cavity of epistaxis patients(90).

### *Study Quality and Risk of Bias*

Figure 2 summarizes the risk of bias using the Cochrane risk of bias tool. The majority of studies had an unclear risk of bias for at least one methodological criterion. The majority of studies described an adequate randomization technique, although two trials were deemed to be at high risk of bias as one trial allocated patients into groups according to the day of the week and one trial alternately assigned patients into groups(91,102). Less than half of the trials adequately described their allocation concealment technique, with the same two trials being deemed to be at high risk of bias in this domain.

The majority of trials were deemed to have adequately blinded their participants and personnel, as well as their outcome assessment for transfusion rate and were therefore at a low risk for both performance bias and detection bias. The majority of studies had complete data or had adequately described their reasons for missing data, with one study being deemed to be at high risk of attrition bias(100). A small portion of studies were deemed to have a low risk of reporting bias, as not many studies were registered on clinicaltrials.gov or had an available study protocol. The majority of studies were found to have a low risk of other potential biases. A breakdown of the risk of bias found in each study can be found in Appendix 2.

### *Effect of topical TXA on transfusion rate*

Thirty-six trials involving 3,370 patients reported blood transfusion. The administration of topical TXA significantly reduced the odds of receiving a blood transfusion (pooled OR 0.28, 95% CI 0.20 to 0.38; P < 0.001, $I^2$=46.4%) (figure 3). In subgroup analyses by surgery type, there was a significant reduction in transfusion risk for orthopedic procedures (pooled OR 0.22, 95% CI 0.16 to 0.30; P<0.01). There was no significant difference in transfusion risk for cardiac procedures (pooled OR 0.87, 95% CI 0.56 to 1.35; P=0.54), orthognathic procedures (pooled OR 1.00, 95% CI 0.02 to 52.15; P=N/A), spinal procedures (pooled OR 0.15, 95% CI 0.02 to 1.31; P=0.09), and thoracic procedures (pooled OR 0.73, 95% CI 0.26 to 2.08; P=0.53). P=0.53), although a small number of studies were included in these subgroups.

The sensitivity analysis using the fixed-effects Peto odds ratio, revealed similar results (Peto OR 0.31, 95% CI 0.26 to 0.37; P < 0.001) (appendix 3). When the analysis was restricted to the 20 trials deemed to have adequate allocation concealment, similar results were obtained (pooled OR 0.32, 95% CI 0.22 to 0.46; P < 0.001) (appendix 3). For the subgroup analysis by baseline rate of transfusion, subgroups included baseline risks of <10%, 10-20%, 20-30%, 30-40% and >40%. With the exception of a baseline risk of <10% (pooled OR 0.47, 95% CI 0.18 to 1.25; P=0.13), a significant decrease in transfusion risk was seen across all subgroups (appendix 3).

### *Effect of topical TXA dose on transfusion rate*

Thirty-two of the 36 trials that reported transfusion data were included in a univariate meta-regression analysis. In four trials, we were unable to convert the dose of topical TXA into the appropriate mg/mL due to a lack of information provided in the related publications(100,125,129,130). The concentration of topical TXA used in the trials ranged from 1 mg/mL to 100 mg/mL. Dosage of topical TXA did not influence effectiveness of topical TXA used in the trial (Coefficient = -0.002, 95% CI -0.015 to 0.011; P = 0.754).

### *Effect of topical TXA on blood loss*

Forty-two trials involving 3,666 patients reported blood loss data. Topical TXA resulted in a mean blood loss reduction of 276.6 mL compared to placebo (WMD -276.6, 95% CI -327.8 to -225.4; P < 0.0001) (figure 4). When the analysis was restricted to the 22 trials deemed to have adequate allocation concealment, similar results were seen (WMD -311.5, 95% CI -384.1 to -239.0; P < 0.00001). Large reductions in blood loss were reported in orthopedic surgery trials, while no statistically significant benefit was reported in the single thoracic surgery Trial. There was substantial statistical heterogeneity between subgroups ($Chi^2$ = 275.6, df = 5 (P <0.00001); $I^2$ = 98.2%).

### *Effect of topical TXA on the rate of venous thromboembolic events*

Thirty trials involving 2,845 patients reported data on the rate of venous thromboembolic events (either pulmonary embolism or deep vein thrombosis) in their trial. Nineteen trials reported no venous thromboembolic events in either arm of their trial. There was no difference in the odds of developing a venous thromboembolic complication between the topical TXA and control groups (pooled OR=0.78, 95% CI 0.47 to 1.29; P=0.33, $I^2$=0%) (figure 5). In our sensitivity analysis using the fixed-effects Peto odds ratio, similar results were obtained (Peto OR=0.79, 95% CI 0.49 to 1.27; P=0.33, $I^2$=0%) (appendix 3).

### *Effect of topical TXA on the risk of death*

Nine trials involving 894 patients reported mortality data. Seven of the nine trials reported zero deaths in each group. The administration of topical TXA did not increase the risk of death (pooled OR=0.52, 95% CI 0.18 to 1.55; P=0.24, $I^2$=0%) (figure 6).

### *Effect of topical TXA on the risk of stroke*

Seven trials involving 552 patients reported stroke data. Six of the seven studies reported zero events in both arms of their trial. The administration of topical TXA did not increase the risk of stroke (pooled OR=0.75, 95% CI 0.18 to 3.18; P=0.70, $I^2$=0%) (figure 7).

### *Effect of topical TXA on the risk of myocardial infarction*

Six trials involving 362 patients reported myocardial infarction data. Four of the six studies reported zero events in both arms of their trial. The administration of topical TXA did not increase the risk of myocardial infarction (pooled OR=0.58, 95% CI 0.13 to 2.57; P=0.47) (figure 8).

### *Publication Bias*

Publication bias was assessed for clinical outcomes of transfusion risk, blood loss and thromboembolic events (appendix 3). Slight asymmetry was seen in the funnel plots for transfusion risk and blood loss, with the plots suggesting the presence of small study effects favouring topical TXA. No asymmetry was seen in the funnel plot for thromboembolic events, suggesting low risk of bias.

## Discussion

There is considerable interest in topical TXA, given the potential benefits and theoretical decreased risk of adverse events compared to systemic TXA. Since the last systematic review in 2013, twenty-five additional trials have been reported and are included in this review. The results of our review suggest that the topical application of tranexamic acid during surgery is highly effective in reducing both blood loss and the subsequent rate of blood transfusions compared to placebo. In addition, we observed no increased risk of thromboembolic events, stroke, myocardial infarction, or mortality.

Thirty-six randomized controlled trials involving 3,370 patients in our review reported on transfusion rate, and we found a 72% reduction in the odds of receiving a blood transfusion in patients who had received TXA topically. In a systematic review and meta-analysis of 129 randomized controlled trials involving a total of 10,488 patients treated with TXA by any form of administration, Ker *at al*. reported a 30% reduction in the need for transfusion(27), a similar magnitude of effect has been noted in reviews of pelvic and orthopedic surgeries(10,13). This finding may indicate that topical TXA is more effective at reducing transfusion risk compared to intravenous administration. Topical versus intravenous TXA has been examined in orthopedic surgeries such as knee and hip replacements(141–143) and no differences between administration route were observed. To our knowledge, trials including non-orthopedic procedures have not been conducted.

Administration of topical TXA significantly reduces estimated blood loss. These findings are consistent with many large trials(11,144), and reviews(27,30,56) of both topically and intravenously administered TXA. Blood loss is a challenging outcome to accurately estimate, and measurement techniques vary across studies. None of the trials included in our analysis were adequately powered to detect a difference in thromboembolic events between groups, one of the main safety concerns surrounding TXA. However, our pooled analysis suggests that there is no increased risk of thromboembolic events associated with topical TXA compared to placebo (pooled OR=0.78, 95% CI 0.47 to 1.29; P=0.33, $I^2$=0%).

These findings are consistent with trials of intravenously administered TXA, which have not found an increased risk of thromboembolic events (10,12,27,56). However, it is worth noting the confidence interval remains wide for safety estimates and less than two-thirds of the studies in our review reported on thromboembolic events (30/53). Therefore, high-quality randomized controlled trials designed and powered to detect differences in thromboembolic events are needed to definitively establish the safety of TXA, especially in understudied and high risk populations such as cancer patients(83). Of note, none of the studies included in our review examined the effects of topical TXA in an oncology population.

There is no accepted standard dose of TXA for systemic or topical use (28,29). The studies included in our analysis used a wide range of doses of topical TXA (1mg/mL to 100mg/mL). According to our meta-regression analysis, the relationship between topical TXA administration and transfusion risk reduction was not dose-dependent, suggesting topical TXA remains effective at small doses. Given that small retrospective studies have reported an increase in risk of seizure associated with high dose intravenous TXA(31–34). However, no prospective trials have demonstrated such relationship. Further study to identify optimal drug doses are needed.

Our review has limitations. We were limited by the quality of the published studies, many of which had unclear risk of bias as they did not report some methodological details. We found substantial statistical heterogeneity in our clinical outcomes of blood transfusion and blood loss. This heterogeneity remained within the blood loss subgroups and in the sensitivity analysis removing trials with poor allocation concealment in both outcomes. There are a number of factors which could explain this heterogeneity. Transfusion in clinical practice can vary within healthcare systems and even within hospitals. Considering the wide range of studies, it is likely that transfusion thresholds varied from study to study. Surgical quality across studies is another factor which could influence the magnitude of effect observed. With respect to blood loss, this is a difficult outcome to measure accurately and consistently. Differences in measuring techniques across studies could explain some of the heterogeneity observed. It is important

to note that the variation seen in these outcomes were in the magnitude of effect, and not the direction. Finally, few trials reported data on the rate of mortality, stroke or MI, making the effect estimates for these outcomes very imprecise and preclude definitive conclusions.

## Conclusion

The topical application of tranexamic acid effectively reduces both transfusion risk and blood loss. This effect does not appear to be dose-dependent. Our review suggests the lack of a relationship between topical TXA administration and an increased risk of adverse events including thromboembolism, although more high-quality evidence from trials designed and powered to detect differences in safety outcomes are needed before definitive conclusions can be drawn. Outside of orthopedic surgery, the comparison of topically administered tranexamic acid to intravenously administered tranexamic acid warrants further exploration.

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**Conflict of Interest Statement: The authors have no conflicts of interest to declare.**

***Table 1. Characteristics of included studies***

| Study | Host Country(ies) | Sample Size | Procedure | Method of topical TXA Administration | Transfusion risk reported (Y/N) | Blood loss reported (Y/N) | VTE risk reported (Y/N) |
|---|---|---|---|---|---|---|---|
| **Drosos (2016)[134]** | Greece | 90 | TKA | N.R. | Y | Y | Y |
| **Keyhani (2016)[135]** | Iran | 120 | TKA | Intra-articular injection | Y | Y | Y |
| **Tzatzairis (2016)[136]** | Greece | 120 | TKA | Intra-articular injection | Y | Y | Y |
| **Zhang (2016)[137]** | China | 75 | THA | Intra-articular injection | Y | Y | Y |
| **Aguilera (2015)[122]** | Spain | 150 | TKA | Sprayed via syringe onto wound prior to closure | Y | Y | N |
| **Ali Shah (2015)[123]** | Pakistan | 100 | Open heart surgeries | Wound irrigation prior to closure | N | Y | N |
| **Ausen (2015) [124]** | Norway | 56 | Bilateral reduction mammoplasty | Poured into wound prior to closure | N | N | N |
| **Digas (2015) [125]** | Greece | 85 | TKA | Intra-articular injection | Y | Y | Y |
| **Eftekharian (2015) [126]** | Iran | 56 | Bimaxillary osteotomy | Wound irrigation throughout procedure | Y | Y | Y |
| **Gillespie (2015)[127]** | USA | 111 | TSA | Wound irrigation prior to closure | Y | Y | Y |
| **Lin (2015) [128]** | Taiwan | 120 | TKA | Intra-articular injection | Y | Y | Y |
| **Oztas (2015) [129]** | Turkey | 90 | TKA | Intra-articular injection | Y | Y | Y |
| **Vandesande (2015)* [130]** | Belgium | 63 | THA | N.R. | Y | Y | N |
| **Wang, C (2015)[132]** | China | 60 | TKA | Intra-articular injection | Y | Y | Y |
| **Wang, G (2015)[131]** | China | 100 | TKA | Intra-articular injection | Y | Y | Y |
| **Xu (2015)[139]** | China | 224 | THA | Intra-articular injection | Y | Y | Y |
| **Yang (2015)[133]** | China | 80 | TKA | Intra-articular injection | Y | Y | Y |
| **Emara (2014)[116]** | Egypt | 60 | Hemiarthroplasty surgeries | Wound irrigation prior to closure | Y | Y | Y |
| **Hosseini (2014)[117]** | Iran | 71 | off-pump CABG | Wound irrigation prior to closure | N | Y | Y |
| **Martin (2014)[118]** | USA | 100 | TKA/THA | Wound irrigation prior to closure | Y | N | Y |
| **Sarzaeem (2014)[119]** | Iran | 200 | TKA | Wound irrigation prior to closure (grp 2)<br>Intra-articular injection (grp 3) | Y | Y | Y |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Wei (2014)[120]** | China | 333 | THA | Intra-operative wound irrigation and intra-articular injection | Y | Y | Y |
| **Yue (2014)[121]** | China | 103 | Unilateral total hip replacement | TXA soaked gauze inserted into wound intra-operatively and intra-articular injection | Y | Y | Y |
| **Alshryda (TRANX-K) (2013)[111]** | United Kingdom | 157 | TKA | Solution sprayed onto wound prior to closure | Y | Y | Y |
| **Alshryda (TRANX-H) (2013)[110]** | United Kingdom | 173 | Unilateral total hip replacement | Solution sprayed onto wound prior to closure | Y | Y | Y |
| **Georgiadis (2013)[112]** | USA | 101 | TKA | Wound irrigation prior to closure | Y | Y | Y |
| **Nouraei (2013)[113]** | Iran | 80 | Cardiac surgery | Wound irrigation prior to closure | Y | Y | Y |
| **Sa-ngasoonsgsong (2013)[114]** | Thailand | 135 | TKA | Intra-articular injection | Y | Y | Y |
| **Van Elst (2013)*[115]** | Belgium | 67 | THA | Intra-articular injection | N | N | Y |
| **Abdullah (2012)*[105]** | Pakistan | 52 | Transurethral resection of the prostate | Wound irrigation | N | N | N |
| **Canata (2012)*[106]** | N.R. | 96 | TKA | Infiltration of TXA** | N | N | N |
| **Dell'Amore (2012)[107]** | Italy | 89 | Pulmonary resection | Wound irrigation prior to closure | Y | Y | Y |
| **Roy (2012)[108]** | India | 50 | TKA | Intra-articular injection | Y | Y | Y |
| **Seo (2012)[109]** | South Korea | 150 | TKA | Intra-articular injection | Y | Y | Y |
| **Ishida (2011)[102]** | Japan | 100 | TKA | Intra-articular injection | Y | Y | N |
| **Kaewpradub (2011)[101]** | Thailand | 40 | Bimaxillary osteotomy | Wound irrigation, intra-operatively | N | Y | N |
| **Kurt (2011)[103]** | Turkey | 100 | Cardiac surgery | Wound irrigation prior to closure | N | Y | N |
| **Sa-ngasoonsgsong (2011)[104]** | Thailand | 48 | TKA | Intra-articular injection | Y | Y | Y |
| **Saberi (2010)[138]** | Iran | 100 | Spinal surgery | Wound irrigation prior to closure | Y | Y | N |
| **Wong (2010)[100]** | Canada | 124 | TKA | Wound soaked in TXA for 5 minutes prior to closure | Y | Y | Y |
| **Fawzy (2009)[99]** | Saudi Arabia | 38 | Isolated CABG | Wound irrigation prior to closure | Y | Y | N |
| **Athanasiadis (2007)[97]** | Australia | 30 | Sinus surgery | Solution sprayed into nasal cavity | N | N | N |
| **Baric (2007)[98]** | Croatia | 300 | Elective cardiac surgery | Wound irrigation prior to closure | Y | Y | N |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Abul-Azm (2006)[95]** | Egypt | 200 | Elective open heart surgery | Wound irrigation prior to closure | N | Y | N |
| **Jabalameli (2006)[96]** | Iran | 56 | Sinus surgery | "Administered topically" | N | Y | N |
| **Yasim (2005)[94]** | Turkey | 300 | TKA | Wound irrigation prior to closure | N | Y | N |
| **Krohn (2002)[93]** | Norway | 30 | Spinal surgery | Wound irrigation prior to closure | Y | Y | N |
| **De Bonis (2000)[92]** | Italy | 40 | Primary coronary artery surgery | Wound irrigation prior to closure | Y | Y | N |
| **Blinder (1999)[91]** | Israel | 150 | Dental extraction | Mouthwash rinsed for 2 minutes, 4 times/day for 4 days post-op | N | N | N |
| **Tibbelin (1995)[90]** | Sweden | 68 | Epistaxis | TXA gel applied to nasal cavity | N | N | N |
| **Ramstrom (1993)[89]** | Denmark & Sweden | 93 | Dental surgery | Wound irrigation prior to closure and mouthwash rinsed for 2 minutes, 4 times/day for 7 days post-op | N | N | N |
| **Sindet-Pedersen (1989)[88]** | Denmark & Sweden | 45 | Oral surgery | Wound irrigation prior to closure and mouthwash rinsed for 2 minutes, 4 times/day for 7 days post-op | N | N | N |
| **Gersel-Pedersen (1979)[87]** | Denmark | 120 | Bilateral molar extraction | TXA soaked cones applied to wound prior to closure | N | N | N |

- *= abstract only*

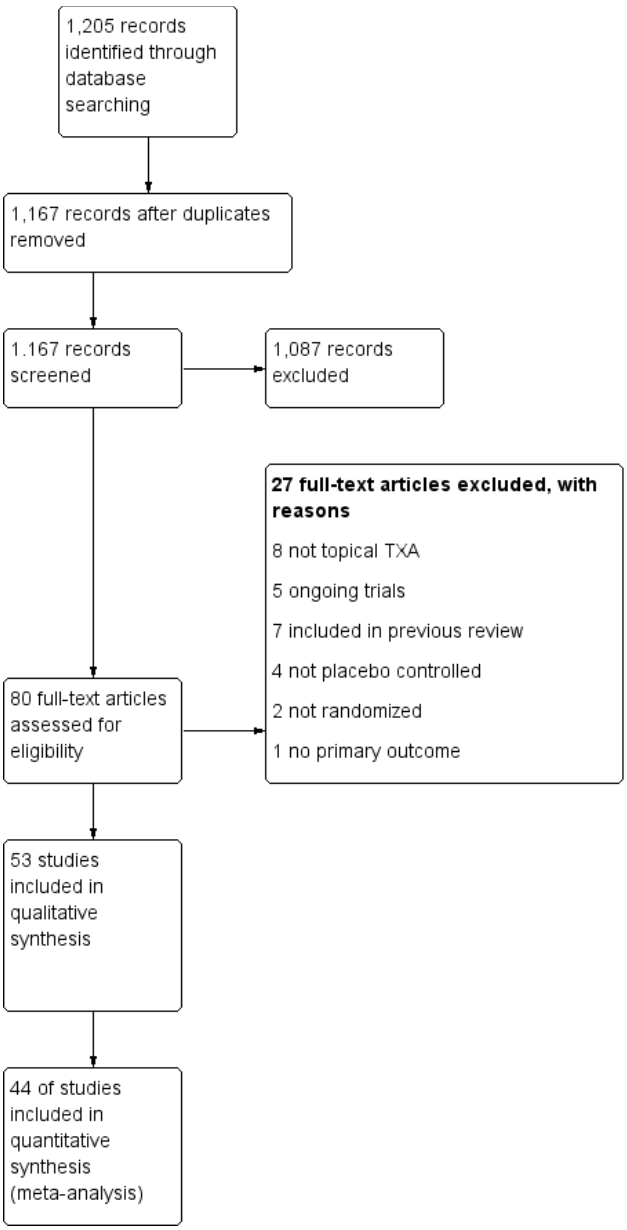



***Figure 1.*** Selection flow diagram

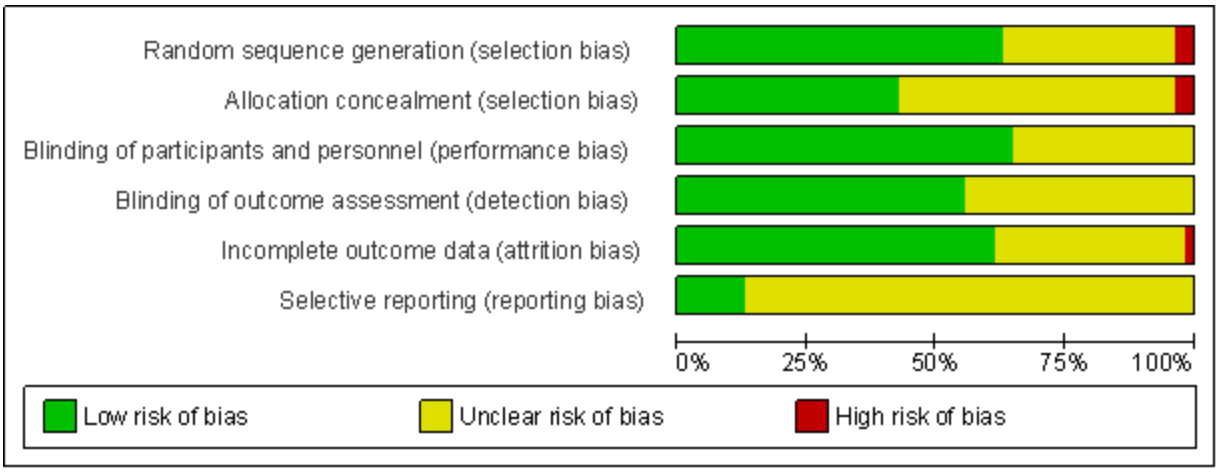



***Figure 2.*** Risk of bias summary

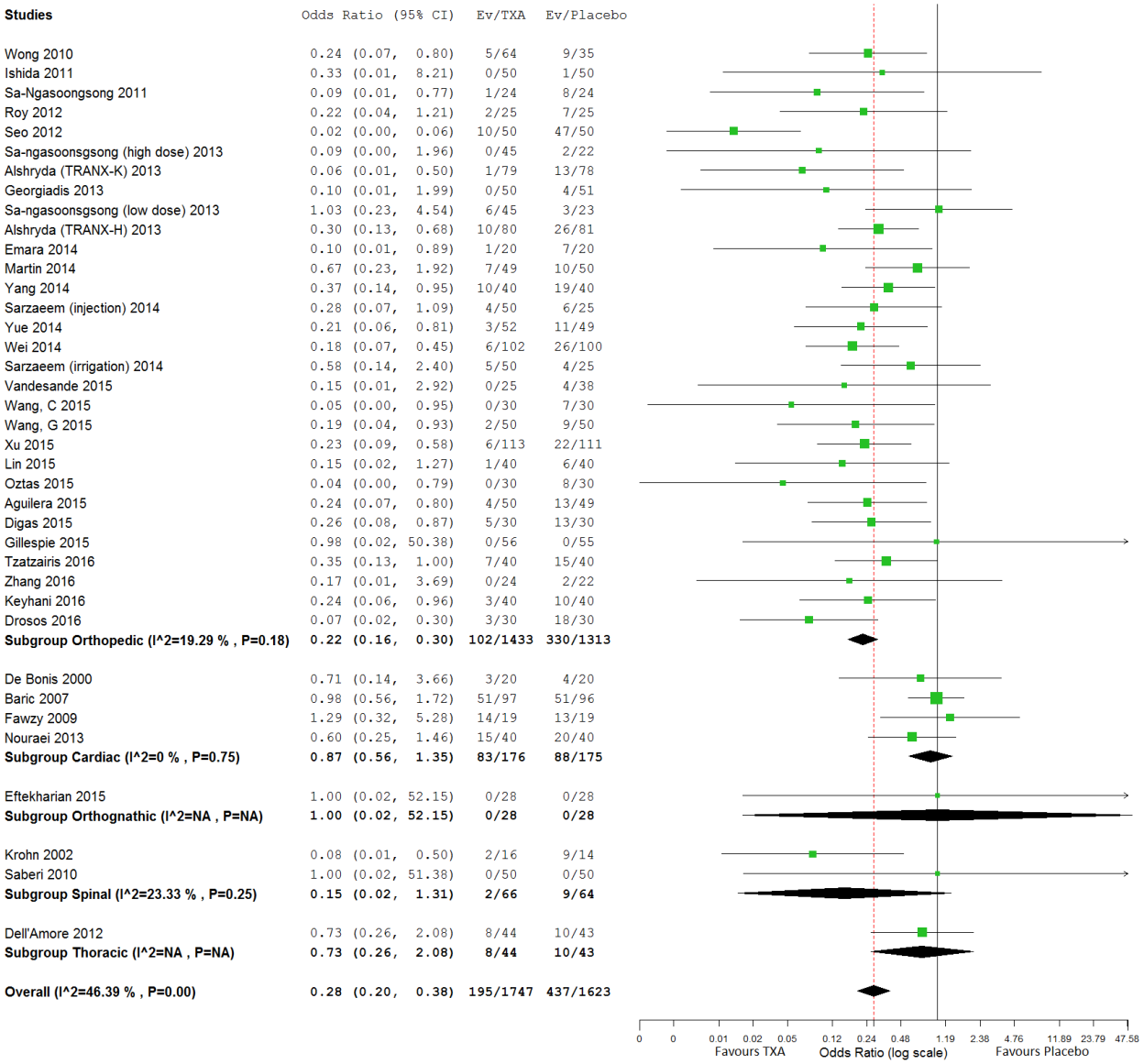



***Figure 3.*** Odds ratio (95% CI) and pooled estimates for risk of blood transfusion

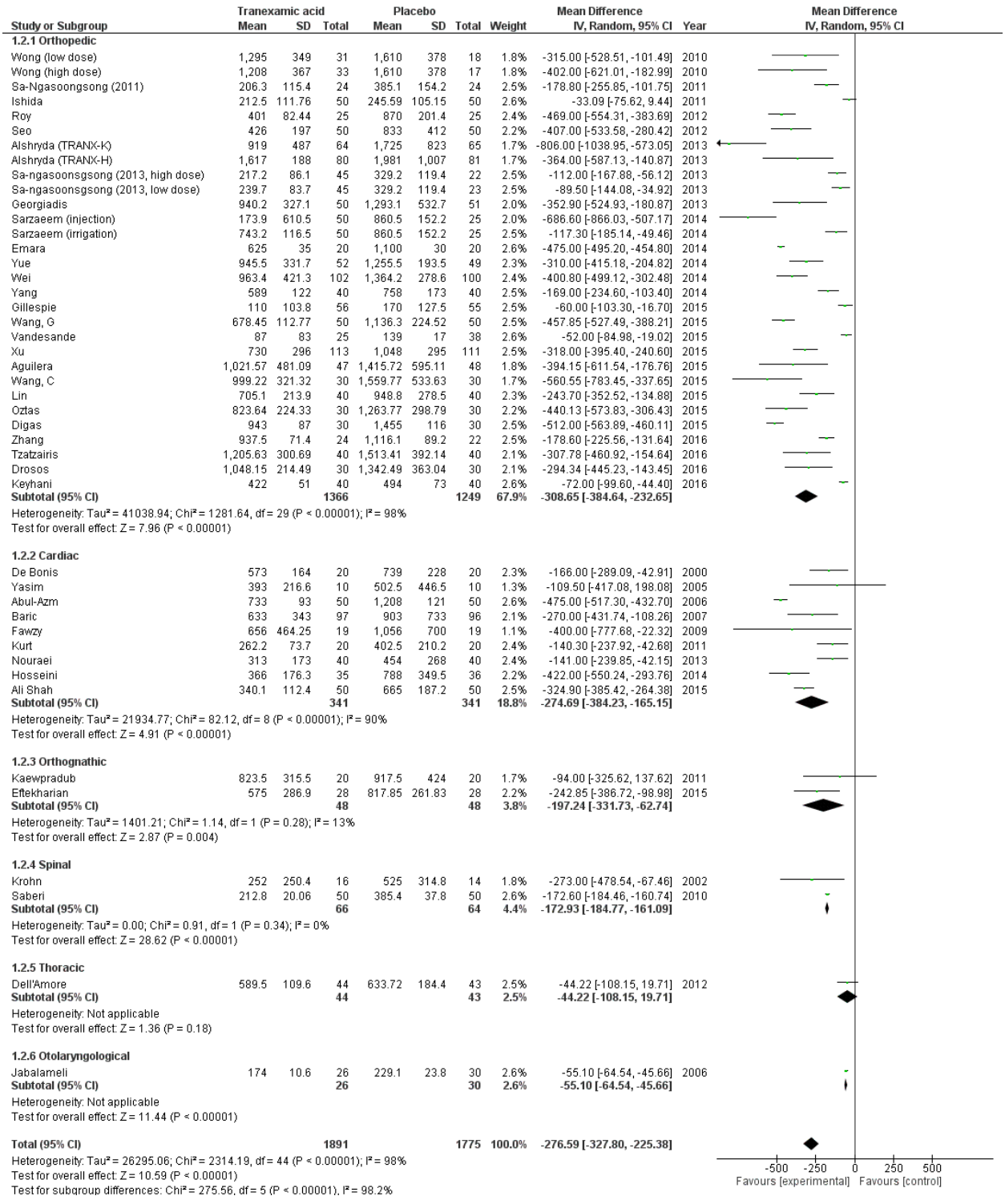



***Figure 4.*** Mean difference (95% CI) for estimated blood loss

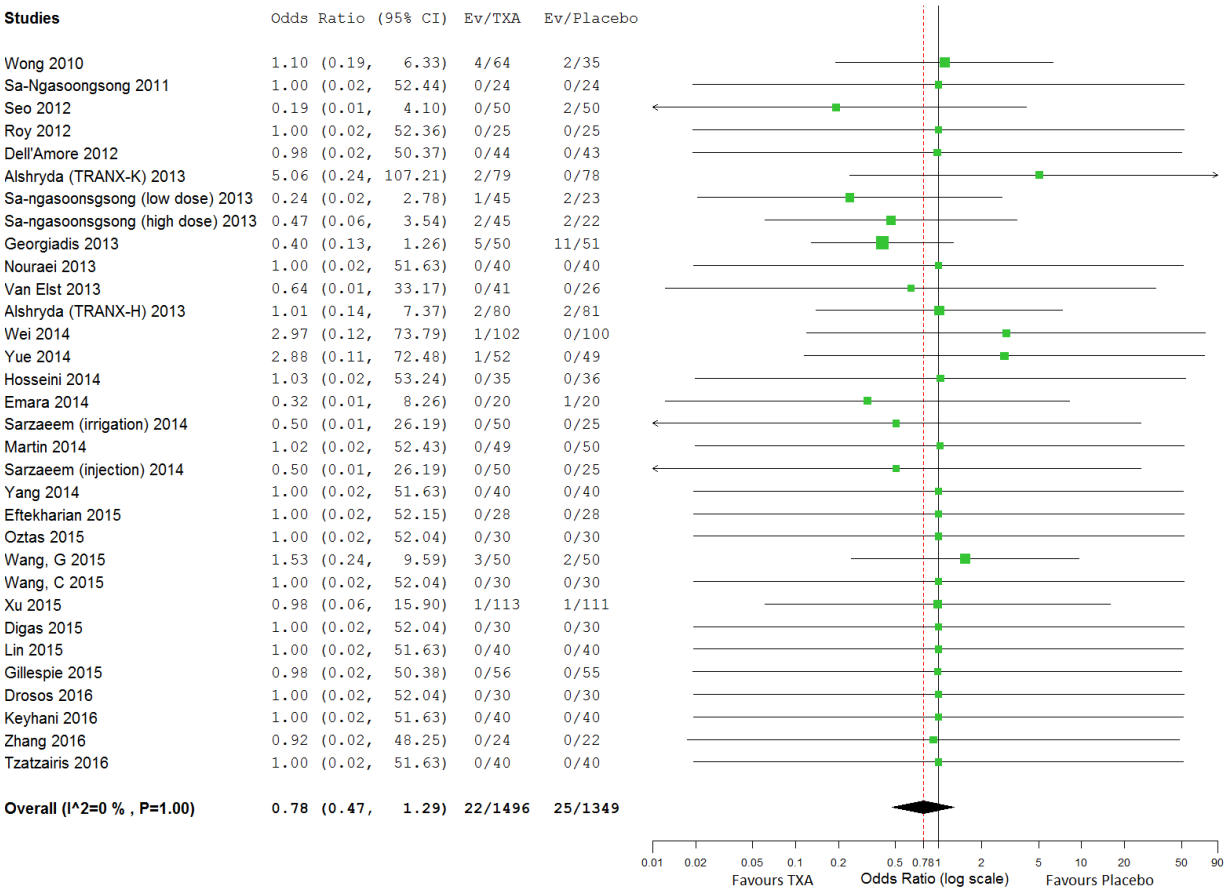



***Figure 5.*** Odds ratio (95% CI) and pooled estimates for the incidence of venous thromboembolic events

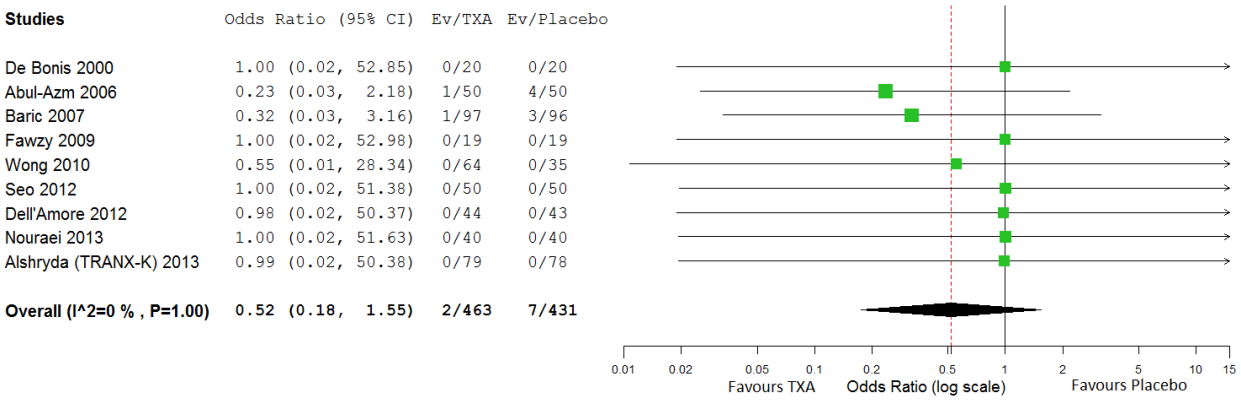



***Figure 6.*** Odds ratios (95% CI) and pooled estimates for the incidence of mortality

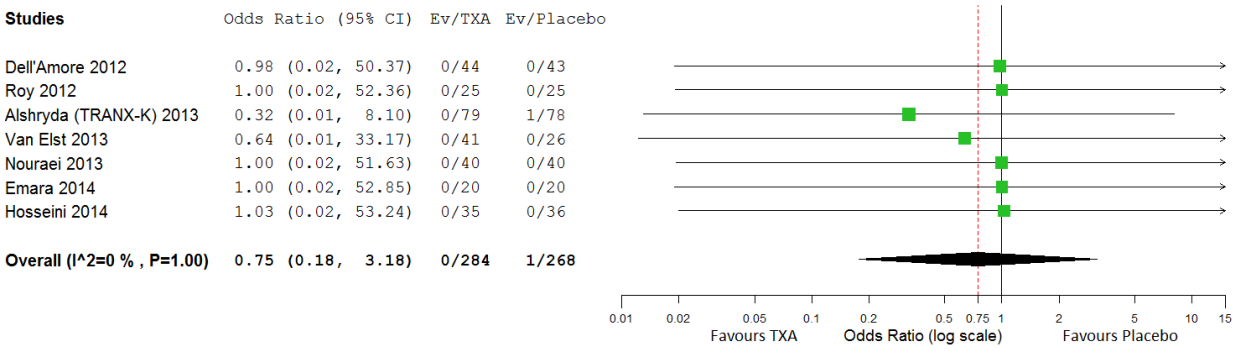



***Figure 7.*** Odds ratios (95% CI) and pooled estimates for the incidence of stroke

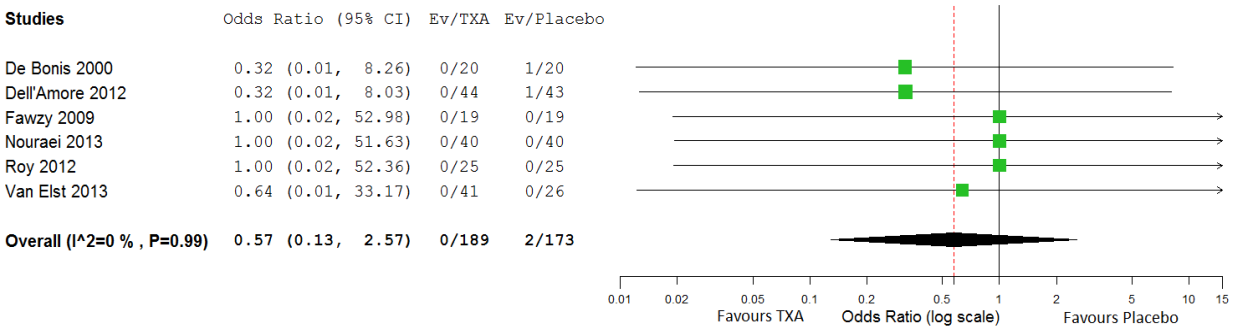



***Figure 8.*** Odds ratios (95% CI) and pooled estimates for the incidence of myocardial infarction

# Supplemental Material

## Appendix 1: Search strategy

1. exp Antifibrinolytic Agents/

2. (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.

3. exp Tranexamic Acid/

4. (tranexamic or cyclohexanecarboxylic or methylamine or amcha or amca or kabi or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol or aminomethylcyclo-hexane or aminomethylcyclohexanecarbonic or aminomethylcyclohexanecarboxylic or AMCHA or amchafibrin or amicar or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA or Lysteda or transcam).ab,ti.

5. 1 or 2 or 3 or 4

6. exp Administration, Topical/

7. (topical* or intra-articular* or intraarticular* or (local* adj3 appl*) or irrigat* or mouthwash* or rins* or intra-nasal* or intranasal* or rectal* or intra-vaginal* or intravaginal* or spray*).ab,ti.

8. 6 or 7

9. 5 and 8

10. randomi?ed.ab,ti.

11. randomized controlled trial.pt.

12. controlled clinical trial.pt.

13. placebo.ab.

14. clinical trials as topic.sh.

15. randomly.ab.

16. trial.ti.

17. Comparative Study/

18. exp clinical trial/

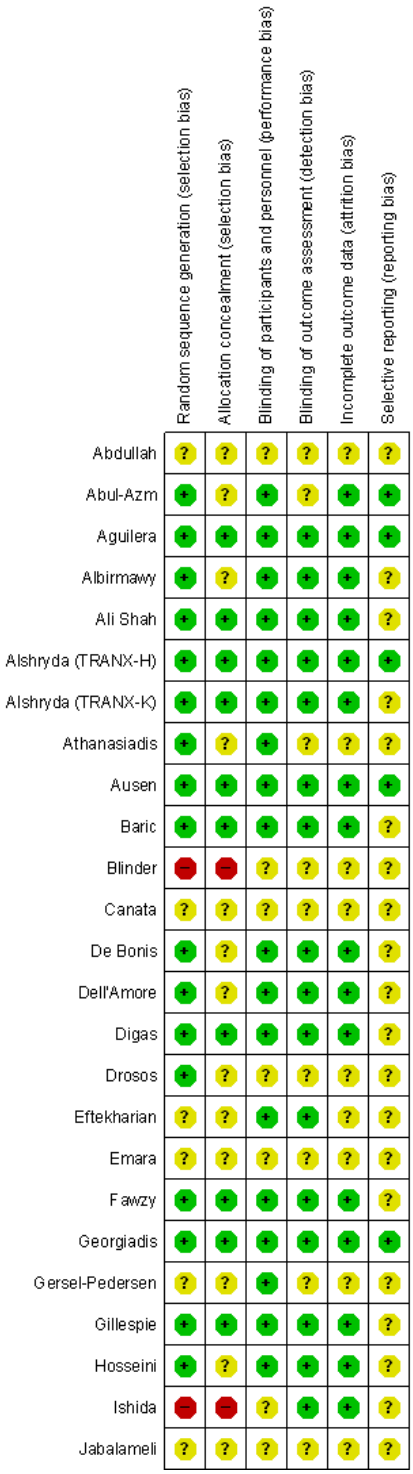
19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

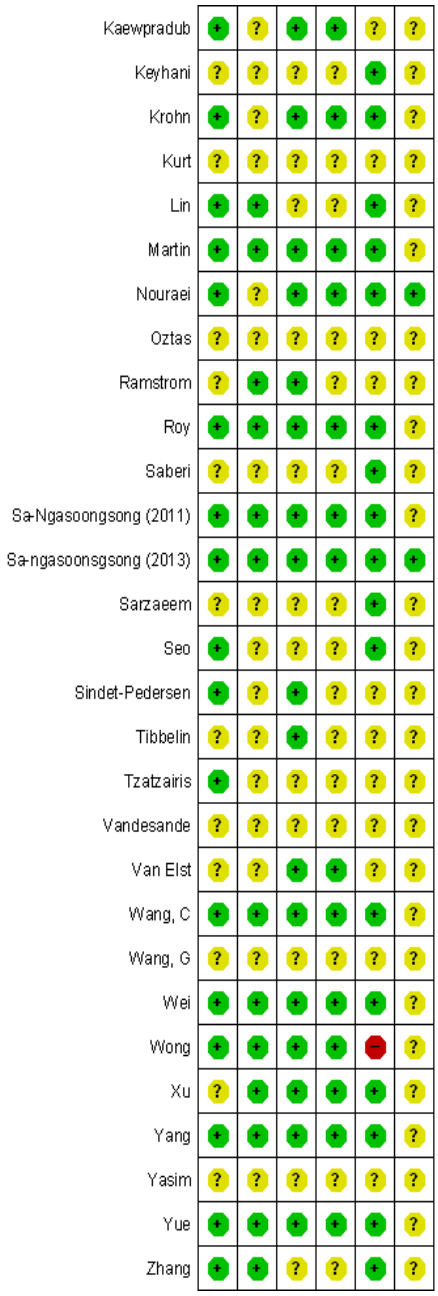
20. (animals not (humans and animals)).sh.

21. 19 not 20

22. 9 and 21

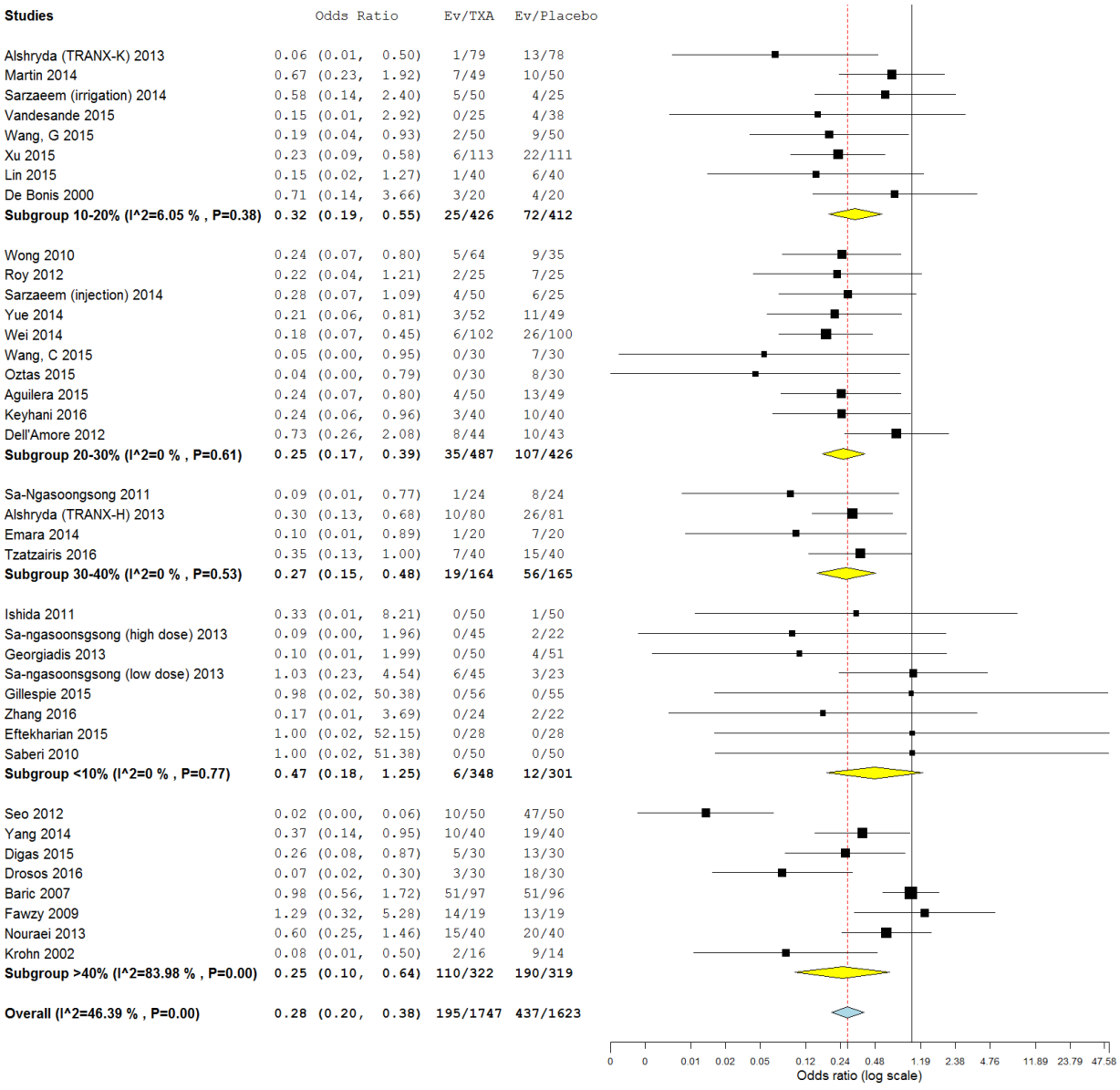
## Appendix 2: Risk of bias assessment



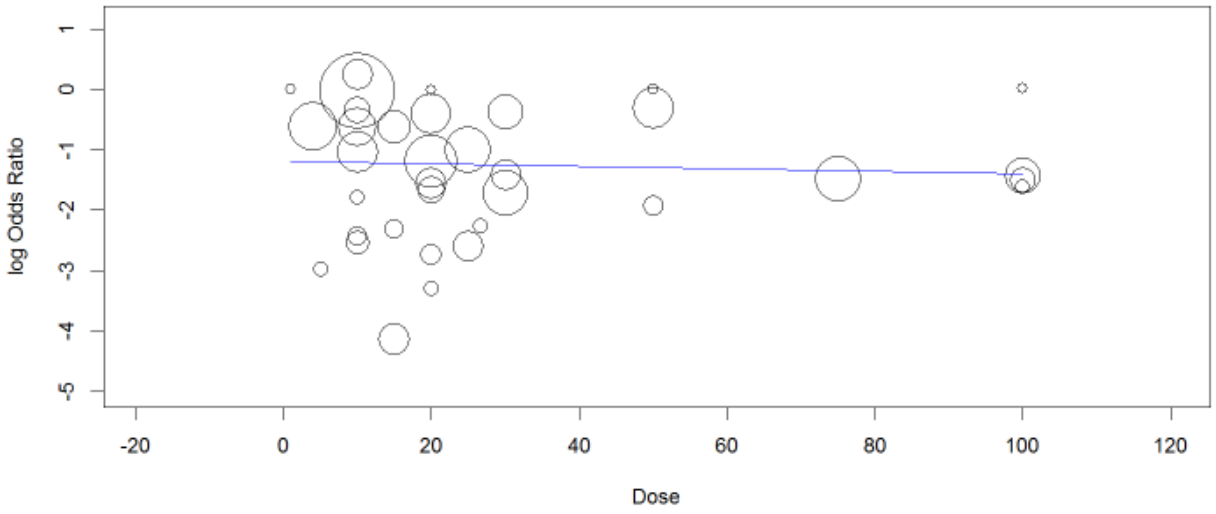

Kaewpradub
Keyhani
Krohn
Kurt
Lin
Martin
Nouraei
Oztas
Ramstrom
Roy
Saberi
Sa-Ngasoongsong (2011)
Sa-ngasoonsgsong (2013)
Sarzaeem
Seo
Sindet-Pedersen
Tibbelin
Tzatzairis
Vandesande
Van Elst
Wang, C
Wang, G
Wei
Wong
Xu
Yang
Yasim
Yue
Zhang

## Appendix 3: Additional figures

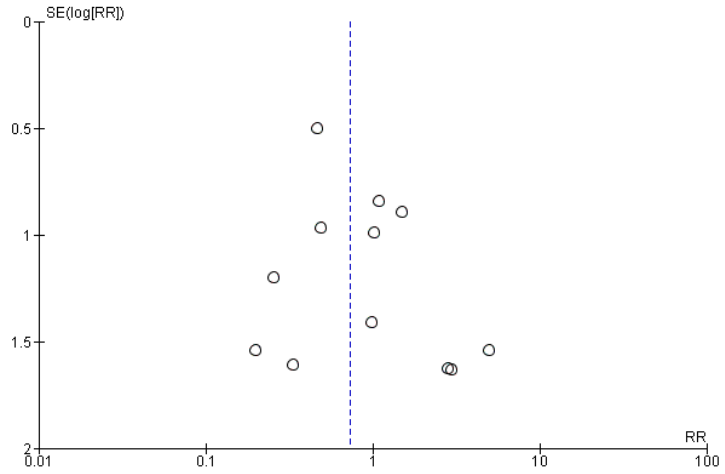
**A3 a)** Odds Ratio (95% CI) and pooled estimates for risk of blood transfusion subgrouped by baseline rate of transfusion



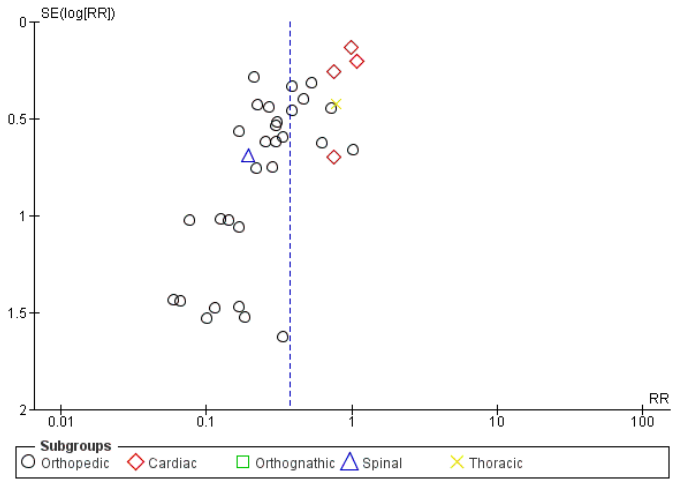
**A3 b)** Meta-regression for the impact of dosage on the effect of tTXA on transfusion risk



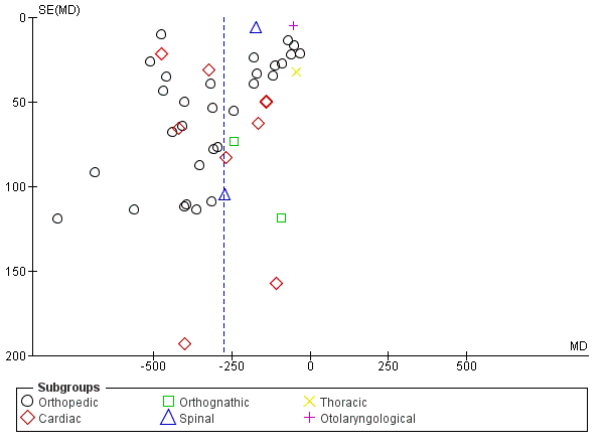

**A3 c)** Funnel plot for the incidence of VTE



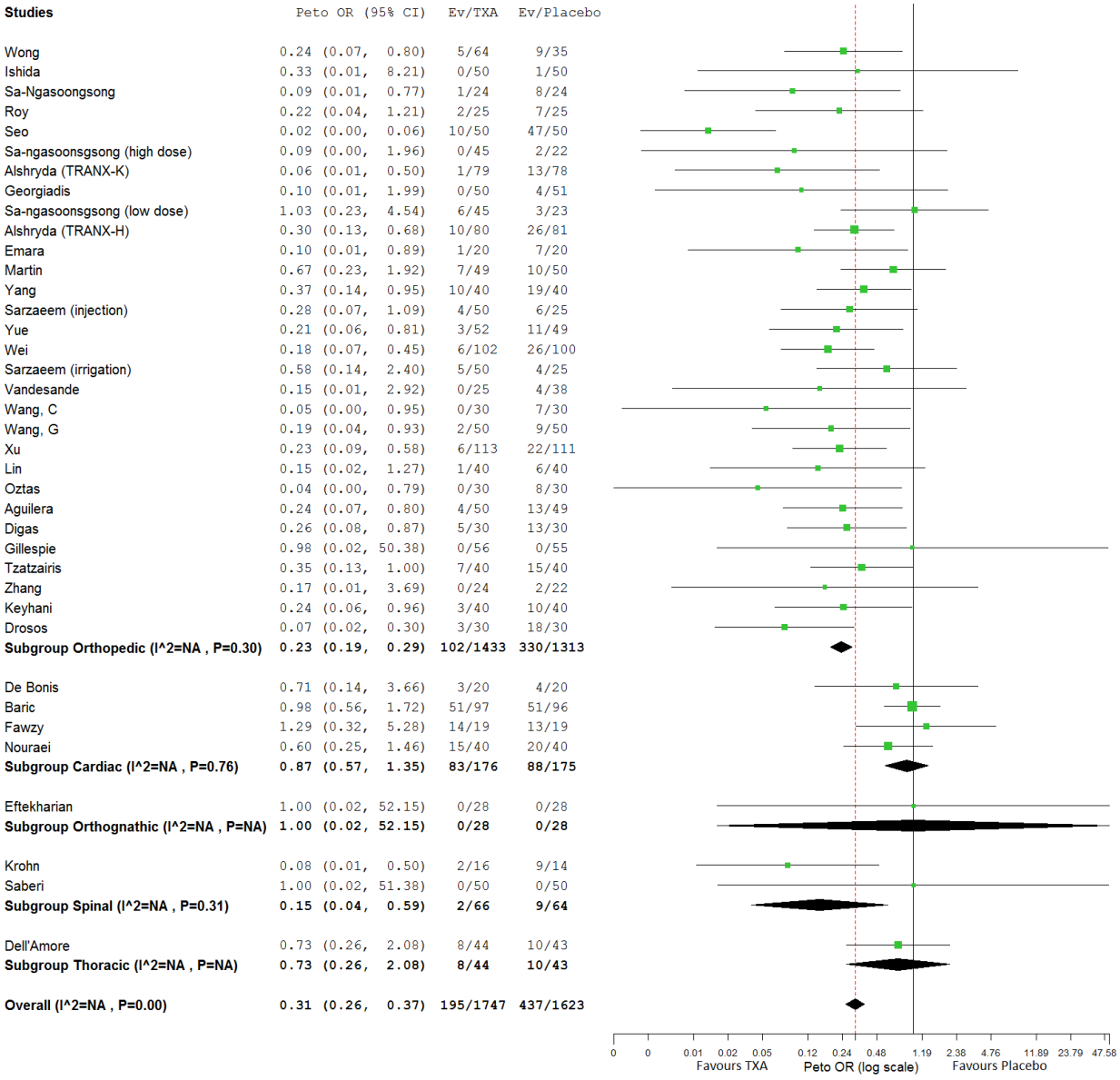
**A3 d)** Funnel plot for transfusion risk



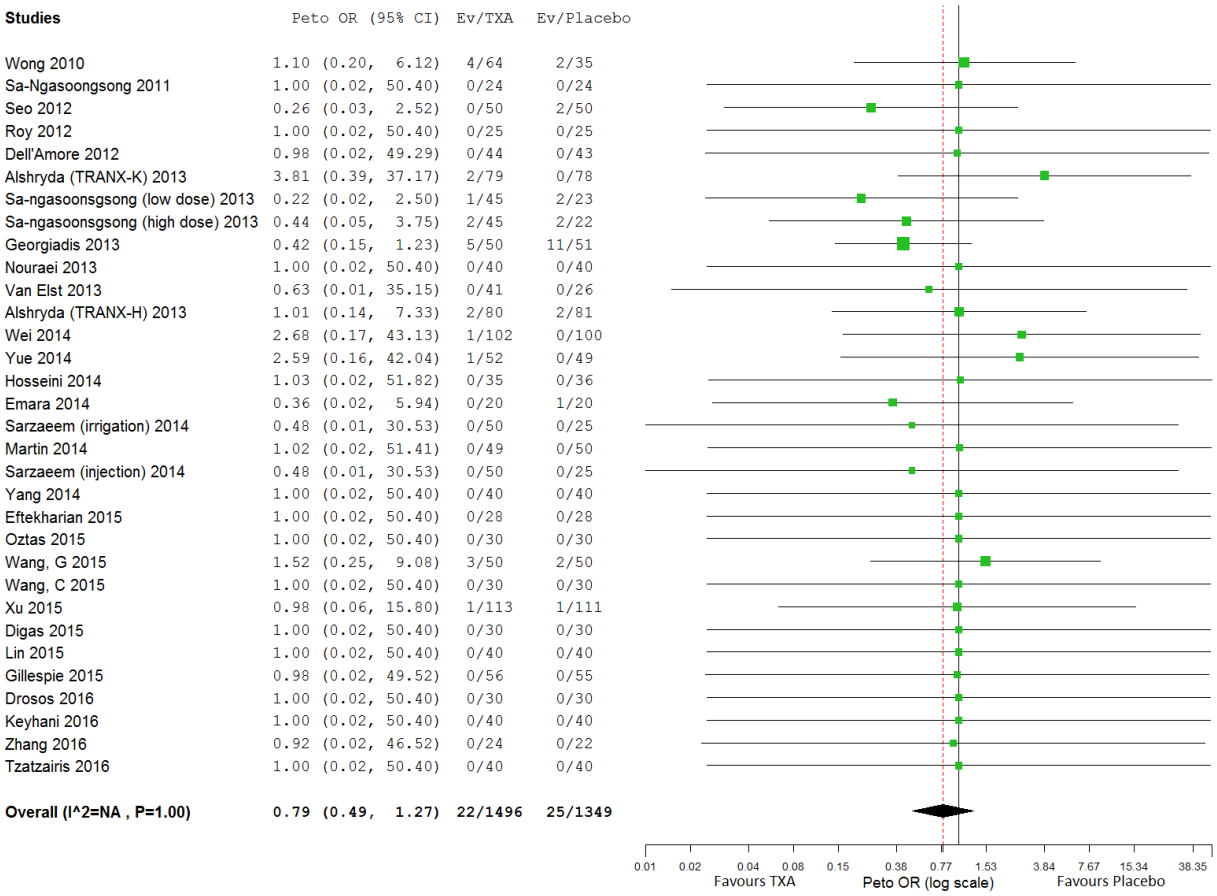

**A3 e)** Funnel plot for blood loss



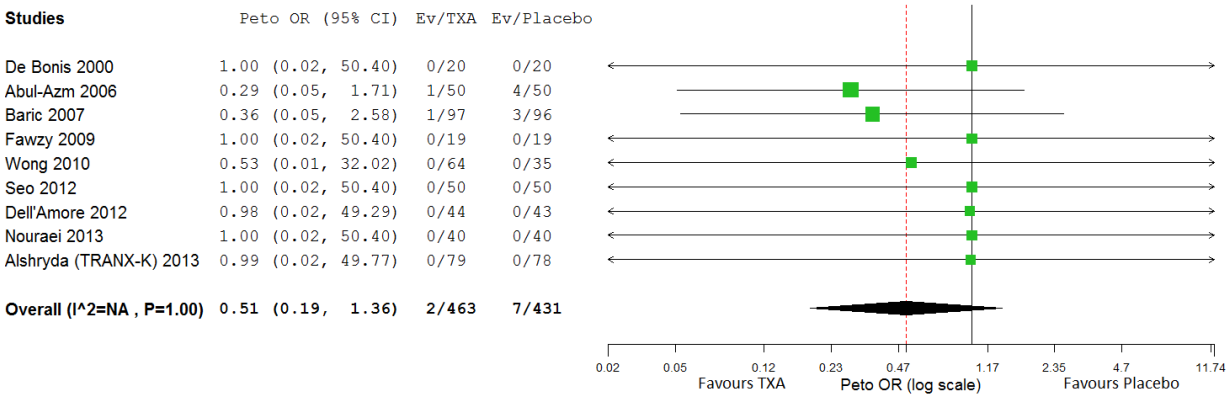
**A3 f)** Peto odds ratios (95% CI) and pooled estimates for transfusion risk



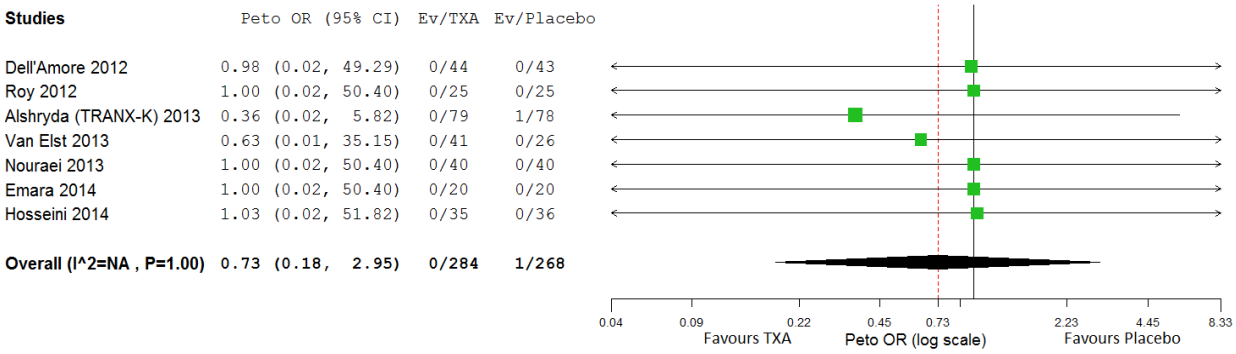
**A3 g)** Peto odds ratios (95% CI) and pooled estimates for the incidence of VTE



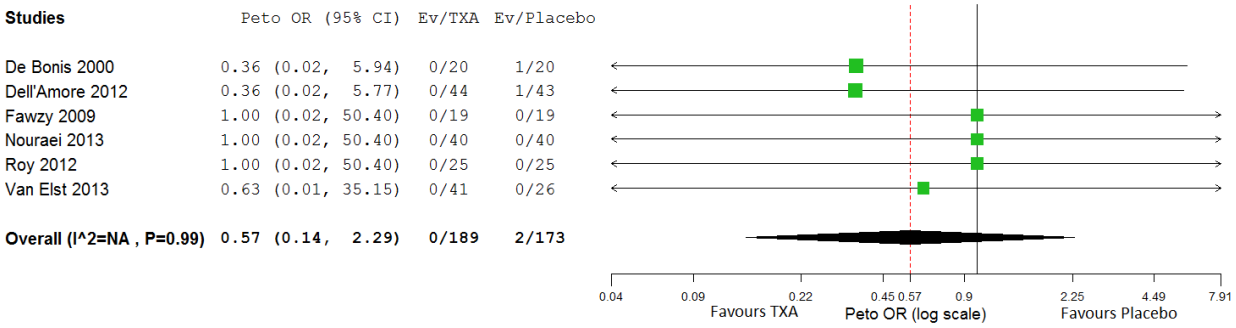

**A3 h)** Peto odds ratios (95% CI) and pooled estimates for the incidence of mortality



**A3 i)** Peto odds ratios (95% CI) and pooled estimates for the incidence of stroke




**A3 j)** Peto odds ratios (95% CI) and pooled estimates for the incidence of myocardial infarction



# CHAPTER 6

## Use of lysine analogues at The Ottawa Hospital

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[b]University of Ottawa, School of Epidemiology, Community Medicine and Preventive Medicine, 30 Marie Curie Street, Ottawa, ON, Canada

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**School of Epidemiology, Public Health and Preventive Medicine**

**Faculty of Medicine**

**University of Ottawa**

In chapter 3, we investigated the use of lysine analogues in the oncology population and in chapter 5, we investigated the use of topically applied tranexamic acid. In both cases, lysine analogues were proven to be highly effective at reducing blood loss and associated transfusion requirements. However, the effect of topical lysine analogues during major intraabdominal surgery has not been studied. Furthermore, we cannot establish if lysine analogue administration increases or decreases VTE risk because of low statistical power to assess VTE outcomes. A large clinical trial properly powered to detect a difference in VTE events may present the only opportunity to ease the safety concerns held by some physicians regarding lysine analogues.

In the following chapter, we address the third objective of this thesis, to explore the extent to which lysine analogues are currently used at TOH during high transfusion risk surgery, as well as the reasons why surgeons may not use lysine analogues. We also sought to evaluate surgeon interest in a potential clinical trial. In order to address this objective, we invited surgeons who currently perform procedures considered to be at high-risk for transfusion to complete an online survey exploring their lysine analogue use patterns.

In the ensuing manuscript (Chapter 7), we provide details to the methodological process by which the survey was developed, as well as how to target population of our survey was identified. We discuss the results of the survey and discuss how our findings will direct future research efforts and impact potential clinical trials.

# Chapter 7

## Lysine analogue use during high-risk surgery: a survey from a single institution

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Rodney H Breau[a,c] MD FRCSC

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Associate Scientist, Ottawa Hospital Research Institute

The Ottawa Hospital/University of Ottawa

**Word count: 2760**

**Author Contributions**

Dr. Rodney Breau is the primary thesis supervisor and contributed to the conception and design of the study, as well as the analysis and the drafting of the manuscript. Dr. Brian Hutton (thesis co-supervisor), Dr. Dean Fergusson (TAC member) and Dr. Alan Tinmouth both contributed to the design and analysis of the study, as well as the drafting of the manuscript.

**Additional Information**

Appendices included in the publication are found at the end of the manuscript, while additional appendices not included in the initial publication are found in the appendices section at the end of the thesis (page 109). Institutional ethics approval was obtained before survey dissemination, a copy of which is found in the appendices.

## Abstract

**Background:** Antifibrinolytic haemostatic agents such as lysine analogues have been shown to be incredibly effective at reducing blood loss and associated transfusions relating to surgery. However, they remain underused in various clinical scenarios, potentially due to lingering safety concerns. Our objective was to explore surgeon use of lysine analogues across various specialties at our center, a large tertiary care academic institution.

**Methods:** We administered a survey to surgeons who perform high transfusion risk surgeries at The Ottawa Hospital. Design and distribution of the survey followed a modified Dillman technique. Substantial effort, including design techniques, key informant interviews, cognitive interviews and pilot-testing was put into the survey design to ensure the survey questionnaire was relevant, clear and concise. The final survey consisted of 19 questions divided into three sections; respondent demographics, haemostatic agent use, and potential clinical trial opinions.

**Results:** In total 34 surgeons were invited to participate in the survey, with a total of 29 responses being received (85%). When asked to indicate the frequency of lysine analogue use, “Never” accounted for 43.9% of the responses, while “Rarely (<10%)” accounted for an additional 30.3% of the responses. Reasons for non-use included “unfamiliar with benefits” (n=5), “unfamiliar with side-effects” (n=4), and “prefer alternatives” (n=5). Seventeen surgeons (58.6%) felt a trial was needed to demonstrate the safety of lysine analogues in their respective field.

**Conclusions:** Our survey has identified that lysine analogues are infrequently used at our institution, and the timing of administration often varied. Importantly, many surgeons at our institution are unfamiliar with the benefits and side-effects of lysine analogues, and use topical haemostatic agents far more frequently. Our results demonstrate that future trials exploring the efficacy and safety of lysine analogues in certain populations are needed

## Introduction

Thousands of Canadians undergo major surgical procedures in a hospital setting each year(21). Profuse, unexpected bleeding remains one of the most dangerous complications associated with surgery and often presents challenges to the attending surgeon and surgical team(1,2). Allogenic blood transfusions are often administered in the presence of major bleeding, and although potentially life-saving, they are not without risk. Red blood cell (RBC) transfusions can be associated with an increased risk of infection and immune reactions for recipients and are often a source of morbidity(7,8).

Antifibrinolytic haemostatic agents such as lysine analogues have been shown to be incredibly effective at reducing blood loss and associated transfusions relating to surgery(10,12,27). The use of these agents is at the discretion of the attending surgeon and anesthesiologist. Lysine analogues are commonly seen in cardiac procedures(12,145), and have become increasing popular in orthopedic procedures as well(146,147). Despite proven efficacy, physician uptake of these agents in other potential areas of use remains slow or even non-existent(19,148,149) with questions concerning their safety representing a potential reason for the lack of use (83). The lack of a standard dosing protocol may also contribute to this lag in uptake(28,29). Due to the mechanism of action of lysine analogues, there exists a potential for an increased risk of thrombosis(15). The relationship between lysine analogues and thrombosis has been investigated on multiple occasions, however the exact nature of the relationship remains uncertain(11,27). Until a clinical trial of lysine analogues properly designed and powered to detect differences in thrombotic events is performed, this relationship will likely remain unclear.

Our objective was to explore surgeon use of lysine analogues across various specialties at our institution. To do this, we surveyed surgeons of high transfusion risk procedures at our institution about their transfusion practices, as well as their knowledge and use of lysine analogues. We also sought to measure surgeon interest in a potential clinical trial in high transfusion risk procedures.

## Methods

### *Study Population*

The survey was developed for surgeons who perform high transfusion risk surgeries at The Ottawa Hospital (TOH). The procedures of interest were identified using the National Surgical Quality Improvement Program (NSQIP) database. The NSQIP database contains up to 135 variables on each patient entered into the database, including data on demographics, baseline comorbidities, operative information and 30-day post-operative morbidity and mortality(150). There are currently over 500 hospitals world-wide (though mostly in North America) which presently contribute patient data to this database. The NSQIP database contains a variable for receipt of a blood transfusion defined as "At least 1 unit of packed or whole red blood cells given from the surgical start time up to and including 72 hours postoperatively". Using this variable, we identified the top 15 non-cardiac procedures at highest risk for receipt of a blood transfusion. These procedures were then grouped by specialty; general surgery, vascular surgery, orthopedic surgery, urologic surgery and gynecologic surgery. Orthopedic surgeons were excluded due to the use of lysine analogues already being standard of care at TOH.

### *Survey Design and Distribution*

Contact was made with the head of each of these departments by the corresponding author (RHB) for a complete list of surgeons within this department who may perform the procedures in question. Identified surgeons were invited via e-mail to participate in the online survey using Google Forms (Google, Mountain View, CA, USA). Reminders were sent by e-mail to non-responders at 2-week intervals for 4 weeks using a modified Dillman Technique(151). No financial or other incentives were offered for completion of the survey. Local Research Ethics Board approval was obtained prior to survey dissemination.

The survey was developed by clinicians and researchers with expertise in the field of surgery, anesthesia, blood transfusion, clinical trials, and survey methodology. Substantial effort, including

design techniques, key informant interviews, cognitive interviews and pilot-testing was put into the survey design to ensure the survey questionnaire was relevant, clear and concise. The survey went through multiple rounds of pilot-testing with colleagues and potential responders for comments and feedback. The final survey consisted of 19 questions divided into three sections; respondent demographics, haemostatic agent use, and potential clinical trial opinions (*Appendix 1*).

Demographic questions included surgical procedures performed, years in practice, and geographic location of fellowship training. Participants were asked to indicate how many of the selected procedures they performed personally per year, and how many of those patients require a blood transfusion. Surgeons were asked to indicate how often they administered lysine analogues during their each of their selected surgical procedures, how they use them and which one they use. Surgeons also indicated reasons for not using lysine analogues, as well as other techniques used to limit blood loss. Lastly, surgeons were asked to indicate their thoughts on a potential clinical trial of lysine analogues, including important primary endpoints and acceptable increase in VTE risk. Surgeons were given three choices of primary outcomes of a hypothetical trial of lysine analogues in their respective field and asked to indicate what they believe would be the most clinically relevant outcome by ranking the three outcomes in order of importance

### *Data Analysis*

Survey responses were imported into a Microsoft Excel spreadsheet for analysis (version 15.0, Microsoft Corporation, Seattle, Washington, USA). Data from questions involving categorical outcomes were summarized using proportions. Data from free-text questions were collated.

## Results

### *Demographics*

In total 34 surgeons at TOH were invited to participate in the survey, with a total of 29 responses being received (85%). Ten of 13 invited general surgeons (77%), six of six vascular surgeons (100%), nine of ten

urologic surgeons (90%) and four of five gynecologic surgeons (80%) completed the survey. Characteristics of responding surgeons are summarized in *Table 1*. The experience of survey respondents was evenly distributed among possible responses, with the years since surgical training completion ranging from less than five, to more than 20. Approximately two-thirds of responding surgeons (65.5%) received their surgical training in Canada, with others receiving their training in the United States (27.6%), with one respondent receiving their training in Australia and another in the UK. Only three of 25 responding surgeons did not receive surgical subspecialty training. The surgical volume varied depending on the type of procedure, and is characterized in *Table 2.*

### *Existing Transfusion Rates*

Surgeons were asked to indicate the percentage of their surgical patients who required a peri-operative blood transfusion. Their responses are summarized in *Table 3* and compared to transfusion data from the NSQIP database. Self-reported transfusion rates were low, with the majority of responses corresponding to a transfusion rate of either <10% or 10-19%. Procedures with reported transfusion rates >30% during the peri-operative period included radical cystectomy, aortic aneurysm repair and aorto-bifem bypass.

### *Lysine Analogue Use*

All respondents that reported they used lysine analogues stated that they used tranexamic acid as opposed to aminocaproic acid. When asked to indicate how often they administered lysine analogues during their each of their selected surgical procedures, “Never” accounted for 43.9% of the responses, while “Rarely (>10%)” accounted for an additional 30.3% of the responses. “Sometimes (10-40%)”, “Often (40-75%)” and “Always (>75%)”, accounted for 13.6%, 9.1% and 3.0% of the responses, respectively. Procedures for which lysine analogues were often or always used by at least one surgeon include splenectomy, hepatectomy, large abdominal tumor resection, pancreatectomy, radical

cystectomy, aortic aneurysm repair and aorto-bifem bypass. A detailed breakdown of lysine analogue use by procedure type can be found in *Table 4*.

Surgeons who reported lysine analogue use were then asked to indicate their timing of lysine analogue administration (*Table 3)*. Twelve surgeons (60%) reported using a lysine analogue in a reactionary fashion (intra-operatively, if needed). Eight surgeons (40%) reported using a lysine analogue as a preventive measure, with six surgeons using them as intra-operative prophylaxis, one surgeon using them as post-operative prophylaxis, and one surgeon administering them as pre-operative prophylaxis.

When asked to indicate their reason(s) for non-use, a number of reasons were reported (*Table 5).* The most common responses were "unfamiliar with benefits" (n=5; 25%), "unfamiliar with side-effects" (n=4; 20%), and "prefer alternatives" (n=5; 25%). When asked to identify other techniques which they use to prevent blood loss and transfusion*,* twenty-eight of the responding surgeons (96.6%) reported using topical haemostatic agents as a blood loss and transfusion prevention method *(Table 5)*. Other common blood loss and transfusion prevention techniques included restrictive transfusion triggers (n=7; 24.1%), autologous blood recovery (n=6; 20.7%) and pre-operative iron therapy (n=6, 20.7%).

### *Trial Interest*

Surgeons were asked to indicate whether they felt a clinical trial of lysine analogue use was needed to demonstrate their efficacy and/or safety in their respective fields *(Table 6)*. When an answer of no was given, the surgeon was asked to indicate why. In total, 19 (70.4%) surgeons indicated that they believe a trial is needed to demonstrate the efficacy of lysine analogues in their field. Four surgeons (14.8%) indicated that they do not believe a trial is needed efficacy of lysine analogues in their field; all indicated that they already believe lysine analogues have been proven efficacious. Seventeen surgeons (63.0%) felt a trial was needed to demonstrate the safety of lysine analogues in their respective field. Six

surgeons (22.2%) indicated that they do not believe a trial is necessary to demonstrate they safety of lysine analogues in the respective fields due to the belief that the drug has already been proven safe.

When asked to rank their preferred primary endpoints, 21 (72.4%) surgeons thought the most clinically relevant primary outcome of such a trial would be the proportion of patients transfused, five surgeons (17.2%) indicated that the incidence of thromboembolic events (deep vein thrombosis and pulmonary embolism) would be the most clinically relevant primary endpoint and three surgeons (10.3%) thought that the total number of units transfused would be the most clinically relevant primary endpoint *(Table 6)*.

When asked to indicate the magnitude of reduction in transfusion risk necessary for them to consider incorporating routine lysine analogue use into their practice, and the potential increase in thromboembolic risk that would be tolerable to them given the transfusion and blood loss benefits, the majority of surgeons (69.0%) indicated that a 20% relative risk reduction of transfusion would be enough for them to consider incorporating routine lysine analogue us into their practice. Twenty-six surgeons (89.7%) responded that an increase in the relative risk of thromboembolic events of <20% would be tolerable. A breakdown of all responses is seen in *Table 6.*

## Discussion

Despite improvements in surgical techniques and haemostatic drug development, surgical blood loss and related transfusions remain an important patient safety concern in many surgical procedures(7,8). In our survey, we found that lysine analogue use at our institution appears to be infrequent, and the method of use variable. Survey respondents indicated their frequency of lysine analogue use in their surgical procedures, with lysine analogues never being used in 43.9% of procedures and rarely used in 30.3% of procedures. Only two surgeons reported always using lysine analogues (hepatic surgery and splenectomy). Data surrounding the most effective timing of lysine analogue administration remains

inconsistent. This inconsistency was reflected in our survey, with twelve surgeons administering lysine analogues in as a reactionary measure in the presence of major bleeding, and eight as a prophylactic measure. As part of a larger international survey(152), Canadian Hospitals were surveyed about their practices related to the use of alternatives to allogenic blood transfusions(149). Published in 2000, one finding from this survey was that TXA was rarely used with the exception of in cardiac procedures. Almost two decades later, despite mounting evidence of its efficacy, it remains rarely used at our institution.

There exist randomized trials in many specialties demonstrating the efficacy of lysine analogues(11,97,121), however there is a lack of evidence in others. Among the procedures performed by the surgeons participating in our survey, randomized trial evidence exists in hepatectomy(39), and hysterectomy(153) only. High-quality evidence also exists in cardiac surgery, which some surgeons extrapolate to vascular procedures, as indicated by one survey respondent. A randomized trial of tranexamic acid in cystectomy is currently underway (NCT01869413). Despite the fact that many large systematic reviews including multiple populations exist, the lack of evidence in some specific populations may be a reason for the lag in physician uptake in certain specialties. When asked to indicate reasons for non-use, five surgeons indicated that they were unfamiliar with benefits and four indicated that they were unfamiliar with side-effects, demonstrating that the lack of evidence in their specific specialty may be a concern. In addition, 19 surgeons indicated that they felt a clinical trial was necessary to demonstrate the efficacy of lysine analogues in their respective surgical fields, with 21 surgeons also indicating that the most clinically relevant endpoint of a trial of lysine analogue would be the proportion of patients transfused.

Almost all responding surgeons (n=28) indicated use of topical haemostatic agents such as Surgicel and Gelfoam to prevent blood loss. Many of these agents have become available in recent years, however there exist few high-powered randomized clinical trials demonstrating their efficacy(154), compared to

the many trials of such nature with lysine analogues. Other popular methods for reduction of blood loss identified in our survey include restrictive transfusion triggers, autologous blood recovery and pre-operative iron therapy. All have shown to be effective techniques(155–157), however with some limitations. A systematic review of 75 trials demonstrated a higher risk of infection associated with pre-operative iron therapy(158). With autologous blood recovery, there exists concerns regarding the theoretical possibility of an increased risk of cancer dissemination in oncology patients(159,160). This may present an issue, as many surgical procedures with high levels of associated blood loss and transfusion risk are routinely performed in oncology populations. Routine lysine analogue use may limit the need for some of these techniques, and has the potential to eliminate other potential risks.

The safety concerns surrounding lysine analogues, specifically the potential for an increased thrombosis risk, will likely continue to exist until a clinical trial properly designed and powered to evaluate this relationship is carried out. Many large randomized trials(11) and systematic reviews(27,56) have already failed to definitively classify the nature of this relationship. Surgeons were asked to indicate whether or not they felt as if a clinical trial was needed to demonstrate the safety of lysine analogues in their respective surgical fields, with 17 surgeons indicating that they felt as if a trial of such nature was needed. Five surgeons indicated that they felt the most clinically relevant endpoint of a trial of lysine analogue use would be the incidence of thromboembolic events. The issue with performing such a trial is achieving proper power, as the baseline incidence of thromboembolic events is already very low. To get an idea of the potential sample size for a trial of this nature, surgeons were asked to indicate an increase in VTE risk which would be acceptable to them given the blood loss and transfusion benefits of lysine analogues. Twenty-six surgeons indicated that they would only accept a relative increase in VTE risk of less than 20%, which would represent an absolute increase of less than 1% given a baseline risk ≤5%, making properly powering a trial very difficult. Safety concerns regarding the consequence of VTE remain a barrier for the implementation of routine lysine analogue use.

There are limitations to our study. We did not survey anaesthesiologists, who are often responsible for the decision to order the use of lysine analogues, and therefore we may be underestimating lysine analogue use at our institution. It would be of value to survey this population as well. We identified surgeons in each specialty by contacting the head of the department, making it unlikely we omitted possible respondents. This method coupled with our reasonable response rate (85%), allowed us to make the conclusion that our results can be generalized to the surveyed specialties throughout our institution. However, because of the lack of a standard protocol for lysine analogue use, our results may not be generalizable to other institutions, although a survey of urologic oncologists(19) and hepatic surgeons(161) across Canada suggest similar lysine analogue usage rates. Information of non-responders was not available to assess for potential biases, although the possibility of participation bias may exist as surgeons who chose not to respond may have not been familiar with lysine analogues.

## Conclusions

Our survey has identified that lysine analogues are infrequently used at our institution, and the timing of administration often varied. Importantly, many surgeons at our institution are unfamiliar with the benefits and side-effects of lysine analogues, and use topical haemostatic agents far more frequently. Our results demonstrate that future trials exploring the efficacy and safety of lysine analogues in certain populations are needed.

***Table 1 Demographic characteristics of survey respondents***

| | Surgical Specialty | | | | |
|---|---|---|---|---|---|
| | **General Surgery** | **Vascular** | **Urology** | **Gynecology** | **Total** |
| **Respondents / total invites sent** | 10 / 13 | 6 / 6 | 9 / 10 | 4 / 5 | 29/34 |
| **Specific procedures performed** | Open splenectomy, n=5<br>Hepatectomy, n=3<br>Large abdominal tumor resection, n=5<br>Pancreatectomy, n=4<br>Whipple procedure, n=3<br>Open colectomy, n=10<br>Open rectal resection, n=6 | Aortic aneurysm repair, n=6<br>Aorto-bifem bypass with vein or graft, n=6<br>Axilary-femoral bypass, n=6 | Radical cystectomy, n=3<br>Open nephrectomy, n=8 | Open radical hysterectomy, n=4 | |
| **Years since training completion** | | | | | |
| **<5 years** | 4 (13.8%) | 1 (3.4%) | 3 (10.3%) | 0 | 8 (27.6%) |
| **5-10 years** | 3 (10.3%) | 0 | 2 (6.9%) | 0 | 5 (17.2%) |
| **11-15 years** | 1 (3.4%) | 1 (3.4%) | 2 (6.9%) | 0 | 4 (13.8%) |
| **16-20 years** | 0 | 2 (6.9%) | 0 | 2 (6.9%) | 4 (13.8%) |
| **>20 years** | 2 (6.9%) | 2 (6.9%) | 2 (6.9%) | 2 (6.9%) | 8 (27.6%) |
| **Location of surgical training** | | | | | |
| **Canada** | 4 (13.8%) | 5 (7.2%) | 6 | 4 (13.8%) | 19 (65.5%) |
| **USA** | 4 (13.8%) | 1 (4%) | 3 (10.3%) | 0 | 8 (27.6%) |
| **Other** | 2 (6.9%) | 0 | 0 | 0 | 2 (6.9%) |
| **Subspecialty training** | | | | | |
| **Yes** | 10 (34.5%) | 5 (17.2%) | 8 (27.6%) | 3 (10.3%) | 26 (89.7%) |
| **No** | 0 | 1 (3.4%) | 1 (3.4%) | 1 (3.4%) | 3 (10.3%) |

***Table 2. Surgical volume of survey respondents***

| | Surgeries per year | | | | |
|---|---|---|---|---|---|
| **Procedure** | **<10** | **10-24** | **25-49** | **50-75** | **>75** |
| **Splenectomy** | 5 (83.3%) | 1 (16.7%) | 0 | 0 | 0 |
| **Hepatectomy** | 1 (25.0%) | 2 (50.0%) | 1 (25.0%) | 0 | 0 |
| **Large abdominal tumor resection** | 2 (40.0%) | 3 (60.0%) | 0 | 0 | 0 |
| **Pancreatectomy** | 3 (60.0%) | 2 (40.0%) | 0 | 0 | 0 |
| **Whipple procedure** | 2 (50.0%) | 2 (50.0%) | 0 | 0 | 0 |
| **Open colectomy** | 3 (30.0%) | 2 (20.0%) | 4 (40.0%) | 1 (10.0%) | 0 |
| **Open rectal resection** | 1 (16.7%) | 1 (16.7%) | 4 (66.7%) | 0 | 0 |
| **Radical cystectomy** | 0 | 1 (33.3%) | 0 | 0 | 2 (66.7%) |
| **Open nephrectomy** | 4 (50.0%) | 2 (25.0%) | 1 (12.5%) | 1 (12.5%) | 0 |
| **Aortic aneurysm repair** | 0 | 3 (50.0%) | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) |
| **Aorto-bifem bypass with vein or graft** | 2 (33.3%) | 2 (33.3%) | 1 (16.7%) | 1 (16.7%) | 0 |
| **Axilary-femoral bypass** | 0 | 6 (100%) | 0 | 0 | 0 |
| **Open hysterectomy** | 0 | 0 | 0 | 2 (50.0%) | 2 (50.0%) |
| **Total** | **23 (31.5%)** | **27 (37.0%)** | **12 (16.4%)** | **6 (8.2%)** | **5 (6.8%)** |

***Table 3. Reported peri-operative transfusion rate of survey respondents***

| | Transfusion rate | | | | | NSQIP-reported transfusion rate |
|---|---|---|---|---|---|---|
| **Procedure** | **<10%** | **10-19%** | **20-29%** | **30-50%** | **>50%** | |
| **Splenectomy** | 3 (75.0%) | 1 (25.0%) | 0 | 0 | 0 | 28.92% |
| **Hepatectomy** | 1 (33.3%) | 2 (66.7%) | 0 | 0 | 0 | 17.0% |
| **Large abdominal tumor resection** | 2 (50.0%) | 2 (50.0%) | 0 | 0 | 0 | 25.75% |
| **Pancreatectomy** | 4 (100%) | 0 | 0 | 0 | 0 | 30.26% |
| **Whipple procedure** | 2 (66.7%) | 1 (33.3%) | 0 | 0 | 0 | 18.31% |
| **Open colectomy** | 9 (90.0%) | 1 (10.0%) | 0 | 0 | 0 | 22.6% |
| **Open rectal resection** | 6 (100%) | 0 | 0 | 0 | 0 | N/A |
| **Radical cystectomy** | 0 | 0 | 0 | 3 (100%) | 0 | 40.76% |
| **Open nephrectomy** | 7 (87.5%) | 1 (12.5%) | 0 | 0 | 0 | 27.49% |
| **Aortic aneurysm repair** | 0 | 1 (16.7%) | 1 (16.7%) | 2 (33.3%) | 2 (33.3%) | 40.0% |
| **Aorto-bifem bypass with vein or graft** | 0 | 4 (66.7%) | 1 (16.7%) | 0 | 1 (16.7%) | 28.65% |
| **Axilary-femoral bypass** | 5 (83.3%) | 1 (16.7%) | 0 | 0 | 0 | 26.57% |
| **Open hysterectomy** | 3 (75.0%) | 1 (25.0%) | 0 | 0 | 0 | 28.36% |
| **Total** | **42 (62.3%)** | **15 (22.4%)** | **2 (3.0%)** | **5 (7.5%)** | **3 (4.5%)** | |

***Table 4. Frequency of lysine analogue use by responding surgeons***

| | Frequency of Lysine Analogue Use | | | | |
|---|---|---|---|---|---|
| **Procedure** | **Never** | **Rarely (<10%)** | **Sometimes (10-40%)** | **Often (40-75%)** | **Always (>75%)** |
| **Splenectomy** | 2 (50.0%) | 0 | 1 (25.0%) | 0 | 1 (25.0%) |
| **Hepatectomy** | 0 | 0 | 1 (33.3%) | 1 (33.3%) | 1 (33.3%) |
| **Large abdominal tumor resection** | 1 (25.0%) | 1 (25.0%) | 1 (25.0%) | 1 (25.0%) | 0 |
| **Pancreatectomy** | 0 | 2 (50.0%) | 1 (25.0%) | 1 (25.0%) | 0 |
| **Whipple procedure** | 0 | 2 (66.7%) | 1 (33.3%) | 0 | 0 |
| **Open colectomy** | 7 (77.8%) | 1 (11.1%) | 1 (11.1%) | 0 | 0 |
| **Open rectal resection** | 5 (7.6%) | 1 (1.5%) | 0 | 0 | 0 |
| **Radical cystectomy** | 0 | 0 | 2 (66.7%) | 1 (33.3%) | 0 |
| **Open nephrectomy** | 5 (62.5%) | 2 (25.0%) | 1 (12.5%) | 0 | 0 |
| **Aortic aneurysm repair** | 2 (33.3%) | 3 (50.0%) | 0 | 1 (16.7%) | 0 |
| **Aorto-bifem bypass with vein or graft** | 2 (33.3%) | 3 (50.0%) | 0 | 1 (16.7%) | 0 |
| **Axilary-femoral bypass** | 3 (50.0%) | 3 (50.0%) | 0 | 0 | 0 |
| **Open hysterectomy** | 2 (50.0%) | 2 (50.0%) | 0 | 0 | 0 |
| **Total** | **29 (43.9%)** | **20 (30.3%)** | **9 (13.6%)** | **6 (9.1%)** | **2 (3.0%)** |

***Table 5. Trends in lysine analogue use among survey respondents***

| | Surgical Specialty | | | | |
|---|---|---|---|---|---|
| | **General surgery** | **Urologic surgery** | **Vascular surgery** | **Gynecologic surgery** | **Total** |
| **Timing of lysine analogue administration** | | | | | |
| Intra-operatively if needed | 5 (25.0%) | 4 (20.0%) | 2 (10.0%) | 1 (5.0%) | 12 (60.0%) |
| Intra-operative prophylaxis | 3 (15.0%) | 1 (5.0%) | 1 (5.0%) | 1 (5.0%) | 6 (30.0%) |
| Post-operative prophylaxis | 1 (5.0%) | 0 | 2 (10.0%) | 0 | 1 (5.0%) |
| Pre-operative prophylaxis | 0 | 0 | 1 (5.0%) | 0 | 1 (5.0%) |
| Combination of above 3 | 0 | 0 | 0 | 0 | 0 |
| **Reasons for non-use** | | | | | |
| Unfamiliar with benefits | 2 (10.0%) | 1 (5.0%) | 2 (10.0%) | 0 | 5 (25.0%) |
| Prefer alternative | 1 (5.0%) | 2 (10.0%) | 2 (10.0%) | 0 | 5 (25.0%) |
| Unfamiliar with side-effects | 1 (5.0%) | 0 | 3 (15.0%) | 0 | 4 (20.0%) |
| Safety concerns | 1 (5.0%) | 0 | 1 (5.0%) | 0 | 2 (10.0%) |
| Unfamiliar with method of use | 0 | 0 | 1 (5.0%) | 1 (5.0%) | 2 (10.0%) |
| Cost | 1 (5.0%) | 0 | 1 (5.0%) | 0 | 2 (10.0%) |
| Lack of availability | 0 | 0 | 0 | 0 | 0 |
| **Other blood loss/transfusion prevention techniques used** | | | | | |
| Topical haemostatic agents | 10 (34.5%) | 8 (27.6%) | 6(20.7%) | 4 (13.8%) | 28 (96.6%) |
| Restrictive transfusion triggers | 6 (20.7%) | 0 | 0 | 1 (3.4%) | 7 (24.1%) |
| Autologous blood recovery (Cellsaver) | 0 | 0 | 5 (17.2%) | 1 (3.4%) | 6 (20.7%) |
| Pre-operative iron therapy | 5 (17.2%) | 0 | 0 | 1 (3.4%) | 6 (20.7%) |
| Fibrinogen concentrate | 1 (3.4%) | 0 | 2 (6.9%) | 0 | 3 (10.3%) |
| Acute normovolemic hemodilution | 3 (10.3%) | 0 | 0 | 0 | 3 (10.3%) |
| Other intravenous medications (i.e. Factor VII) | 1 (3.4%) | 0 | 2 (6.9%) | 0 | 3 (10.3%) |
| Autologous blood banking | 1 (3.4%) | 0 | 1 (3.4%) | 0 | 2 (6.9%) |
| Topical lysine analogues | 0 | 0 | 0 | 0 | 0 |

***Table 6. Clinical trial interest among survey respondents***

| | Surgical Specialty | | | | |
|---|---|---|---|---|---|
| | **General surgery** | **Urologic surgery** | **Vascular surgery** | **Gynecologic surgery** | **Total** |
| **Trial need to demonstrate efficacy?** | | | | | |
| Yes | 5 (50.0%) | 7 (100%) | 4 (66.7%) | 3 (75.0%) | 19 (70.4%) |
| No | 3 (30.0%) | 0 | 0 | 1 (25.0%) | 4 (14.8%) |
| Unsure | 2 (20.0%) | 0 | 2 (33.3%) | 0 | 4 (14.8%) |
| **Trial needed to demonstrate safety?** | | | | | |
| Yes | 4 (40.0%) | 6 (85.7%) | 4 (66.7%) | 3 (75.0%) | 17 (63.0%) |
| No | 4 (40.0%) | 1 (14.3%) | 0 | 1 (25.0%) | 6 (22.2%) |
| Unsure | 2 (20.0%) | 0 | 2 (33.3%) | 0 | 4 (14.8%) |
| **Desired primary outcome** | | | | | |
| Proportion of patients transfused | 10 (100%) | 6 (66.7%) | 2 (33.3%) | 3 (75.0%) | 21 (72.4%) |
| Incidence of thromboembolic events | 0 | 2 (22.2%) | 3 (50.0%) | 0 | 5 (17.2%) |
| Total units transfused | 0 | 1 (11.1%) | 1 (16.7%) | 1 (25.0%) | 3 (10.3%) |
| **Desired efficacy (relative transfusion risk reduction)** | | | | | |
| 20% | 8 (80.0%) | 5 (55.5%) | 4 (66.7%) | 3 (75.0%) | 20 (69.0%) |
| 30% | 1 (20.0%) | 2 (22.2%) | 0 | 1 (25.0%) | 4 (13.8%) |
| 40% | 0 | 2 (22.2%) | 0 | 0 | 2 (6.9%) |
| 50% | 1 (20.0%) | 0 | 0 | 0 | 1 (3.4%) |
| >50% | 0 | 0 | 2 (33.3%) | 0 | 2 (6.9%) |
| **Tolerable risk (relative VTE risk increase)** | | | | | |
| >20% | 8 (80.0%) | 8 (88.9%) | 6 (100%) | 4 (100%) | 26 (89.7%) |
| 20% | 2 (20.0%) | 1 (11.1%) | 0 | 0 | 3 (10.3%) |
| 30% | 0 | 0 | 0 | 0 | 0 |
| 40% | 0 | 0 | 0 | 0 | 0 |

# Supplemental Material

## Appendix 1: Final survey administered to surgeons

### Lysine analogue use in surgery

March 8, 2017

Dear Survey Respondent,

You are invited to participate in a short survey on the use of lysine analogues during surgery. Lysine analogues are haemostatic agents shown to be effective at reducing blood loss and transfusions. You were selected as a possible participant in this study because you are a surgeon at The Ottawa Hospital.

The survey is designed to explore current knowledge and use of lysine analogues, as well as potential reasons why you may not use this drug. The survey will take less than 10 minutes to complete and its completion implies your consent. No benefits accrue to you for answering the survey, but your responses will be valuable in assisting with the design of a potential clinical trial.

All information obtained will remain confidential and will not be disclosed accept in the aggregate. If you decide to participate, you are free to discontinue participation at any time without prejudice.

If you have any questions, please ask. If you have additional questions later, contact Joshua Montroy, or Rodney Breau.

Thank you for your time.

Sincerely,

Dr. Rodney Breau

Dr. Dean Fergusson

Joshua Montroy

## Section I Demographics

1. Do you perform any of the following surgeries (check all that apply)?
   - Cystectomy
   - Hepatectomy
   - Vertebral resection
   - Femoral fracture repair
   - Total hip arthroplasty
   - Pancreatectomy
   - Open total rectal resection
   - Aortic aneurysm repair
   - Open radical or debulking hysterectomy
   - Open nephrectomy
   - Open splenectomy
   - Large abdominal tumour resection
   - Open colectomy
   - Whipple procedure
   - Aorto-bifem bypass with vein or graft
   - Axilary-femoral bypass

2. Indicate the number of years since you completed residency and fellowship
   - >5 years
   - 5-10 years
   - 11-15 years
   - 16-20 years
   - >20 years

3. Did you receive fellowship subspecialty training?
   - No
   - Yes

4. Where did you complete your most recent surgical training?
   - Canada
   - USA
   - UK
   - Other, please specify: _____

5. For each surgery, approximately how many of the listed surgeries do you personally perform per year over the last five years?

| | **<10** | **10-24** | **25-49** | **50-75** | **>75** | **Not performed** |
|---|---|---|---|---|---|---|
| **Radical cystectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Hepatectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Vertebral resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Femoral fracture repair** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Total hip arthroplasty** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Pancreas resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open splenectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Open radical or debulking hysterectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open nephrectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Large abdominal tumour resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open total colectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Whipple procedure** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open total rectal resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Aorto-bifem bypass with vein or graft** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Axilary-femoral bypass** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Aortic aneurysm repair** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |

6. Estimate the percentage of your surgical patients (for the listed surgeries) who require a peri-operative blood transfusion.

| | **<10%** | **10-19.9%** | **20-29.9%** | **30-49.9%** | **>50%** |
|---|---|---|---|---|---|
| **Radical cystectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Hepatectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Vertebral resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Femoral fracture repair** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Total hip arthroplasty** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Pancreas resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open splenectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open radical or debulking hysterectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open nephrectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Large abdominal tumour resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open total colectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Whipple procedure** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open total rectal resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Aorto-bifem bypass with vein or graft** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Axilary-femoral bypass** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Aortic aneurysm repair** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |

7. Estimate the percentage of your surgical patients (for the listed surgeries) who require a post-operative blood transfusion (from surgery to 30 days post-operative)

| | **<10%** | **10-19.9%** | **20-29.9%** | **30-49.9%** | **>50%** |
|---|---|---|---|---|---|
| **Radical cystectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Hepatectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Vertebral resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |

| | | | | | |
|---|---|---|---|---|---|
| **Femoral fracture repair** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Total hip arthroplasty** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Pancreas resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open splenectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open radical or debulking hysterectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open nephrectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Large abdominal tumour resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open total colectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Whipple procedure** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open total rectal resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Aorto-bifem bypass with vein or graft** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Axilary-femoral bypass** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Aortic aneurysm repair** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |

## Section II Haemostatic Agent Use

8. Are you aware of the haemostatics agents known as lysine analogues? (e.g. Cyklokapron, Tranexamic acid, Aminocaproic acid, Amicar)
    - Yes
    - No
9. How often do you administer lysine analogues during any of the listed surgeries? (check all that apply)

| | Never | Rarely(<10%) | Sometimes(10% to 40%) | Often(40% to 75%) | Always (>75%) | Never |
|---|---|---|---|---|---|---|
| **Radical cystectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Hepatectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Vertebral resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Femoral fracture repair** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Total hip arthroplasty** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Pancreas resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open splenectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open radical or debulking hysterectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Open nephrectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Large abdominal tumour resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open total colectomy** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Whipple procedure** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Open total rectal resection** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Aorto-bifem bypass with vein or graft** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Axilary-femoral bypass** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |
| **Aortic aneurysm repair** | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ | ⬭ |

10. Which of the following lysine analogues do you administer to patients? (check all that apply)
    - o Tranexamic acid (Cyklokapron®)
    - o Aminocaproic acid (Amicar®)
    - o None

11. How do you typically administer lysine analogues to your patients (check all that apply)?
    - o As pre-operatively prophylaxis
    - o As intra-operatively prophylaxis
    - o As post-operatively prophylaxis
    - o Combination of above 3 techniques
    - o Intra-operatively if needed
    - o Not applicable

12. If you do not administer lysine analogues during the procedures listed above, what are the reasons? (check all that apply):
    - o Not applicable (I do administer lysine analogues)
    - o Unfamiliar with benefits
    - o Unfamiliar with side effects
    - o Lack of availability
    - o Unfamiliar with method of use
    - o Cost
    - o Safety concerns
    - o Prefer alternatives to prevent blood loss

13. What other techniques do you use to limit surgical blood loss or transfusion in your patients?
    - Topical haemostatic agents (e.g. Surgicel, Gelfoam, Tisseal, Floseal)
    - Autologous blood recovery (Cellsaver®)
    - Autologous blood banking
    - Acute normovolemic hemodilution
    - Pre-operative iron therapy
    - Other intravenous medications (i.e. Factor VII)
    - Restrictive transfusion triggers (intra and post-op)
    - Not applicable

**Section III Potential Clinical Trial**

14. Do you feel as if a trial is needed to demonstrate the efficacy of lysine analogues? If not, why?
    - Yes
    - No:_____

15. Do you feel as if a trial is needed to demonstrate the safety of lysine analogues? If not, why?
    - Yes
    - No:_____

16. Consider a randomized controlled trial of lysine analogue administration to minimize blood loss and transfusion. For which procedure(s) would you be willing to enrol patients?
    - I am not interested in a trial of this nature
    - I would be willing to enroll all patients in a trial
    - Cystectomy
    - Hepatectomy
    - Vertebral resection
    - Femoral fracture repair
    - Total hip arthroplasty
    - Pancreatectomy
    - Open total rectal resection
    - Aortic aneurysm repair
    - Open radical or debulking hysterectomy
    - Open nephrectomy
    - Open splenectomy
    - Large abdominal tumour resection
    - Open colectomy
    - Whipple procedure
    - Aorto-bifem bypass with vein or graft
    - Axilary-femoral bypass

17. Consider a randomized controlled trial of lysine analogue administration in the above listed surgeries. Can you indicate what you would consider to be the most clinically

relevant primary endpoint by ranking these endpoints (1 being most important, 3 being least important):

- Proportion of patients transfused:_____
- Total units transfused:_____
- Incidence of thromboembolic events (DVT & PE):_____

18. To consider incorporating lysine analogues into routine practice, they would need to reduce the relative risk of transfusion risk what percent?
    - 20% (e.g. 30% risk to 26% risk)
    - 30% (e.g. 30% risk to 21% risk)
    - 40% (e.g. 30% risk to 18% risk)
    - 50% (e.g. 30% risk to 15% risk)
    - >50%

19. If lysine analogues were to reduce the red blood cell transfusion rate by 33% (for example from 30% down to 20%), what relative increase in risk of thromboembolic events (confirmed DVT & PE) would be acceptable?
    - < 20% (e.g. 5% risk to <6% risk)
    - 20% (e.g. 5% risk to 6% risk)
    - 30% (e.g. 5% risk to 6.5% risk)
    - 40% (e.g. 5% risk to 7% risk)

# Chapter 8

# Discussion

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## 8.1 Summary of Findings

This thesis had three specific objectives. The first objective was to evaluate the existing literature studying the use of lysine analogues in the oncology population. In order to achieve this objective, we performed, to our knowledge, the first systematic review and meta-analysis evaluating the safety and efficacy of lysine analogues in this population. The second objective was to evaluate the existing literature on the use of topically administered lysine analogues. To address this objective, we again performed a systematic review and meta-analysis of available data. The final objective of this thesis was to investigate the extent of lysine analogue use at our institution, and to determine reasons for non-use as well as surgeon interest in a clinical trial of lysine analogue administration. An online survey of surgeons performing procedures at a high risk of transfusion at our institution was carried out in order to fulfill this objective. The following discussion will highlight the novel findings of our research, as well as potential limitations to our methodology. We will also discuss how these results will impact future research in the field.

Throughout this thesis, we have emphasized the concerns surrounding the relationship between lysine analogue administration and risk of VTE, as well as the potential reasons for these concerns. High-quality randomized controlled trials designed and powered to detect differences in VTE risk are difficult to carry out due to the baseline risk of developing a VTE being low. Due to the severity of these complications(162), a very slight increase in risk is often considered clinically meaningful, adding to the difficulties of properly powering a trial. With those factors in mind, if clinicians and researchers properly power a trial of lysine analogues to detect a difference in the risk of VTE, the trial will need to be very large and inclusive. Some surgeons may have reservations about entering a trial of such nature, due to existing safety concerns, exemplified by one survey respondent who replied “not sure due to the effect on thrombotic complications post op. acute DVT, arterial thrombosis, MI etc” when asked to indicate if

he felt a trial of lysine analogues was needed to demonstrate efficacy in his surgical field. It is concerns of this nature which we have aimed to minimize by addressing the first two objectives of this thesis.

### 8.1.1 Lysine Analogues in Cancer Patients

Chapter 3 investigated the use of lysine analogues in the oncology community and evaluated their safety and efficacy in this population. Chapter 2 detailed the increased risks which are present in the oncology population with regards to VTE. Should oncology patients be excluded from a clinical trial of lysine analogues attempting to demonstrate safety, properly powering such a trial would become even more challenging. Our review indicated that the safety of lysine analogues has not been extensively studied in cancer patients, with only 11 studies being identified. This is a notable finding given the high prevalence of VTE in cancer patients and the increased interest in these drugs for cancer patients who are undergoing major surgical procedures(55).

The administration of a lysine analogue significantly decreased both transfusion risk (pooled RR 0.52, 95% CI 0.34-0.80) and blood loss (SMD -1.57, 95% CI -2.21 to -0.92), which represents similar efficacy to that seen in other non-cancer populations. A similar safety profile to that in non-cancer patients was also observed, with no increased risk of VTE being observed for patients who received lysine analogues compared to control (Peto OR 0.60; 95% CI 0.28-1.30). However the potential for an increase in risk could not be ruled out due to the imprecision of the effect estimate and the width of the confidence intervals. The fact that no increase in VTE risk was observed may be enough to ease the concerns of some physicians, however some may remain skeptical due to our inability to rule out the possibility of an increase in risk. The same issue encountered in massive studies such as the CRASH-2 trial(11), and a 10,000 patient meta-analysis(27) has hindered our ability to make a definitive conclusion regarding the relationship between lysine analogues and VTE risk in cancer patients.

### 8.1.2 Topical Lysine Analogues

Given our findings from chapter 3, in which we could not definitively establish the relationship between lysine analogues and VTE risk in cancer patients (even though no increased risk was observed), we felt the need to explore an alternative method of use in an attempt to ease possible safety concerns held by some surgeons. Chapter 2 provided background knowledge concerning the topical application of lysine analogues. If the topical application of these agents is proven to be effective, coupled with the reported decrease in systemic absorption compared to intravenous administration(50,51), perhaps more surgeons will feel comfortable administering lysine analogues in this manner.

The administration of topical TXA significantly reduced the odds of receiving a blood transfusion (pooled OR 0.28, 95% CI 0.20 to 0.38; P < 0.001) and significantly reduced mean blood loss (WMD -276.6, 95% CI -327.8 to -225.4; P < 0.0001). These results suggest that the topical application of tranexamic acid may be at least as effective as intravenous administration. Indeed, randomized trials of topical versus intravenous TXA has been examined in orthopedic surgeries such as knee and hip replacements(141–143) and no differences in efficacy or safety outcomes between administration routes were observed. The topical application of TXA has been mainly studied in orthopedic procedures compared to other specialties. This is notable, because the medication can be given within a contained joint cavity, as opposed to open abdominal surgery. In our subgroup analyses by surgical specialty, there was a significant reduction in transfusion risk for orthopedic procedures, however there was no significant difference in transfusion risk for cardiac procedures, orthognathic procedures, spinal procedures, or thoracic procedures. No studies have been conducted in major intraabdominal procedures. Applying TXA topically may present challenges outside the realm of orthopedics due to questions surrounding the optimal dosing strategy, as well as the optimal timing of administration.

There was no difference in the odds of developing a venous thromboembolic complication between the topical TXA and control groups (pooled OR=0.78, 95% CI 0.47 to 1.29; P=0.33). These findings are consistent with trials of intravenously administered TXA, which also do not suggest an increased risk of

thromboembolic events (10,12,27,56). However, once again, it is worth noting the confidence interval remains wide for safety estimates and the possibility of an increase in risk cannot be definitively ruled out. This finding serves to strengthen the argument that a trial properly powered to detect differences in safety endpoints, specifically VTE, are needed to allay safety concerns. The comparison of topical and intravenous administration of lysine analogues warrants future investigation, as there may be potential maintain benefits while reducing potential harms.

### 8.1.3 Safety of Lysine Analogues

The safety concerns associated with lysine analogues are thoroughly outlined in chapter 2 and throughout the thesis. In cancer patients, no increased risk of VTE being observed for patients who received lysine analogues compared to control (Peto OR 0.60; 95% CI 0.28-1.30), and a similar odds ratio was observed for patients who received topical TXA compared to placebo (pooled OR=0.78, 95% CI 0.47 to 1.29). The safety results seen in our reviews from chapters 3 and 5 are in agreement with other estimates in current literature, suggesting no increased risk in VTE associated with lysine analogue use. However, confidence intervals remain wide and the potential for a slight increase in risk cannot be definitively ruled out. However, our effect estimates, along with many others in the literature(24,27), are in fact below one and are trending towards favouring the lysine analogue group. There is evidence to suggest that the receipt of a transfusion may be associated with an increased risk of thrombosis(163–165). If this is the case, then it is conceivable that by reducing the rate of transfusion with lysine analogues, we may also lowering the risk of thrombosis. This reduction in thrombotic risk may offset any potential increase in risk introduced by the mechanism of lysine analogues. Better yet, if there is in fact no increase in thrombotic risks associated with lysine analogues, then the administration may reduce not only blood loss and transfusion requirements, but thrombotic risk as well. The relationship between transfusions and thrombotic risks warrants further investigation.

Another safety issue concerning lysine analogues is fact that the optimal dosing strategy (either topical or intravenous) has yet to be established. This is important, considering that there exists some evidence that a higher dose of TXA is associated with an increased seizure risk(31–33). In both of our reviews, the dosing strategy varied considerably across studies. In our review of lysine analogues in cancer patients, the dosage was weight adjusted in six studies with dose ranging from 10-20mg/kg for TXA and 100-150 mg/kg for EACA(35–37,69,71,72), and the dosage was not weight adjusted in four studies, with dosage varying from 500-2000mg of TXA(39,40,70,74). In our review of topical TXA, the dosage varied from 1 mg/mL to 100 mg/mL. A notable finding from our review of topical TXA came from our meta-regression analysis, where the relationship between topical TXA administration and transfusion risk reduction did not appear to be dose-dependent, suggesting topical TXA remains effective at small doses. Intravenously administered TXA has also been shown to be effective at low doses(166,167).

The optimal timing of administration of lysine analogues has also yet to be definitively established. Variability existing in our review of lysine analogues in cancer patients, with some studies administering the drug pre-operatively, and others intra-operatively or post-operatively. This variable was also seen in our review of topical TXA, and was reflected in our survey of physicians. Approximately 40% of surgeons administered lysine analogues intra-operatively only if needed, while 20% administered them as an intra-operative prophylactic measure. One surgeon (3.4%) administered lysine analogues as post-operative prophylaxis, and another administered them as pre-operative prophylaxis. We did not collect information on administered dose in our survey of surgeons, however we did collect information regarding the timing of administration, with variability being observed. Determining the optimal dosing strategy, as well as the optimal timing of administration of lysine analogues is crucial in order to plan a future clinical trial.

Another issue surrounding lysine analogues during surgery, is how to effectively concomitantly administer VTE prophylaxis medications. Often, DVT prophylaxis is given peri-operatively to surgical

patients via anti-coagulants such as low molecular weight heparin in order to prevent VTE. Use of lysine analogues and anti-coagulants may seem counterintuitive. In our first review of lysine analogues in cancer patients, only two studies (18%) detailed their use of DVT prophylaxis within their trial methodology. In our review of topical TXA, 14 trials (26%) detailed their use of DVT prophylaxis. To our knowledge, there is no existing literature detailing the effects of administering both of these agents simultaneously. This could provide an opportunity for future research.

### 8.1.4 Lysine Analogue use at TOH

With the mounting evidence of the efficacy of lysine analogues, and the evidence presented in chapters 3 and 5, coupled with the inability to definitely classify the relationship between their use and VTE risk, it is becoming clear that a trial powered to detect differences in VTE and other safety endpoints is warranted. In chapter 7 we investigated the use of lysine analogues at our institution, as well as trial interest, by surveying surgeons at our institution. When asked to indicate their lysine analogue use for each of their surgical procedures performed, “Never” accounted for 44% of the responses, while “Rarely (>10%)” accounted for an additional 30% of the responses. As part of a larger international survey(152), Canadian Hospitals were surveyed about their practices related to the use of alternatives to allogenic blood transfusions(149). Published in 2000, one finding from this survey was that TXA was rarely used with the exception of in cardiac procedures. Almost two decades later, despite mounting evidence of its efficacy, it remains rarely used at our institution. Our survey results also highlight the need for a standard dosing/administration protocol, as mentioned above, as the timing of administration of lysine analogues varied at our institution. Twelve surgeons administered lysine analogues in a reactionary fashion, and eight administered as a prophylactic measure.

Most surgeons who responded to our survey felt as if a trial of lysine analogues was needed to demonstrate efficacy (66%) or safety (59%) in their respective surgical field. Surgeons were asked to

indicate the increase in thromboembolic risk that would be tolerable to them given the transfusion and blood loss benefits. The reasoning behind this question was to obtain a minimal clinically important difference value to perform a sample size calculation in order to get an idea of the required sample size. Twenty-six of 29 surgeons (90%) responded that an increase in the relative risk of thromboembolic events of <20% would be tolerable, which corresponded to the lowest risk increase we provided in the question. This would represent an absolute increase of less than 1% given a baseline risk ≤5%. If we assume a 5% baseline risk, a 20% relative increase in risk would correspond to a 6% risk, which would require over 8,000 patients per arm with 80% power and alpha of 0.05. A trial is unlikely to be powered to detect such a small difference in risk. However, it is clear from our survey that surgeon interest in a trial exists, and perhaps a trial can be powered to detect a slightly higher increase in risk (i.e. 30% relative increase).

### 8.2 Future Directions

It has become increasingly evident that a large, pragmatic clinical trial of lysine analogue administration designed and powered to detect differences in safety endpoints would be needed to definitively establish the effect on VTE and to change physician behaviour. Research into the optimal dose and administration is also needed. As mentioned above, lysine analogues appear to be used infrequently at our institution. Considering the sizeable amount of existing evidence demonstrating benefit, it is possible that this represents a knowledge translation problem. Addressing the barriers to lysine analogue use may improve clinical practice and certainly would make accrual to clinical trials easier.

The theoretical domain framework (TDF) is a systematic and theoretically based approach to behaviour change that is used to detect key barriers to changing practice and to devise practical interventions to counter them(168). This framework consists of 14 domains including knowledge, skills, and beliefs about consequences. All domains can be found below in *Table 1*. Important domains within the TDF are often identified in various clinical settings through in-person interviews with medical professionals(169–171).

From our survey results, we can speculate as to some important domains within this framework that are barriers to lysine analogue use at our institution. Five surgeons (17.2%) indicated that they do not administer lysine analogues due to their unfamiliarity with the benefits of the drug, four (13.8%) indicated that they were unfamiliar with side-effects of the drug, and two (6.9%) indicated that they are unfamiliar with the method of use. These results could suggest that knowledge may be a barrier to implementation. Five surgeons (17.2%) also indicated that they prefer alternatives, meaning behavioural regulation may also be a potential barrier. It is possible that surgeons simply do not want to change what they are currently doing. Two surgeons (6.9%) indicated that they did not use lysine analogue due to safety concerns, suggesting that beliefs about consequences may be another potential barrier to implementation. In summary, potential barriers to lysine analogue use at our institution include of knowledge of the drug, beliefs about consequences of use, and behavioural regulation of surgeons.

***Table 1. The domains of the Theoretical Domains Framework (TDF)***

| Theoretical Domain | Definition |
|---|---|
| Knowledge | An awareness of the existence of something |
| Skills | An ability or proficiency acquired through practice |
| Professional role and identity | A coherent set of behaviors and displayed personal qualities of an individual in a social or work setting |
| Beliefs about capabilities | Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use |
| Optimism | The confidence that things will happen for the best, or that desired goals will be attained |
| Beliefs about consequences | Acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation |
| Reinforcement | Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus |
| Intentions | A conscious decision to perform a behavior or a resolve to act in a certain way |
| Goals | Mental representation of outcomes or end states that an individual wants to achieve |
| Memory, attention and decision processes | The ability to retain information, focus selectively on aspects of the environment, and choose between two or more alternatives |
| Environmental context and resources | Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behavior |

| | |
|---|---|
| Social Influences | Those interpersonal processes that can cause an individual to change their thoughts, feelings, or behaviors |
| Emotion | A complex reaction pattern, involving experiential, behavioral, and physiological elements, by which the individual attempts to deal with a personally significant matter or event |
| Behavioural Regulation | Anything aimed at managing or changing objectively observed or measured actions |

As discussed below in the limitations section, we did not survey anaesthesiologists at our institution about their lysine analogue use patterns. Considering they are a key part of the surgical team, it would be of interest to administer a survey to this population, similar to the one we administered to surgeons. This project is currently underway, and comparing their use of lysine analogues and their thoughts on a trial to those of the surgeons is of great interest. With responses and opinions from both surgeons and anaesthesiologists, we will have a more complete picture of the current practice patterns at our institution and will have better insight into the feasibility of designing a trial of lysine analogues powered to detect differences in safety outcomes.

### 8.3 Limitations

The research presented throughout this thesis contains some important limitations. The limitations are discussed in detail in the manuscripts presented in chapters 3, 5, and 7, and will also be briefly summarized here. In the systematic reviews presented in chapters 3 and 5, we were limited by the quality of included studies, many of which were found to be at an unclear risk of bias as they did not report some methodological details of their trial. In both reviews, slight asymmetry seen in the funnel plots of both transfusion risk and blood loss outcomes, suggesting the possibility of a small degree of publication bias. In addition, substantial statistical heterogeneity was seen for the outcomes of transfusion risk and blood loss in both reviews. Blood loss can be a difficult outcome to accurately and consistently measure. Transfusion triggers also vary across healthcare systems and across surgical specialties. This leads to clinical heterogeneity and is a potential explanation for the statistical

heterogeneity. It is important to state that the variation seen in these outcomes was in the magnitude of effect, and not the direction. Finally, the potential under-reporting of adverse events in clinical trials is a noteworthy issue (79-81). Nine of eleven studies included in the review from chapter 3 reported on the incidence of VTE events in their trial, with only four of those studies detailing VTE surveillance methods. Only 30 of 53 studies included in the review from chapter 5 reported the incidence of VTE events. Selective reporting of outcomes may be an issue with lysine analogue trials and warrants investigation.

With regard to the survey detailed in chapter 7, the major limitation concerns the sample population. We surveyed surgeons only, and did not survey anaesthesiologists. Anaesthesiologists are often responsible for the decision to order lysine analogues as part of the surgical process, and we may be missing key information regarding lysine analogue use at our institution by omitting them from the survey. Information of non-responders was not available to assess for potential biases, although the possibility of participation bias may exist as surgeons who chose not to respond may have not been familiar with lysine analogues.

### 8.4 Conclusions

Lysine analogues are highly effective haemostatic agents used for the reduction of blood loss and transfusion requirements. However, they remain underused in certain clinical settings where they could be of great benefit, primarily due to safety concerns. Our survey has identified that lysine analogues are infrequently used at our institution during cancer surgery, and the timing of administration often varied. Many surgeons at our institution are unfamiliar with the benefits or side-effects of lysine analogues, and use other topical haemostatic agents far more frequently, many of which may be less effective than lysine analogues according to the literature. Legitimate concerns exist regarding lysine analogue use in cancer patients, and chapter 3 demonstrated that these agents have similar safety and efficacy profiles in this population as seen in non-cancer populations. If surgeons feel more comfortable administering these agents topically as opposed to intravenously, chapter 5 demonstrated that there have been no

studies of the approach, so the benefits and harms are not established. Safety concerns still exist concerning VTE risk due to imprecise effect estimates and under powering of trials for this outcome. Evidence from trials designed and powered to detect differences in safety outcomes are needed before definitive conclusions can be drawn. The feasibility of such a trial at our institution was explored by our survey, with many surgeons expressing interest in a trial of this nature.

# Appendices

## Appendix 1: PRISMA Checklist

**1a)** PRISMA checklist, Chapter 3 review

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 11 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 13 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 14 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 15 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 15 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 16 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 16 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 16 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 16 |

| | | | |
|---|---|---|---|
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 17 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 17 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 17 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 17 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 17 |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 17 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 17 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 18 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 18 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 19 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 20/21 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 20/21 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 20/21 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 20 |

| | | | |
|---|---|---|---|
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 21 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 23 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 24 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 25 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

**1b)** PRISMA checklist, Chapter 4 review

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 38 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 40 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 41 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 42 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 42 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 42 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 43 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 43 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 43 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 43 |

| | | | |
|---|---|---|---|
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 43 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 43 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 44 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 44 |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 44 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 44 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 45 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 45 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 46 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 46-48 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 46-48 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 49 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 46-48 |
| **DISCUSSION** | | | |

| | | | |
|---|---|---|---|
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 49 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 50 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 51 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 51 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

## Appendix 2: REB Survey Approval

Ottawa Hospital Research Institute / Institut de recherche de l'Hôpital d'Ottawa

uOttawa

University of Ottawa Heart Institute / Institut de cardiologie de l'Université d'Ottawa

***Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa***

March 28, 2017

Dr. Rodney Breau
Ottawa Hospital - General Campus
Department of Surgery
Division of Urology

Dear Dr. Breau:

| | |
|---|---|
| **Re: Protocol #** | **Knowledge and usage of lysine analogues in the high risk surgical population** |
| **Protocol approval valid until -** | **March 27, 2018** |

Thank you for your e-mail of March 22, 2017. I am pleased to inform you that this protocol underwent delegated review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made to the protocol or the consent form without the OHSN-REB's review and approval.

Approval is for the following:
-Electronic OHSN-REB Application
-Protocol (Version 2) dated March 20, 2017
-Case Record From /Appendix A (Version 2) dated March 20, 2017 (Lysine Analogue use in Surgery Letter to Survery respondent and Survey)

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHSN-REB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

Jim Robblee, M.D.
Vice-Chairperson
Ottawa Health Science Network Research Ethics Board
JR/jl

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