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Topical application of tranexamic acid for the reduction of bleeding (Review)

Ker K, Beecher D, Roberts I

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[Intervention Review]

Topical application of tranexamic acid for the reduction of bleeding

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ABSTRACT

Background

Intravenous tranexamic acid reduces bleeding in surgery, however, its effect on the risk of thromboembolic events is uncertain and an increased risk remains a theoretical concern. Because there is less systemic absorption following topical administration, the direct application of tranexamic acid to the bleeding surface has the potential to reduce bleeding with minimal systemic effects.

Objectives

To assess the effects of the topical administration of tranexamic acid in the control of bleeding.

Search methods

We searched the Cochrane Injuries Group Specialised Register; Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library;* Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid OLDMEDLINE®; Embase Classic + Embase (OvidSP); PubMed and ISI Web of Science (including Science Citation Index Expanded and Social Science Citation Index (SCI-EXPANDED & CPCI-S)). We also searched online trials registers to identify ongoing or unpublished trials. The search was run on the 31st May 2013.

Selection criteria

Randomised controlled trials comparing topical tranexamic acid with no topical tranexamic acid or placebo in bleeding patients.

Data collection and analysis

Two authors examined the titles and abstracts of citations from the electronic databases for eligibility. Two authors extracted the data and assessed the risk of bias for each trial. Outcome measures of interest were blood loss, mortality, thromboembolic events (myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism) and receipt of a blood transfusion.

Main results

We included 29 trials involving 2612 participants. Twenty-eight trials involved patients undergoing surgery and one trial involved patients with epistaxis (nosebleed). Tranexamic acid (TXA) reduced blood loss by 29% (pooled ratio 0.71, 95% confidence interval (CI) 0.69 to 0.72; P < 0.0001). There was uncertainty regarding the effect on death (risk ratio (RR) 0.28, 95% CI 0.06 to 1.34; P = 0.11), myocardial infarction (RR 0.33, 95% CI 0.04 to 3.08; P = 0.33), stroke (RR 0.33, 95% CI 0.01 to 7.96; P = 0.49), deep vein

thrombosis (RR 0.69, 95% CI 0.31 to 1.57; P = 0.38) and pulmonary embolism (RR 0.52, 95% CI 0.09 to 3.15; P = 0.48). TXA reduced the risk of receiving a blood transfusion by a relative 45% (RR 0.55, 95% CI 0.55 to 0.46; P < 0.0001). There was substantial statistical heterogeneity between trials for the blood loss and blood transfusion outcomes.

Authors' conclusions

There is reliable evidence that topical application of tranexamic acid reduces bleeding and blood transfusion in surgical patients, however the effect on the risk of thromboembolic events is uncertain. The effects of topical tranexamic acid in patients with bleeding from non-surgical causes has yet to be reliably assessed. Further high-quality trials are warranted to resolve these uncertainties before topical tranexamic acid can be recommended for routine use.

PLAIN LANGUAGE SUMMARY

Topical treatment with a blood-clot promoting drug to reduce bleeding

Hundreds of thousands of people worldwide suffer ill health caused by severe bleeding. Tranexamic acid is a drug that helps blood to clot and so it could help people who are bleeding. We already know that giving tranexamic acid intravenously (directly into the vein) reduces bleeding in accident victims and in patients having operations. But some doctors don't always give it this way because they are worried that it might have bad side effects in certain patients, such as causing blood clots where they are not wanted. An alternative way to give this drug is to mix it with sterile water and apply it directly to the bleeding surface (this is known as 'topical' application). Because less of the drug might be absorbed into the body when it is given this way, it could be less likely to have bad side effects.

This review looked at trials assessing the effects of topical tranexamic acid in patients who are bleeding. Twenty-nine trials were found; 28 involved patients bleeding during operations and one involved people with nosebleeds. When the results of these trials were gathered together they showed that when tranexamic acid was given topically, it reduced the amount of blood that patients lost and made it less likely that they had a blood transfusion.

The authors of this review concluded that topical tranexamic acid reduces bleeding in patients who are having an operation. But because there are no trials, we are not sure if it also reduces bleeding from other causes, such as childbirth or bleeding from stomach ulcers.

BACKGROUND

Intravenous administration of tranexamic acid reduces bleeding during surgery. A systematic review of 129 randomised controlled trials, including 10,488 surgical patients, showed that tranexamic acid reduced the probability of receiving a blood transfusion by about one third (risk ratio 0.62, 95% confidence interval 0.58 to 0.65; P < 0.001), an effect that remained large when the analysis was restricted to high-quality trials (Ker 2012). However, the effect of tranexamic acid on the risk of thromboembolic events was less certain. This was largely because many trials did not report data on myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism, raising the possibility of bias from the selective reporting of outcomes. Although there is no evidence that tranexamic acid increases the risk of thromboembolic events, it remains a theoretical concern that may dissuade some clinicians from using this treatment in their clinical practice.

Concerns about thromboembolic events have stimulated increasing interest in the topical use of tranexamic acid. Studies suggest that plasma concentrations following the topical application of tranexamic acid are less than one tenth of the level after intravenous administration (Almer 1992; McCormack 2012; Sindet-Pedersen 1987; Wong 2010). Because there is less systemic absorption, the direct application of tranexamic acid to the bleeding surface has the potential to reduce bleeding with minimal systemic effects.

Description of the condition

There are many clinical scenarios in which topical administration of tranexamic acid to the bleeding surface might be possible. These include epistaxis, traumatic hyphema, gastrointestinal bleeding, surgical bleeding and uterine bleeding. All of these conditions are common and several of them are life threatening. If the topical application of tranexamic acid could safely reduce bleeding in these conditions, this would be of substantial clinical importance.

Description of the intervention

Tranexamic acid is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by blocking the lysine binding site on plasminogen (McCormack 2012). It is a competitive inhibitor of the activation of plasminogen to plasmin and at higher concentrations a non-competitive inhibitor of plasmin.

How the intervention might work

Topical application of tranexamic acid has the potential to inhibit local fibrinolysis at the site of bleeding but with minimal systemic absorption. In this way, it could reduce bleeding and the need for blood transfusion without systemic side effects such as thromboembolic events.

Why it is important to do this review

Acute severe haemorrhage is an important cause of mortality and morbidity worldwide. Hundreds of thousands of people die as a consequence of acute gastrointestinal and obstetric bleeding every year (AbouZahr 2003; van der Werf 2003; van Leerdam 2008). Furthermore, an estimated 234 million people undergo major surgery, one million of whom die and millions more suffer complications (Weiser 2008) including those caused by blood loss. If topical administration of tranexamic acid was shown to be a safe and effective way to reduce acute severe haemorrhage this would be of importance to global health. Reducing bleeding would also reduce the morbidity associated with anaemia and would reduce the need for blood transfusion (Shander 2011). Blood is a scarce resource and transfusion is not without risk (Goodnough 2008). A cost-effective strategy to reduce the need for transfusion with few or no side effects would be a major medical advance. This review aimed to quantify the effectiveness and safety of the topical administration of tranexamic acid in reducing bleeding from a variety of causes.

OBJECTIVES

To assess the effects of the topical administration of tranexamic acid in the control of bleeding.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

People of all ages with bleeding of any severity.

Types of interventions

Topical administration of tranexamic acid versus no tranexamic acid or placebo.

Types of outcome measures

Primary outcomes

- Blood loss (millilitres (ml); mean ± standard deviation)
- Death (n or N)

Secondary outcomes

- Myocardial infarction (n or N)
- Stroke (n or N)
- Deep vein thrombosis (n or N)
- Pulmonary embolism (n or N)
- Receipt of blood transfusion (n or N)

As assessed at the end of the follow-up period scheduled for each trial.
We did not exclude trials based on the outcomes above.

Search methods for identification of studies

We did not restrict the searches by language or publication status.

Electronic searches

One author (DB) searched the following electronic databases:
1. Cochrane Injuries Group Specialised Register (31 May 2013);
2. Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*) (2013, Issue 5 of 12);
3. Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid OLDMEDLINE® (1946 to May 2013);
4. Embase Classic + Embase (OvidSP) (1947 to 31 May 2013);
5. ISI Web of Science: Science Citation Index Expanded (1970 to May 2013);
6. ISI Web of Science: Conference Proceedings Citation Index-Science (1990 to May 2013).

The search strategies are reported in Appendix 1.

Searching other resources

We searched the following online trials registers on 31 May 2013 for published and unpublished studies:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- Current controlled trials (www.controlled-trials.com).

We screened reference lists of the eligible trials and any review articles for further potentially eligible studies. We searched the internet using the Google search engine (www.google.com) with selected terms from the above strategy for any further unpublished or grey literature.

Data collection and analysis

Selection of studies

Two review authors (KK and IR) examined the titles and abstracts of the citations from the electronic databases for eligibility. We resolved disagreements through discussion. We obtained the full text of all potentially eligible records and two review authors (KK and IR) assessed whether each met the predefined inclusion criteria.

Data extraction and management

Two review authors (DB and KK) extracted data on the number of trial participants, type of bleeding, dose and timing of tranexamic acid, type of comparator and outcome data using an extraction form developed and piloted specifically for this review.

Assessment of risk of bias in included studies

Two review authors (DB and KK) assessed the risk of bias in the included trials using The Cochrane Collaboration's 'Risk of bias' tool as described in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The following domains were assessed for each trial: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. We completed a 'Risk of bias' table, incorporating a description of the trial against each of the domains and a judgement of the risk of bias, as follows: 'low risk', 'high risk' or 'unclear risk' of bias.

Measures of treatment effect

For the primary outcome 'blood loss', we estimated the difference in mean blood loss between the topical tranexamic acid and no tranexamic acid groups. We also estimated the proportional change in blood loss with topical tranexamic acid. Specifically, we expressed the change in blood loss with topical tranexamic acid as a proportion of the blood loss in the control group. For the purpose of the meta-analysis, we transformed the blood loss data into the logarithmic scale and conducted the analysis using the transformed values. A meta-analysis of the differences in means using the transformed data on blood loss corresponds to a meta-analysis of the ratio of the geometric means on the original scale. The pooled estimates were back-transformed to give the blood loss ratios and 95% confidence intervals on the original scale.
For the dichotomous secondary outcomes, we calculated risk ratios and 95% confidence intervals for each trial.

Dealing with missing data

We analysed trial results on an intention-to-treat basis where the necessary data were available. We contacted the original trial investigators to obtain missing data. For trials for which we could not obtain missing data, we used the data available from the trial report and conducted an available-case analysis (Higgins 2011b).

Assessment of heterogeneity

We examined the trial characteristics in terms of participants, interventions and outcomes for clinical heterogeneity. We examined statistical heterogeneity by visual inspection of forest plots, and by the I^2 statistic and the Chi^2 test. The I^2 statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity; substantial heterogeneity is considered to exist when I^2 is greater than 50% (Deeks 2011). For the Chi^2 test, we used a P value of less than 0.10 to indicate the presence of statistically significant heterogeneity.

Assessment of reporting biases

We investigated the presence of reporting (publication) bias using funnel plots for outcomes for which there were 10 or more trials included in the analysis.

Data synthesis

The effect estimates were combined using the fixed-effect model (also known as the weighted-average method). We considered this approach to be preferable to the random-effects model, which can give too much weight to smaller trials that are often of poorer methodological quality.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses to examine whether the effect of topical tranexamic acid varied by the site of bleeding. We had also planned to explore the effect by the type of topical application, however, there were insufficient data for this analysis.
We carried out a random-effects model meta-regression to investigate the association between the effect of tranexamic acid on blood

loss and dose of tranexamic acid. The dose used in each trial was converted into the equivalent mg per ml for analysis.

Sensitivity analysis

We conducted a sensitivity analysis to quantify the effect of tranexamic acid when restricted to trials with adequate allocation concealment for outcomes with at least one trial contributing data to the analysis.

Summary of findings

We presented the main results of the review in a 'Summary of findings' table. We included the following outcomes:

- blood loss;
- death;
- myocardial infarction;
- stroke;
- deep vein thrombosis;
- pulmonary embolism;
- receipt of blood transfusion.

We used GRADEpro software to prepare the summary of findings table. We judged the overall quality of the evidence for each outcome as 'high', 'moderate', 'low' or 'very low' according to the GRADE approach (Schünemann 2011). We considered the following:

- impact of risk of bias of individual trials;
- precision of pooled estimate;
- inconsistency or heterogeneity (clinical, methodological and statistical);
- indirectness of evidence;
- impact of selective reporting and publication bias on effect estimate.

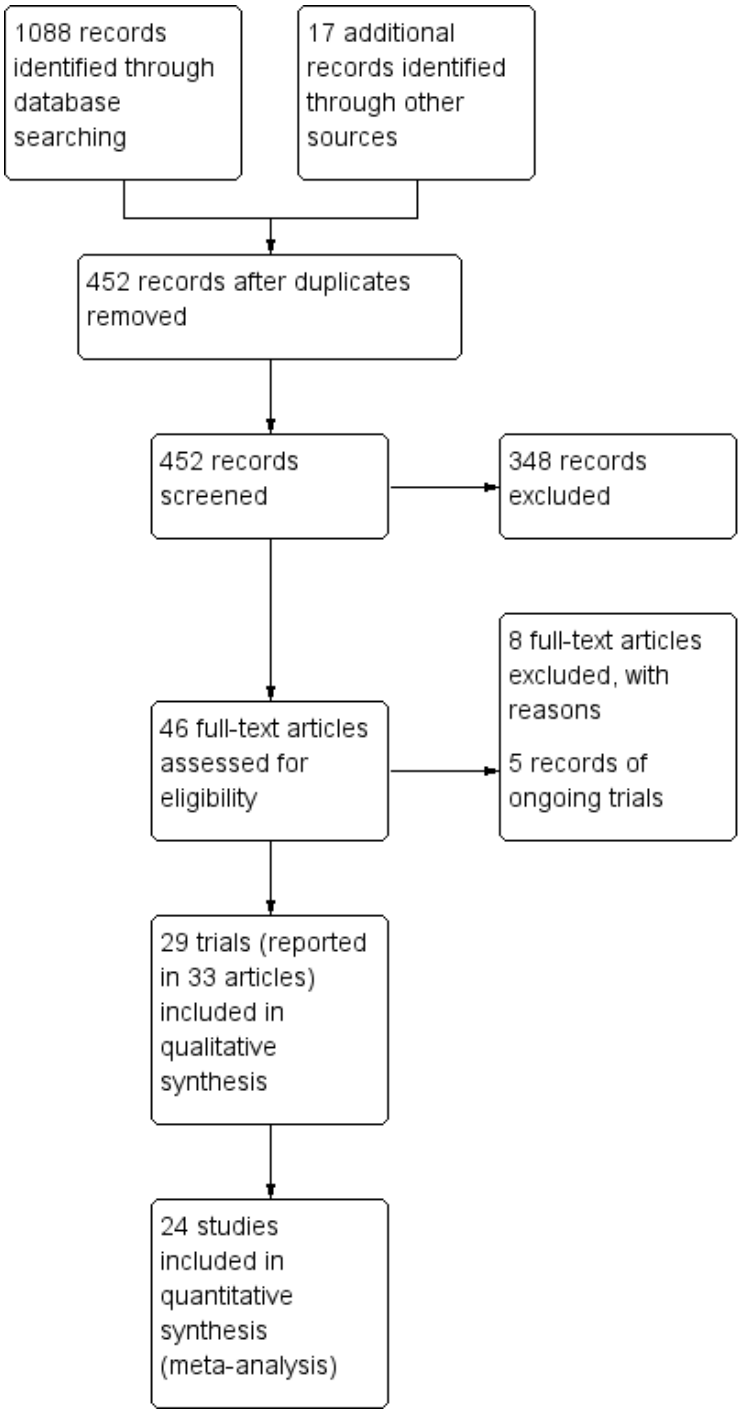
RESULTS

Description of studies

Results of the search

The trial selection process is summarised in Figure 1. The combined search strategy identified 452 records, of which 43 were judged to be potentially eligible and the full texts were obtained. After a full text review, 29 trials (reported in 33 articles) were included in the review.

Figure 1. Study flow diagram.



Included studies

Full details of each trial are presented in the Characteristics of included studies table; a summary is given below.

Setting

The trials were conducted in Australia, Belgium, Canada, Croatia, Denmark, Egypt, India, Iran, Israel, Italy, Japan, Norway, Saudi Arabia, South Korea, Sweden, Thailand, Turkey, the UK and the USA. The publication dates of the trial reports ranged from 1979 to 2013.

Participants

Twenty-eight trials assessed the effect of topical tranexamic acid in surgical patients. Of these trials, nine involved knee arthroplasty, six cardiac surgery, four dental surgery, two spinal surgery, one hip arthroplasty, one prostate resection, one pulmonary resection, three otolaryngological surgery and one orthognathic surgery. The single non-surgical trial assessed the effect of topical tranexamic acid for epistaxis.

Interventions

In 23 of the 28 surgical trials, tranexamic acid was administered in saline solution directly on to the operative site, either by pouring or spraying into the surgical wound or as a mouthwash in the dental surgery trials. In four of the trials involving knee arthroplasty and the one trial of hip arthroplasty, tranexamic acid was given via an intra-articular injection. In all of these trials tranexamic acid was applied at the end of surgery, prior to wound closure.

In the epistaxis trial, tranexamic acid in gel form was applied to the nasal cavity.

Twenty-five trials were placebo-controlled. In the remaining three trials, topical tranexamic acid was compared to a no treatment control group.

Outcomes

The amount of blood loss in millilitres measured by surgical drains or weighing of swabs and sponges was reported in 18 trials. Three trials estimated blood loss from the difference between pre- and post-operative haemoglobin or haematocrit levels.

Mortality data were reported in nine trials. Myocardial infarction data were reported in six trials, stroke data in five trials, deep vein thrombosis in nine trials, and pulmonary embolism in eight trials. The number of patients who received a blood transfusion was reported in 15 trials.

Five trials did not present any data on the outcome measures of interest to this review or reported data in a format that was unsuitable for inclusion in the pooled analyses.

Risk of bias in included studies

The review authors' judgements regarding each risk of bias item for each included trial are presented in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Sequence generation

One trial allocated patients into groups according to the day of the week and one trial alternately assigned patients into groups; both were judged to be at high risk of bias. Seventeen trials used an adequate method of sequence generation and were judged to be at low risk of bias; of these, nine trials referred to a random numbers table, seven used computer-generated randomisation and one used the drawing of lots. The remaining 10 trials were rated as unclear due to insufficient information.

Allocation concealment

Allocations in two trials were judged to be inadequately concealed and at high risk of bias. Six trials used a method of central allocation and two trials used sequentially numbered, opaque, sealed envelopes; all eight were considered to be adequately concealed and at low risk of bias. The remaining 19 trials were rated as unclear due to insufficient information.

Blinding

Blinding of participants and personnel

Twenty trials were judged to be adequately blinded and at low risk of performance bias. None of the trials were judged to be at high risk of bias for this domain. The remaining nine trials were rated as unclear due to insufficient information.

Blinding of outcome assessment: blood loss, receipt of blood transfusion, thromboembolic events

Of the 20 trials that contributed data on blood loss, blood transfusion or thromboembolic events, none were at high risk of bias, five were rated as unclear and 11 were judged to be at low risk of bias.

Blinding of outcome assessment: death

All nine trials that reported the number of deaths were judged to be at low risk of bias as we judged that the outcome measurement was unlikely to be influenced by lack of blinding.

Incomplete outcome data

Incomplete outcome data: blood loss

All of the 18 trials that reported blood loss data suitable for inclusion in the meta-analysis were judged to be at low risk of attrition bias for this outcome.

Incomplete outcome data: receipt of blood transfusion

Of the 15 trials that reported the number of patients who received a blood transfusion, 14 were judged to be at low risk of bias and one at high risk of bias.

Incomplete outcome data: thromboembolic events

Of the 13 trials that reported data on thromboembolic events, 12 were judged to be at low risk of bias and one at high risk of bias.

Incomplete outcome data: death

Of the nine trials that reported the number of deaths, eight were judged to be at low risk of bias and one at high risk of bias.

Selective reporting

One trial (Georgiadis 2013) was judged to be at low risk of bias for selective outcome reporting as all prespecified outcomes were reported in the final trial report. This was the only trial for which we found a record in a clinical trial registry that was created prior to the start of patient recruitment. The risk of bias for the remaining 28 trials was judged to be unclear as we had insufficient information to permit judgement.

Effects of interventions

Blood loss

Analysis 1.1

Eighteen trials involving a total of 1651 patients reported blood loss data suitable for inclusion in the meta-analysis.

The back-transformed pooled ratio of blood loss with topical tranexamic acid (TXA) was 0.71 (95% confidence interval (CI) 0.69 to 0.72; $P < 0.0001$) indicating that topical TXA reduced blood loss by 29%. There was substantial statistical heterogeneity between trials ($Chi^2 = 188.32$, $df = 17$ ($P < 0.0001$); $I^2 = 91\%$).

When the analysis was restricted to the five trials with adequate allocation concealment, topical TXA reduced blood loss by 43%

(pooled ratio 0.57, 95% CI 0.52 to 0.62; P < 0.0001). There was substantial statistical heterogeneity between trials (Chi^2 = 27.79, df = 4 (P < 0.0001); I^2 = 86%).

Effect by site of bleeding

There was a statistically significant reduction in blood loss in cardiac, knee arthroplasty, spinal and otolaryngological surgery. The point estimates were consistent with a small reduction in the topical TXA group in the trials involving thoracic surgery and orthognathic surgery although they were imprecise and not statistically significant.

- Cardiac surgery, 7 trials (n = 511): pooled ratio 0.63 (95% CI 0.61 to 0.66; P < 0.0001); Chi^2 = 21.76, df = 6 (P = 0.001); I^2 = 72%.
- Knee arthroplasty, 5 trials (n = 427): pooled ratio 0.57 (95% CI 0.53 to 0.62; P < 0.0001); Chi^2 = 33.89, df = 4 (P < 0.0001); I^2 = 88%.
- Orthognathic surgery, 1 trial (n = 40): ratio 0.93 (95% CI 0.73 to 1.20; P = 0.60).
- Otolaryngological surgery, 2 trials (n = 456): pooled ratio 0.74 (95% CI 0.73 to 0.76; P < 0.0001); Chi^2 = 1.93, df = 1 (P = 0.16); I^2 = 48%.
- Spinal surgery, 2 trials (n = 130): pooled ratio 0.50 (95% CI 0.43 to 0.58; P < 0.0001); Chi^2 = 0.39, df = 1 (P = 0.53); I^2 = 0%.
- Thoracic surgery, 1 trial (n = 87): ratio 0.95 (95% CI 0.86 to 1.05; P = 0.35).

Test for subgroup differences: Chi^2 = 130.34, df = 5 (P < 0.0001); I^2 = 96.2%.

Effect by dose

The concentration of TXA used in the 18 trials ranged from 0.7 mg to 100 mg/ml of saline solution. The result of the meta-regression analysis suggested that the effect of TXA on blood loss did not vary over this range (coefficient = 1.0003; P = 0.84).

Estimated blood loss

Analysis 1.2

Three trials estimated the amount of blood loss based on the difference between pre- and post-operative haemoglobin or haematocrit. Data from these trials were not suitable for inclusion in the pooled analysis and were considered separately. All three trials observed a statistically significant difference in the amount of blood loss with topical TXA.

Mortality

Analysis 1.3

Nine trials involving a total of 894 participants reported mortality data. No deaths occurred in seven trials, therefore the pooled analysis was based on data from two trials involving a total of nine deaths among 293 participants.

There was no difference in the risk of death between the topical TXA and control groups, the pooled risk ratio (RR) was 0.28 (95% CI 0.06 to 1.34; P = 0.11). There was no statistical heterogeneity between trials (Chi^2 = 0.03, df = 1 (P = 0.86); I^2 = 0%).

When the analysis was restricted to the one trial with adequate allocation concealment, there was no difference in the risk of death between the groups (RR 0.33, 95% CI 0.03 to 3.12; P = 0.33).

Thromboembolic events

Myocardial infarction

Analysis 1.4

Six trials involving a total of 362 participants reported data on myocardial infarction. It was reported that no patients suffered myocardial infarction in four trials, therefore the pooled analysis was based on data from two trials involving a total of two events among 127 participants.

There was no difference in the risk of myocardial infarction between the topical TXA and control groups, the pooled RR was 0.33 (95% CI 0.04 to 3.08; P = 0.33). There was no statistical heterogeneity between trials (Chi^2 = 0.00, df = 1 (P = 0.99); I^2 = 0%).

There were no cases of myocardial infarction in the two trials with adequate allocation concealment.

Stroke

Analysis 1.5

Five trials involving a total of 441 participants reported data on stroke. It was reported that no patients suffered a stroke in four trials, thus the analysis was based on data from one trial (with adequate allocation concealment) involving a total of one event among 157 participants.

There was no difference in the risk of stroke between the topical TXA and control groups, the RR was 0.33 (95% CI 0.01 to 7.96; P = 0.49).

Deep vein thrombosis

Analysis 1.6

Nine trials involving a total of 789 participants reported data on deep vein thrombosis. It was reported that no patients suffered a deep vein thrombosis in five trials, therefore the analysis was based on data from four trials involving a total of 21 events among 457 participants.

There was no difference in the risk of deep vein thrombosis between the topical TXA and control groups, the RR was 0.69 (95%

CI 0.31 to 1.57; P = 0.38). There was no statistically significant heterogeneity between trials (Chi² = 3.41, df = 3 (P = 0.33); I² = 12%).

When the analysis was restricted to the three trials with adequate allocation concealment, there was no difference in the risk of death between the groups (pooled RR 0.81, 95% CI 0.34 to 1.92; P = 0.63). There was no statistically significant heterogeneity between trials (Chi² = 2.81, df = 2 (P = 0.25); I² = 29%).

Pulmonary embolism

Analysis 1.7

Eight trials involving a total of 741 participants reported data on pulmonary embolism. It was reported that no patients suffered a pulmonary embolism in six trials, therefore the analysis was based on data from two trials (both with adequate allocation concealment) involving a total of five events among 200 participants.

There was no difference in the risk of pulmonary embolism between the topical TXA and control groups, the RR was 0.52 (95% CI 0.09 to 3.15; P = 0.48). There was no statistically significant heterogeneity between trials (Chi² = 0.00, df = 1 (P = 0.97); I² = 0%).

Blood transfusion

Analysis 1.8

Fifteen trials involving a total of 1623 participants reported data on receipt of blood transfusion. It was reported that no patients received a blood transfusion in one trial, therefore the analysis was based on data from 14 trials involving a total of 311 events among 1523 participants.

Topical TXA reduced the risk of receiving a blood transfusion by 45% (pooled RR 0.55, 95% CI 0.46 to 0.65; P < 0.0001). There was substantial statistical heterogeneity between trials (Chi² = 54.48, df = 13 (P < 0.0001); I² = 76%).

When the analysis was restricted to the seven trials with adequate allocation concealment, topical TXA reduced the risk of receiving a blood transfusion by 33% (pooled RR 0.67, 95% CI 0.54 to 0.84; P = 0.001). There was substantial statistical heterogeneity between trials (Chi² = 25.68, df = 6 (P = 0.0003); I² = 77%).

Reporting bias

There were sufficient data to produce funnel plots for the blood loss and blood transfusion outcomes. There was no clear asymmetry in the funnel plot for blood loss (Figure 3). However, inspection of the funnel plot for blood transfusion suggested the presence of small study effects favouring topical TXA (Figure 4).

Figure 3. Funnel plot of comparison: 1 Topical TXA versus control, outcome: 1.1 Blood loss.

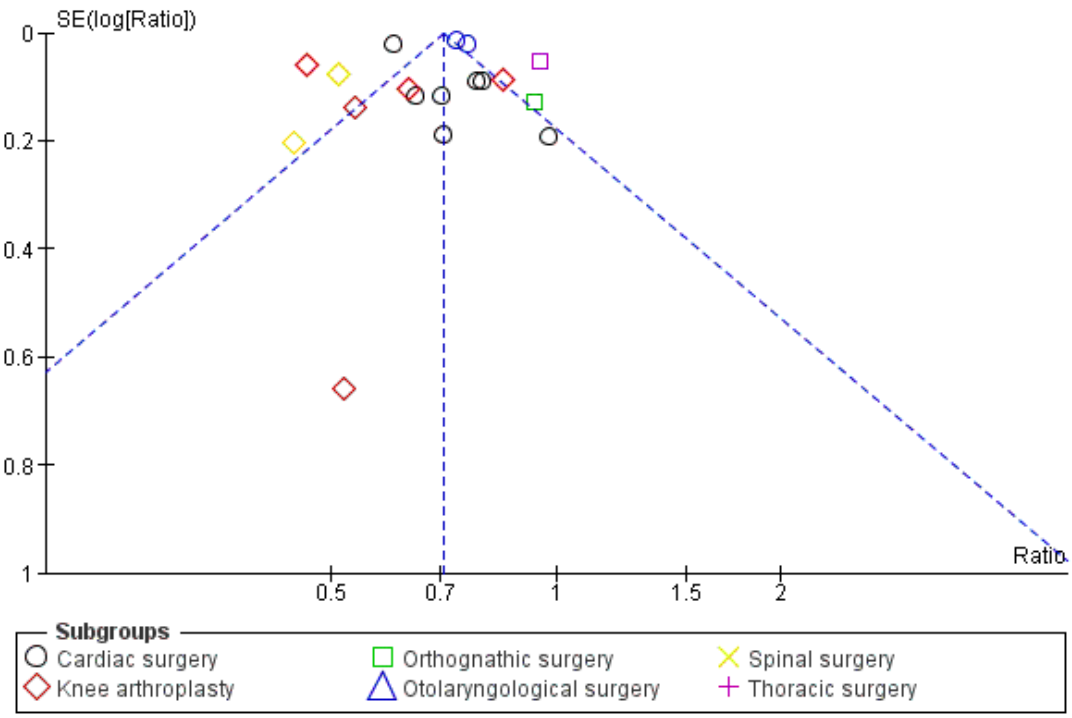
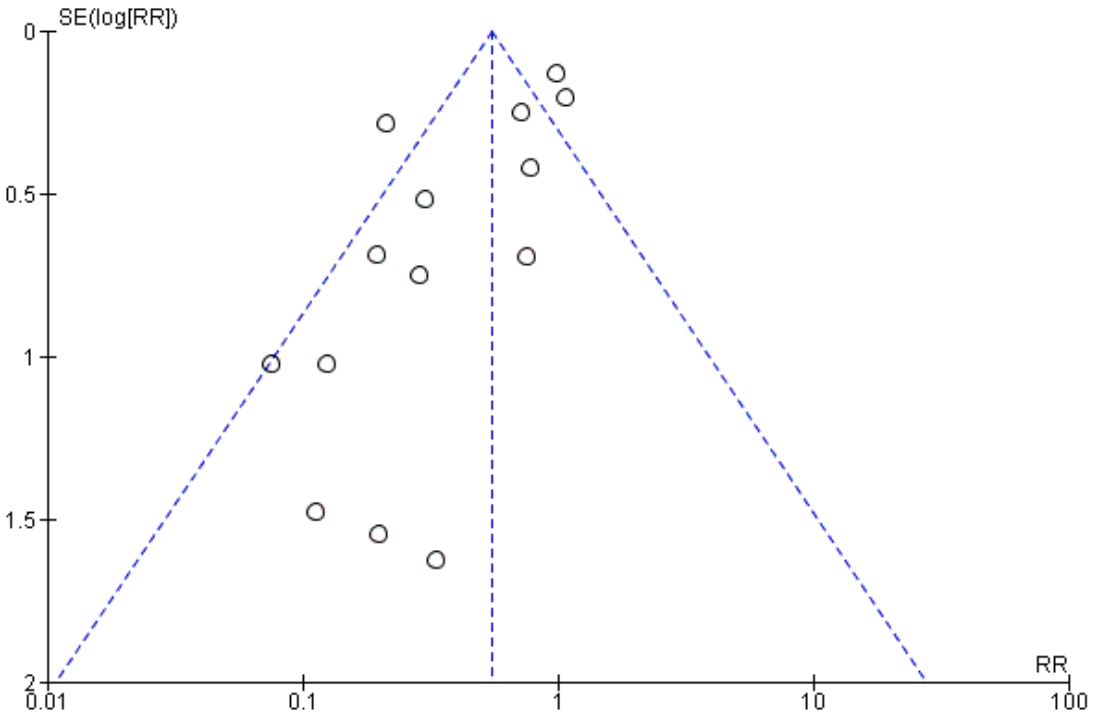


Figure 4. Funnel plot of comparison: 1 Topical TXA versus control, outcome: 1.8 Blood transfusion.



Summary of findings and quality of the evidence

The summary of findings and GRADE evidence profile for the use of topical TXA for surgical bleeding are presented in Figure 5.

Figure 5. Summary of findings table and GRADE evidence profile: Should topical TXA be used for the reduction of surgical bleeding?

Author(s): Katharine Ker, Deirdre Beecher, Ian Roberts
Date: 2013-06-04
Question: Should Topical TXA be used for the reduction of surgical bleeding?
Bibliography: Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. *CDSR*

Outcome	Quality assessment							No. of patients		Effect	Quality
	No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical TXA	Control	Relative (95% CI)	
Blood loss (proportional reduction)											
All included trials	18	randomised trials	serious[1]	serious inconsistency[2]	no serious indirectness	no serious imprecision	none detected	825	826	Ratio 0.71 (0.69 to 0.72)	⊕⊕OO LOW
Adequately concealed trials	9	randomised trials	no serious risk of bias	serious inconsistency[2]	no serious indirectness	no serious imprecision	none detected	229	229	Ratio 0.57 (0.52 to 0.62)	⊕⊕⊕OO MODERATE
Mortality											
All included trials	9	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	2/463 (0.43%)	7/431 (1.6%)	RR 0.28 (0.06 to 1.34)	⊕⊕OO LOW
Adequately concealed trials	4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	1/259 (0.004%)	7/228 (0.03%)	RR 0.33 (0.03 to 3.12)	⊕⊕⊕OO MODERATE
Myocardial infarction											
All included trials	6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	0/189 (0%)	2/173 (1.2%)	RR 0.33 (0.04 to 3.08)	⊕⊕OO LOW
Adequately concealed trials	2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	0/44 (0%)	2/44 (0%)	-	-
Stroke											
All included trials	5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	0/229 (0%)	1/212 (0.47%)	RR 0.33 (0.01 to 7.96)	⊕⊕OO LOW
Adequately concealed trials	2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	0/104 (0%)	1/103 (0.01%)	RR 0.33 (0.01 to 7.96)	⊕⊕OO LOW
Deep vein thrombosis											
All included trials	8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	9/377 (2.4%)	12/332 (3.6%)	RR 0.69 (0.31 to 1.57)	⊕⊕OO LOW
Adequately concealed trials	5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	9/242 (3.72%)	10/213 (4.69%)	RR 0.81 (0.34 to 1.92)	⊕⊕OO LOW
Pulmonary embolism											
All included trials	7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	2/353 (0.57%)	3/308 (0.97%)	RR 0.52 (0.09 to 3.15)	⊕⊕OO LOW
Adequately concealed trials	4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	2/218 (0.92%)	3/189 (1.59%)	RR 0.52 (0.09 to 3.15)	⊕⊕OO LOW
Blood transfusion											
All included trials	14	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	reporting bias[5]	97/788 (12.3%)	178/755 (23.6%)	RR 0.53 (0.43 to 0.64)	⊕OOO VERY LOW
Adequately concealed trials	7	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none detected	74/358 (20.67%)	105/328 (32.01%)	RR 0.67 (0.54 to 0.84)	⊕⊕⊕OO MODERATE

[1] Includes trials at unclear or high risk of bias for allocation concealment
[2] Substantial statistical heterogeneity detected
[3] Few events
[4] Only subset of trials reported outcome data (suspected selective outcome reporting)
[5] Observed asymmetry in funnel plot favouring topical tranexamic acid

DISCUSSION

Summary of main results

There is reliable evidence that the topical application of tranexamic acid reduces bleeding in surgical patients. Data pooled across trials conducted in a range of surgical procedures suggest that the topical application of tranexamic acid reduces surgical blood loss by about one third. However, the magnitude of the effect varies when stratified by the type of surgery. There is no evidence for a dose-response relationship with blood loss over the range of doses assessed by the trials (0.7 to 100 mg/ml). Topical tranexamic acid also reduces the risk of receiving a blood transfusion in surgical patients, however, the effect on the risk of thromboembolic events in this patient group is uncertain. The effects of topical tranexamic acid in patients with bleeding from non-surgical causes have not been assessed by clinical trials and are uncertain.

Overall completeness and applicability of evidence

The pooled analyses which inform the results of this systematic review are based on data from trials conducted in surgery. We found only one trial that had been conducted in a non-surgical setting, although the reported data were not suitable for inclusion in the quantitative analyses. We cannot assume that the same effect would be observed in other bleeding conditions such as gastrointestinal or obstetric bleeding. However, the similar underlying haemostatic response and the observed beneficial effect in surgery raise the possibility that topical tranexamic acid might also be effective in other bleeding conditions and warrants further investigation.

Quality of the evidence

Most of the trials were judged to be at low or unclear risk of bias. When the analysis was restricted to trials with adequate allocation concealment the favourable effect of topical tranexamic acid on both the amount of blood loss and risk of blood transfusion remained large and statistically significant. Systematic error resulting from methodological limitations of the included trials is therefore unlikely to fully explain the observed effect.

None of the trials were adequately powered to detect the impact on the clinically important outcomes of death and thromboembolic events, therefore the pooled estimates are imprecise and compatible with an increase or decrease in risk. Furthermore, less than a third of the included trials reported data on these outcomes, raising the possibility of selective outcome reporting. The effect of such bias on the results of this review is open to question.

Potential biases in the review process

The possibility of publication bias should be considered as a potential threat to the validity of the findings of this systematic review. In light of our extensive and sensitive searching, we believe that it is unlikely that any published trials were missed, although it is possible that we missed unpublished trials. Indeed, the observed asymmetry in the funnel plot for blood transfusion could be explained by publication bias. If there are many unpublished trials showing little or no effect of topical tranexamic acid on blood transfusion, then this meta-analysis may have overestimated the treatment effect. Although some degree of overestimation for this outcome is likely, it seems improbable that publication bias could account for all of the observed effect.

There was substantial statistical heterogeneity for the blood loss and blood transfusion outcomes, which was not explained by type of surgery, dose or adequacy of allocation concealment. Differences in the methods of measuring blood loss and aspects of methodological quality between trials may have contributed to the heterogeneity. It is important to note that the heterogeneity describes variation in the magnitude not the direction of the effect, with all point estimates for blood loss consistent with a reduction with topical tranexamic acid within subgroups.

Agreements and disagreements with other studies or reviews

Our results are consistent with those from other systematic reviews and randomised trials assessing the effect of tranexamic acid. A systematic review of randomised trials assessing the effects of intravenous tranexamic acid in patients undergoing surgery found that it reduced blood loss and the risk of receiving a blood transfusion although the effect on risk of death and thromboembolic events was uncertain (Ker 2012; Ker 2013). The CRASH-2 trial that involved 20,211 bleeding trauma patients found that early administration of intravenous tranexamic acid reduced the risk of death due to bleeding by about a third, with no increase in thromboembolic events (CRASH-2 Collaborators 2011).

AUTHORS' CONCLUSIONS

Implications for practice

The topical application of tranexamic acid reduces bleeding and blood transfusion in patients undergoing surgery. As there is less

systemic absorption following topical administration, clinicians reluctant to administer tranexamic acid intravenously to high-risk surgical patients, out of concern for increased risk of thromboembolic events, may consider topical application as an alternative.

Implications for research

There is a need for high-quality randomised controlled trials to resolve the uncertainties surrounding the effects of topical application of tranexamic acid on risk of thromboembolic events and to assess its effects in patients with bleeding from non-surgical causes.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdullah 2012

Methods	Randomised placebo-controlled trial Setting: not described
Participants	52 patients undergoing transurethral resection of the prostate • Topical TXA group (n=NR): all male, age not reported • Control group (n=NR): all male, age not reported
Interventions	• Topical TXA group: 500mg in 1000ml saline irrigation fluid • Control group: placebo (saline)
Outcomes	Prostatic weight Duration of resection Haemoglobin level
Notes	Conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported

Abdullah 2012 (*Continued*)

Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Abul-Azm 2006

Methods	Randomised placebo-controlled trial Setting: unclear
Participants	100 patients undergoing elective open heart surgery • Topical TXA group (n=50): M/F=24/26; median age (range)=57 (43-73) • Control group (n=50): M/F=28/22; median age (range)=55 (44-78)
Interventions	• Topical TXA group: 2g in 100ml saline poured into pericardial cavity • Control group: placebo (saline)
Outcomes	Blood loss (drainage of mediastinal blood) Death Hospital stay Re-exploration Use of blood product for transfusion Haematology and coagulation variables
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported that "all anaesthesiologists and surgeons were blinded to group allocation"
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	Reported that "all anaesthesiologists and surgeons were blinded to group allocation"

Abul-Azm 2006 (*Continued*)

Blinding of outcome assessment (detection bias) Death	Unclear risk	Reported that "all anaesthesiologists and surgeons were blinded to group allocation"
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Death	Low risk	No exclusions described
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Albirmawy 2013

Methods	Randomised placebo-controlled trial Setting: Egypt
Participants	400 children undergoing primary isolated adenoidectomy • Topical TXA group (n=200): M/F=131/69; mean age (sd)=5.6 (2.5) • Control group (n=200): M/F=119/81; mean age (sd)=4.9 (1.8)
Interventions	• Topical TXA group: 1g in 10ml saline poured into nasopharynx • Control group: placebo (saline)
Outcomes	Blood loss (intra-operative, suctioned blood) Frequency of post-operative bleeding Use of blood product for transfusion Haematology and coagulation variables
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	"The solutions were prepared by one of the co-authors in two identical bottles and delivered to the operative theatre"

Albirmawy 2013 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the surgeon, anaesthetist or the scrub nurse knew the composition of the solution administered
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	Neither the surgeon, anaesthetist or the scrub nurse knew the composition of the solution administered
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Alshryda 2013

Methods	Randomised placebo-controlled trial Setting: UK
Participants	157 patients undergoing knee arthroplasty • Topical TXA group (n=79): M/F=30/49; mean age (sd)=65.5 (9.6) • Control group (n=78): M/F=44/34; mean age (sd)=67.1 (10.2)
Interventions	• Topical TXA group: 1g/50ml saline sprayed into the wound at the end of the operation • Control group: placebo (saline)
Outcomes	Blood loss Blood transfusion Thromboembolic events Haematology variables Joint function Length of stay Quality of life assessment

Alshryda 2013 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Central allocation (web-based)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Surgeons and their team members and patients remained blinded to the allocation."
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	"Surgeons and their team members and patients remained blinded to the allocation."
Blinding of outcome assessment (detection bias) Death	Low risk	"Surgeons and their team members and patients remained blinded to the allocation."
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions and intention-to-treat analysis
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions and intention-to-treat analysis
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions and intention-to-treat analysis
Incomplete outcome data (attrition bias) Death	Low risk	No exclusions and intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Athanasiadis 2007

Methods	Randomised placebo-controlled trial Setting: Australia
Participants	30 patients undergoing sinus surgery: M/F=19/11; median age (range)=51 (19-79) Each patient received both trial treatments: topical tranexamic acid was applied to one side of the nasal cavity and placebo to the other • Topical TXA group 1 versus control (n=10)

	• Topical TXA group 2 versus control (n=10) [*third group of 10 patients received EACA versus control, not included in this review]
Interventions	• Topical TXA group 1: 100mg sprayed into nasal cavity • Topical TXA group 2: 1g sprayed into nasal cavity • Control group: placebo (saline)
Outcomes	Surgical site grade of bleeding Post-operative epistaxis Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	"Sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The surgical team and the independent observer thus were blinded as to which agent the patient was receiving..."
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Baric 2007

Methods	Randomised controlled trial Setting: Croatia
Participants	300* patients undergoing elective cardiac surgery • Topical TXA group (n=97): M/F=77/20; mean age (sd)=61.2 (10.7) • Control group (n=96): M/F=70/26; mean age (sd)=61.2 (10.3) [*third group of 100 patients received aprotinin, not included in this review]
Interventions	• Topical TXA group: 2.5g in 250ml saline poured into pericardial cavity • Control group: placebo (saline)
Outcomes	Blood loss Blood product transfusion Death Haematology and coagulation variables
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Low risk	"The independent pharmacologist in the hospital pharmacy prepared coded solutions with the study drugs and was not directly involved in the clinical treatment of randomised patients...Identical bottles marked with a study number were delivered to the operating theatres. Codes were disclosed at the end of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both the operation theatre staff and that of the intensive care unit were blinded regarding the study drug and codes were disclosed at the end of the study."
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	"Both the operation theatre staff and that of the intensive care unit were blinded regarding the study drug and codes were disclosed at the end of the study."
Blinding of outcome assessment (detection bias) Death	Low risk	"Both the operation theatre staff and that of the intensive care unit were blinded regarding the study drug and codes were disclosed at the end of the study."

Baric 2007 (*Continued*)

Incomplete outcome data (attrition bias) Blood loss	Low risk	"Six patients were withdrawn from the study due to postoperative reopening for bleeding where an evident surgical source for bleeding was discovered. One patient dropped-out from the study due to the technical mistake." Missing outcome data balanced in numbers across groups.
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	"Six patients were withdrawn from the study due to postoperative reopening for bleeding where an evident surgical source for bleeding was discovered. One patient dropped-out from the study due to the technical mistake." Missing outcome data balanced in numbers across groups.
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	"Six patients were withdrawn from the study due to postoperative reopening for bleeding where an evident surgical source for bleeding was discovered. One patient dropped-out from the study due to the technical mistake." Missing outcome data balanced in numbers across groups.
Incomplete outcome data (attrition bias) Death	Low risk	"Six patients were withdrawn from the study due to postoperative reopening for bleeding where an evident surgical source for bleeding was discovered. One patient dropped-out from the study due to the technical mistake." Missing outcome data balanced in numbers across groups.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Blinder 1999

Methods	Randomised placebo-controlled trial Setting: Israel
Participants	150* patients undergoing dental extraction • Topical TXA group (n=50): M/F=33/17; age range=35-79 • Control group (n=50): M/F=35/15; age range=40-86 [*third group of 50 patients received fibrin glue, not included in this review]

Blinder 1999 (*Continued*)

Interventions	• Topical TXA group: 500mg as mouthwash, rinsed for 2 minutes 4 times a day for 4 day post-operatively • Control group: no mouthwash containing TXA	
Outcomes	Post-operative bleeding Anti-coagulant activity	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Assigned according to day of week
Allocation concealment (selection bias)	High risk	Assigned according to day of week therefore not concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Canata 2012

Methods	Randomised controlled trial
Participants	96* patients undergoing knee arthroplasty; mean age (range)=70 (47-83) • Topical TXA group (n=32): M/F=11/21 • Control group (n=32): M/F=7/8 [*third group of 32 patients received a mixture of ropivacaine, clonidine, ketorolac and norepinephrine, not included in this review]
Interventions	• Topical TXA group: received "infiltration of tranexamic acid" (no other details presented) • Control group: "no infiltration was performed"
Outcomes	Blood loss* Receipt of blood transfusion* KOOS outcome score Haemoglobin [*insufficient data reported to allow inclusion in meta-analysis]
Notes	Conference abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information reported
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported

Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

De Bonis 2000

Methods	Randomised placebo-controlled trial Setting: Italy
Participants	40 patients undergoing primary coronary artery surgery • Topical TXA group (n=20): M/F=17/3; mean age (sd)=62 (7) • Control group (n=20): M/F=18/2; mean age (sd)=60 (6)
Interventions	• Topical TXA group: 1g in 100ml saline • Control group: placebo (saline)
Outcomes	Blood loss Receipt of blood products Myocardial infarction Haematology and coagulation variables
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes were prepared and left in a box in the operating theatre. On the day of surgery, the theatre nurse selected the next card from the box and this determined which solution was to be used."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the surgeons, anaesthetists, scrub nurses nor perfusionists knew the composition of the solution administered."
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	"Neither the surgeons, anaesthetists, scrub nurses nor perfusionists knew the composition of the solution administered."

De Bonis 2000 (*Continued*)

Blinding of outcome assessment (detection bias) Death	Low risk	"Neither the surgeons, anaesthetists, scrub nurses nor perfusionists knew the composition of the solution administered."
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Death	Low risk	No exclusions reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Dell'Amore 2012

Methods	Randomised controlled trial Setting: Italy
Participants	89 patients undergoing pulmonary resection • Topical TXA group (n=45): M/F=29/16; mean age (sd)=65.8 (6.4) • Control group (n=44): M/F=31/13; mean age (sd)=67.7 (6.4)
Interventions	• Topical TXA group: 5g 100ml of saline solution poured into chest at end of resection • Control group: placebo (saline)
Outcomes	Blood loss Receipt of blood products Thromboembolic events Haematology and coagulation variables
Notes	Some additional unpublished data provided by trial author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Dell'Amore 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The operation room staff, the ward staff and the intensive care unit staff were all blinded regarding the study solution"
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	"The operation room staff, the ward staff and the intensive care unit staff were all blinded regarding the study solution"
Blinding of outcome assessment (detection bias) Death	Low risk	"The operation room staff, the ward staff and the intensive care unit staff were all blinded regarding the study solution"
Incomplete outcome data (attrition bias) Blood loss	Low risk	2 patients (one from each group) were excluded because of major post-operative bleeding with surgical source Missing outcome data balanced in numbers across groups
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	2 patients (one from each group) were excluded because of major post-operative bleeding with surgical source Missing outcome data balanced in numbers across groups
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	2 patients (one from each group) were excluded because of major post-operative bleeding with surgical source Missing outcome data balanced in numbers across groups
Incomplete outcome data (attrition bias) Death	Low risk	2 patients (one from each group) were excluded because of major post-operative bleeding with surgical source Missing outcome data balanced in numbers across groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported to permit judgement

Fawzy 2009

Methods	Randomised placebo-controlled trial Setting: Saudi Arabia
Participants	38 patients undergoing isolated coronary artery bypass grafting • Topical TXA group (n=19): M/F=18/1; mean age (sd)=55 (11)

Fawzy 2009 (*Continued*)

	• Control group (n=19): M/F=18/1; mean age (sd)=60 (7)
Interventions	• Topical TXA group: 1g 100ml of saline solution poured into pericardial and mediastinal cavities • Control group: placebo (saline)
Outcomes	Blood loss Blood products transfused Death Thromboembolic events Re-exploration Haematology and coagulation variables
Notes	Additional unpublished data obtained from trial author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Low risk	"Research pharmacist who prepared the two solutions in two identical bottles delivered to the operating theatre."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the surgeons, anaesthetists, scrub nurses nor perfusionists knew the composition of the solution administered."
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	"Neither the surgeons, anaesthetists, scrub nurses nor perfusionists knew the composition of the solution administered."
Blinding of outcome assessment (detection bias) Death	Low risk	"Neither the surgeons, anaesthetists, scrub nurses nor perfusionists knew the composition of the solution administered."
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions

Fawzy 2009 (*Continued*)

Incomplete outcome data (attrition bias) Death	Low risk	No exclusions
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported to permit judgement

Georgiadis 2013

Methods	Randomised placebo-controlled trial Setting: USA
Participants	101 patients undergoing total knee arthroplasty • Topical TXA group (n=50): M/F=19/31; mean (sd) age=67.0 (9.0) • Control group (n=51): M/F=12/39; mean (sd) age=64.5 (8.2)
Interventions	• Topical TXA group: 2g in 75ml of saline solution applied to the wound bed after component placement • Control group: placebo (saline)
Outcomes	Blood loss Blood transfusion Venous thromboembolism rates
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	Described as double-blind
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported

Georgiadis 2013 (*Continued*)

Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Low risk	Registered on ClinicalTrials.gov prior to trial completion - prespecified outcomes reported in final trial report

Gersel-Pedersen 1979

Methods	Randomised placebo-controlled trial Setting: Denmark
Participants	120 patients undergoing bilateral molar extraction (240 extractions); mean age (range) =23.2 (14-58) • Topical TXA group (n=120): M/F=NR • Control group (n=120): M/F=NR
Interventions	• Topical TXA group: 40mg - before closure of wound 4 triangular cones were applied in each socket • Control group: placebo (saline)
Outcomes	Development of alveolitis sicca dolorosa Post-operative pain, swelling Bleeding Re-operation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not reported
Allocation concealment (selection bias)	Unclear risk	Information not reported

Gersel-Pedersen 1979 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial described as double-blind
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported to permit judgement

Ishida 2011

Methods	Randomised placebo-controlled trial Setting: Japan
Participants	100 patients undergoing knee arthroplasty • Topical TXA group (n=50): M/F=6/44; mean age (sd)=73.3 (5.0) • Control group (n=50): M/F=6/44; mean age (sd)=73.5 (6.1)
Interventions	• Topical TXA group: 2000mg/20ml injected into knee joint immediately after wound closure through a drain • Control group: placebo (saline)
Outcomes	Blood loss Receipt of blood products Swelling of knee joint Haematology and coagulation variables
Notes	

Ishida 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"patients were alternately assigned"
Allocation concealment (selection bias)	High risk	"patients were alternately assigned"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information reported
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	"Measurements were performed twice each day in each patient by two authors blinded to clinical information"
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions described
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Jabalameli 2006

Methods	Randomised controlled trial. Setting: Iran
Participants	56 patients undergoing sinus surgery; M/F=38/18; age range=18-55 • Topical TXA group (n=26) • Control group (n=30)
Interventions	• Topical TXA group: 1000mg in 20ml saline "administered topically" • Control group: placebo (saline)

Outcomes	Intra-operative bleeding Haemodynamic endpoints	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information reported
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	No information reported
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported to permit judgement

Kaewpradub 2011

Methods	Randomised placebo-controlled trial Setting: Thailand
Participants	40 patients undergoing bimaxillary osteotomy • Topical TXA group (n=20); M/F=5/15; mean age (sd)=26.25 (5.01) • Control group (n=20); M/F=11/9; mean age (sd)=25.55 (7.11)
Interventions	• Topical TXA group: 500mg (10ml) in saline for tissue irrigation and cooling of the instrument • Control group: placebo (saline)
Outcomes	Blood loss Volume of blood transfused Operation time Haematocrit levels Hypotensive time
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"patients were assigned randomly to 2 groups by drawing lots"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial is described as double-blind and reported that "...anaesthesiologist and a surgical team who were blinded to the type of irrigation fluid"
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	Trial is described as double-blind and reported that "...anaesthesiologist and a surgical team who were blinded to the type of irrigation fluid"
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported

Kaewpradub 2011 (*Continued*)

Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported to permit judgement

Krohn 2002

Methods	Randomised placebo-controlled trial Setting: Norway
Participants	30 patients undergoing spinal surgery; median age (IQR)=47 (24-70) • Topical TXA group (n=16); M/F=7/9 • Control group (n=14); M/F=5/9
Interventions	• Topical TXA group: 500mg in 50ml saline, irrigation of wound at end of operation for 2-5 minutes • Control group: placebo (saline)
Outcomes	Blood loss Blood transfusion Plasmin and D-dimer concentrations
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...according to the randomisation table."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"surgeons and the personnel in the postoperative ward were unaware of who received tranexamic acid and who did not"
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	"surgeons and the personnel in the postoperative ward were unaware of who received tranexamic acid and who did not"

Krohn 2002 (*Continued*)

Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Kurt 2011

Methods	Randomised controlled trial Setting: Turkey
Participants	100 patients undergoing cardiac surgery • Topical TXA group (n=20); M/F=17/3; mean age (sd)=56.8 (10.7) • Control group (n=20); M/F=16/4; mean age (sd)=60.2 (10.6)
Interventions	• Topical TXA group: 1mg/kg in 100ml poured into mediastinum • Control group: no TXA
Outcomes	Blood loss Amount of blood transfused Haematology and coagulation variables
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Kurt 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Nouraei 2013

Methods	Randomised placebo-controlled trial Setting: Iran
Participants	80 patients undergoing cardiac surgery • Topical TXA group (n=40); M/F=29/11; mean age (sd)=60 (9.64) • Control group (n=40); M/F=25/15; mean age (sd)=59.64 (10.03)
Interventions	• Topical TXA group: 2g/kg in 500ml poured into pericardial cavity prior to closure • Control group: placebo
Outcomes	Blood loss (mediastinal drainage) Blood transfusion Haematology and coagulation variables Mortality Complications (myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, seizures, re-exploration, renal failure)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer made random number table"
Allocation concealment (selection bias)	Unclear risk	Reported that a 'third party' was used. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported: "This was double-blind study, and with the exception of one nurse who prepared the solution, none of the patients, doctors, nurses or laboratory staff were aware of the type of therapy"
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	Reported: "This was double-blind study, and with the exception of one nurse who prepared the solution, none of the patients, doctors, nurses or laboratory staff were aware of the type of therapy"
Blinding of outcome assessment (detection bias) Death	Low risk	Reported: "This was double-blind study, and with the exception of one nurse who prepared the solution, none of the patients, doctors, nurses or laboratory staff were aware of the type of therapy"
Incomplete outcome data (attrition bias) Blood loss	Low risk	Reported: "This was double-blind study, and with the exception of one nurse who prepared the solution, none of the patients, doctors, nurses or laboratory staff were aware of the type of therapy"
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	Reported: "This was double-blind study, and with the exception of one nurse who prepared the solution, none of the patients, doctors, nurses or laboratory staff were aware of the type of therapy"
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	Reported: "This was double-blind study, and with the exception of one nurse who prepared the solution, none of the patients, doctors, nurses or laboratory staff were aware of the type of therapy"

Nouraei 2013 (*Continued*)

Incomplete outcome data (attrition bias) Death	Low risk	Reported: "This was double-blind study, and with the exception of one nurse who prepared the solution, none of the patients, doctors, nurses or laboratory staff were aware of the type of therapy"
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. Retrospective registration on trial registry

Ramstrom 1993

Methods	Randomised placebo-controlled trial Setting: Denmark and Sweden
Participants	93 patients undergoing dental surgery • Topical TXA group (n=44); M/F=25/19; mean age (sd)=69.8 (7.9) • Control group (n=45); M/F=28/17; mean age (sd)=67.1 (10.5)
Interventions	• Topical TXA group: After surgery but before suturing irrigated with 10ml TXA. Patients given 27 containers of 10ml TXA and instructed to use as mouthwash for 2 minutes, 4 times a day for 7 days • Control group: placebo (saline)
Outcomes	Haematology and coagulation variables
Notes	"Seven patients participated in the study two or three times."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"..use of consecutively numbered medication packages. A written patient information sheet and a sealed envelope with information about the randomisation code for each patient, to be open in case of emergency, were prepared by Kabi Pharmacia (Uppsala, Sweden)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial described as double-blind

Ramstrom 1993 (*Continued*)

Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported to permit judgement

Roy 2012

Methods	Randomised placebo-controlled trial Setting: India
Participants	50 patients undergoing knee arthroplasty • Topical TXA group (n=25); M/F=10/15; mean age (sd)=66.04 (7.15) • Control group (n=25); M/F=9/16; mean age (sd)=66.56 (8.03)
Interventions	• Topical TXA group: 500mg/5ml administered intra-articularly through drain tube immediately after wound closure • Control group: placebo (saline)
Outcomes	Blood loss Blood transfusion Thromboembolic events Haematology variables
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Roy 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	"A random number table was utilized to generate the simple randomization sequence."
Allocation concealment (selection bias)	Low risk	"The tranexamic acid and control solution (both colourless) were prepared and provided in identical disposable syringes tagged with number codes for allocation concealment and blinding by an independent hospital pharmacist."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	Double-blind
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Sa-Ngasoongsong 2011

Methods	Randomised placebo-controlled trial Setting: Thailand
Participants	48 patients undergoing knee arthroplasty • Topical TXA group (n=24); M/F=2/22; mean age (sd)=69.0 (8.2) • Control group (n=24); M/F=6/18; mean age (sd)=69.2 (7.6)

Sa-Ngasoongsong 2011 (*Continued*)

Interventions	• Topical TXA group: 25ml (250mg of TXA in 5ml volume and 20ml of saline) solution injected into knee joint after completion of fascial closure • Control group: placebo (saline)
Outcomes	Blood loss Blood transfusion Deep vein thrombosis Functional outcome
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blinded trial (patient, surgeon and outcome assessor)
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	Triple-blinded trial (patient, surgeon and outcome assessor)
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions or dropouts
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions or dropouts
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions or dropouts
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Saberi 2010

Methods	Randomised placebo-controlled trial Setting: Iran
Participants	100 patients undergoing spinal surgery • Topical TXA group (n=50); M/F=21/29; mean age (sd)=42.78 (11.52) • Control group (n=50); M/F=18/32; mean age (sd)=39.70 (8.46)
Interventions	• Topical TXA group: 250mg in 5ml solution poured into the surgical site ar the end of the operation, left for 5 minutes before surgical closure • Control group: placebo (saline)
Outcomes	Blood loss Length of hospital stay Blood transfusion Side effects
Notes	Article in Persian

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported

Saberi 2010 (*Continued*)

Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Seo 2012

Methods	Randomised placebo-controlled trial Setting: South Korea
Participants	150* patients undergoing knee arthroplasty • Topical TXA group (n=50); M/F=5/45; mean age (sd)=67.5 (6.6) • Control group (n=50); M/F=5/45; mean age (sd)=67.8 (6.1) [*third group of 50 patients received intravenous TXA, not included in this review]
Interventions	• Topical TXA group: 1.5g in 100cc saline injected into the knee joint cavity while suturing • Control group: placebo (saline)
Outcomes	Blood loss Blood transfusion Deep vein thrombosis, pulmonary embolism Death Haemoglobin level
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"..using a random numbers list."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	Not described

Seo 2012 (*Continued*)

Blinding of outcome assessment (detection bias) Death	Low risk	Not described, however judged that the outcome measurement was unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Low risk	No exclusions
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions
Incomplete outcome data (attrition bias) Death	Low risk	No exclusions
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Sindet-Pedersen 1989

Methods	Randomised placebo-controlled trial Setting: Denmark and Sweden
Participants	45* patients undergoing oral surgery • Topical TXA group (n=19); M/F=11/8; mean age=55.65 • Control group (n=20); M/F=11/9; mean age=57.91 [*6 patients excluded after randomisation]
Interventions	• Topical TXA group: before suturing, the operative field was irrigated with 10ml of 4.8% solution of TXA. Patients instructed to rinse mouths with 10ml of solution for 2 minutes, 4 times a day for 7 days • Control group: placebo
Outcomes	Bleeding episodes Haematology and coagulation variables
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random numbers were used to assign consecutive patients to treatment groups."
Allocation concealment (selection bias)	Unclear risk	Not described

Sindet-Pedersen 1989 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial described as double-blind
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Tibbelin 1995

Methods	Randomised placebo-controlled trial Setting: Sweden	
Participants	68 patients with epistaxis • Topical TXA group (n=30); M/F=21/14; mean age (range)=50 (23-89) • Control group (n=38); M/F=28/10; mean age (range)=65 (21-88)	
Interventions	• Topical TXA group: gel (15ml) containing 10% TXA applied to the nasal cavity • Control group: placebo gel	
Outcomes	Re-bleeding Patients' acceptance of treatment	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Tibbelin 1995 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	No data on this outcome reported
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Van Elst 2013

Methods	Randomised placebo-controlled trial Setting: Belgium
Participants	67 patients undergoing hip arthroplasty • Topical TXA group 1 (n=22); M/F=NR; mean age=NR • Topical TXA group 2 (n=19); M/F=NR; mean age=NR • Control group (n=26); M/F=NR; mean age=NR
Interventions	• Topical TXA group 1: 3g TXA administered intra-articularly 15 minutes before opening of the drain • Topical TXA group 2: 3g TXA administered intra-articularly 2 hours before opening of the drain • Control group: placebo

Outcomes	Blood loss (estimated) Thromboembolic events Transfusion need Post-operative swelling and pain Length of hospital stay	
Notes	Conference abstract	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	Described as double-blind
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Wong 2010

Methods	Randomised placebo-controlled trial Setting: Canada
Participants	124 patients undergoing total knee arthroplasty • Topical TXA group 1 (n=44): M/F=6/25; mean age (sd)=67 (11.9) • Topical TXA group 2 (n=40): M/F=14/19; mean age (sd)=63.9 (10.6) • Control group (n=40): M/F=13/22; mean age (sd)=68.4 (10.4)
Interventions	• Topical TXA group 1: 1.5g TXA in 100ml saline, left in place for 5 minutes • Topical TXA group 2: 3g TXA in 100ml saline, in place for 5 minutes • Control group: placebo
Outcomes	Blood loss (estimated) Receipt of blood transfusion Thromboembolic events Surgical infections Length of hospital stay Joint function
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patients, surgeons, anaesthesiologists, health-care providers, research personnel, and outcome assessors were blinded to the randomization."
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Low risk	"The patients, surgeons, anaesthesiologists, health-care providers, research personnel, and outcome assessors were blinded to the randomization."
Blinding of outcome assessment (detection bias) Death	Low risk	"The patients, surgeons, anaesthesiologists, health-care providers, research personnel, and outcome assessors were blinded to the randomization."
Incomplete outcome data (attrition bias) Blood loss	Unclear risk	Blood loss was estimated from difference between pre and post operative haemoglobin level and not included in meta-analysis

Wong 2010 (*Continued*)

Incomplete outcome data (attrition bias) Receipt of blood transfusion	High risk	18 patients who did not receive the assigned intervention were excluded after randomisation (13 from topical TXA group 1, 6 from topical TXA group 2, and 5 from the control group
Incomplete outcome data (attrition bias) Thromboembolic events	High risk	18 patients who did not receive the assigned intervention were excluded after randomisation (13 from topical TXA group 1, 6 from topical TXA group 2, and 5 from the control group
Incomplete outcome data (attrition bias) Death	High risk	18 patients who did not receive the assigned intervention were excluded after randomisation (13 from topical TXA group 1, 6 from topical TXA group 2, and 5 from the control group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Yasim 2005

Methods	Randomised placebo-controlled trial Setting: Turkey
Participants	30* patients undergoing total knee arthroplasty • Topical TXA group (n=10): M/F=6/4; mean age (sd)=50.5 (14.3) • Control group (n=10): M/F=5/5; mean age (sd)=51.7 (10.4) [*third group of 10 patients received aprotinin, not included in this review]
Interventions	• Topical TXA group: 1g of TXA in 100ml saline poured into pericardial space • Control group: placebo (saline)
Outcomes	Blood loss Amount of blood transfused
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Yasim 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Blood loss, receipt of blood transfusion, thromboembolic events	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Death	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Blood loss	Low risk	No exclusions reported
Incomplete outcome data (attrition bias) Receipt of blood transfusion	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Thromboembolic events	Unclear risk	No data on this outcome reported
Incomplete outcome data (attrition bias) Death	Unclear risk	No data on this outcome reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bernardoni-Socorro 1998	Not randomised
Borea 1993	Intervention also included variation in level of anti-coagulant treatment
Carter 2003	Both groups received TXA
Falbe-Hansen 1974	Unable to determine if allocation was random
Hegde 2013	Not randomised
Maniar 2012	All groups received TXA
Mutsuzaki 2012	Not randomised

(*Continued*)

Timocin 1996	Not randomised

Characteristics of ongoing studies *[ordered by study ID]*

NCT01260818

Trial name or title	Prospective Randomized Trial Comparing Topical Tranexamic Acid Plus Standard Of Care Versus Standard Of Care For The Reduction Of Blood Loss Following Primary Total Hip Arthroplasty Surgery
Methods	Randomised, single-blind, placebo-controlled trial. Planned sample size=100
Participants	Patients aged 18-90 years undergoing total hip arthroplasty
Interventions	1g TXA in 100ml saline administered to wound 2 hours before drainage is opened
Outcomes	Blood loss Haemoglobin levels No. of patients receiving transfusion
Starting date	December 2010
Contact information	Yong Li, First Affiliated Hospital of Guangzhou TCM University (liyong1949@gmail.com)
Notes	

NCT01519245

Trial name or title	Topical Application of Tranexamic Acid to Reduce Post-operative Bleeding in Coronary Artery Bypass Surgery
Methods	Randomised, double-blind, placebo-controlled trial. Planned sample size=44
Participants	Patients aged 18 years and over undergoing elective or urgent coronary artery bypass surgery
Interventions	2g TXA in 50ml of saline poured over the heart prior to sternotomy closure
Outcomes	Blood loss No. of transfusions
Starting date	December 2011
Contact information	Kelsey Brose MD, Division of haematology, University of Saskatchewan
Notes	

NCT01683955

Trial name or title	Topical Tranexamic Acid and Acute Blood Loss in Total Hip Arthroplasty
Methods	Randomised, double-blind, placebo-controlled trial. Planned sample size=101
Participants	Patients aged 18 years and over undergoing total hip arthroplasty
Interventions	2g TXA in 100ml applied during surgery
Outcomes	Blood loss Transfusion rate No. units transfused
Starting date	June 2011
Contact information	Michael Laker MD, Henry Ford Health Systems
Notes	

NCT01727843

Trial name or title	Phase III Examining the Topical Application of Tranexamic Acid and Postoperative Blood Loss in Femoral Neck Fractures: a Randomized Control Trial
Methods	Randomised, double-blind, placebo-controlled trial. Planned sample size=126
Participants	Patients aged 65-95 years undergoing surgery for femoral neck fracture repair
Interventions	3g TXA applied directly to the wound at the end of the procedure
Outcomes	Blood loss
Starting date	April 2013
Contact information	granth@queensu.ca
Notes	

TRANX-H

Trial name or title	Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement: a randomised controlled trial (TRANX-H)
Methods	Randomised, double-blind, placebo-controlled trial. Planned sample size=158
Participants	Patients undergoing primary total hip replacement
Interventions	TXA sprayed topically into the exposed tissue around the hip joint prior to wound closure

TRANX-H (*Continued*)

Outcomes	Blood transfusion Blood loss Haemoglobin and haematocrit Quality of life Length of stay
Starting date	August 2009
Contact information	Antoni Nargol, the North Tees & Hartlepool University Hospital, UK
Notes	

DATA AND ANALYSES

Comparison 1. Topical tranexamic acid versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood loss	18	1651	Ratio (Fixed, 95% CI)	0.71 [0.69, 0.72]
1.1 Cardiac surgery	7	511	Ratio (Fixed, 95% CI)	0.63 [0.61, 0.66]
1.2 Knee arthroplasty	5	427	Ratio (Fixed, 95% CI)	0.57 [0.53, 0.62]
1.3 Orthognathic surgery	1	40	Ratio (Fixed, 95% CI)	0.93 [0.73, 1.20]
1.4 Otolaryngological surgery	2	456	Ratio (Fixed, 95% CI)	0.74 [0.73, 0.76]
1.5 Spinal surgery	2	130	Ratio (Fixed, 95% CI)	0.50 [0.43, 0.58]
1.6 Thoracic surgery	1	87	Ratio (Fixed, 95% CI)	0.95 [0.86, 1.05]
2 Estimated blood loss			Other data	No numeric data
3 Mortality	9	894	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.06, 1.34]
4 Myocardial infarction	6	362	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.08]
5 Stroke	5	441	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.96]
6 Deep vein thrombosis	9	789	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.31, 1.57]
7 Pulmonary embolism	8	741	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.09, 3.15]
8 Blood transfusion	15	1623	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.46, 0.65]

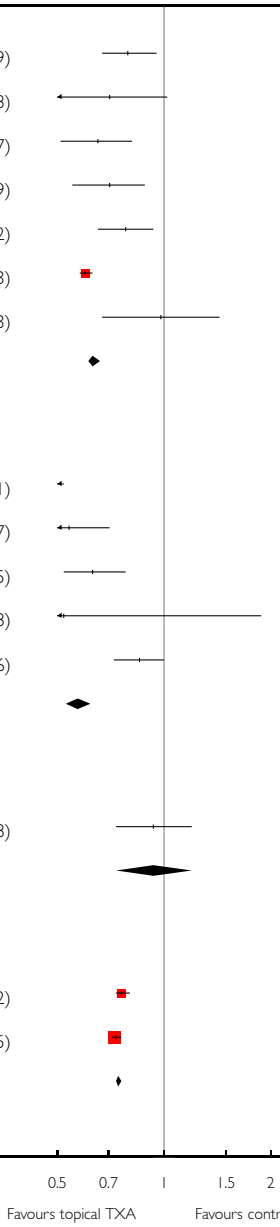
Analysis 1.1. Comparison 1 Topical tranexamic acid versus control, Outcome 1 Blood loss.

Review: Topical application of tranexamic acid for the reduction of bleeding

Comparison: 1 Topical tranexamic acid versus control

Outcome: 1 Blood loss

Study or subgroup	Topical TXA N	Control N	log [Ratio] (SE)	Ratio IV,Fixed,95% CI	Weight	Ratio IV,Fixed,95% CI
1 Cardiac surgery						
Baric 2007	97	96	-0.231 (0.089)		1.3 %	0.79 [0.67, 0.95]
Fawzy 2009	19	19	-0.351 (0.188)		0.3 %	0.70 [0.49, 1.02]
Kurt 2011	20	20	-0.435 (0.117)		0.7 %	0.65 [0.51, 0.81]
Nouraei 2013	40	40	-0.356 (0.119)		0.7 %	0.70 [0.55, 0.88]
De Bonis 2000	20	20	-0.248 (0.092)		1.2 %	0.78 [0.65, 0.93]
Abul-Azm 2006	50	50	-0.503 (0.023)		18.9 %	0.60 [0.58, 0.63]
Yasim 2005	10	10	-0.02 (0.193)		0.3 %	0.98 [0.67, 1.43]
Subtotal (95% CI)	**256**	**255**			**23.3 %**	**0.63 [0.61, 0.66]**
Heterogeneity: Chi^2 = 21.76, df = 6 (P = 0.001); I^2 =72%						
Test for overall effect: Z = 22.29 (P < 0.00001)						
2 Knee arthroplasty						
Roy 2012	25	25	-0.769 (0.061)		2.7 %	0.46 [0.41, 0.52]
Sa-Ngasoongsong 2011	24	24	-0.621 (0.137)		0.5 %	0.54 [0.41, 0.70]
Alshryda 2013	64	65	-0.457 (0.105)		0.9 %	0.63 [0.52, 0.78]
Seo 2012	50	50	-0.658 (0.658)		0.0 %	0.52 [0.14, 1.88]
Ishida 2011	50	50	-0.166 (0.086)		1.4 %	0.85 [0.72, 1.00]
Subtotal (95% CI)	**213**	**214**			**5.5 %**	**0.57 [0.53, 0.62]**
Heterogeneity: Chi^2 = 33.89, df = 4 (P<0.00001); I^2 =88%						
Test for overall effect: Z = 13.01 (P < 0.00001)						
3 Orthognathic surgery						
Kaewpradub 2011	20	20	-0.068 (0.128)		0.6 %	0.93 [0.73, 1.20]
Subtotal (95% CI)	**20**	**20**			**0.6 %**	**0.93 [0.73, 1.20]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
4 Otolaryngological surgery						
Jabalameli 2006	26	30	-0.272 (0.022)		20.6 %	0.76 [0.73, 0.80]
Albirmawy 2013	200	200	-0.309 (0.015)		44.4 %	0.73 [0.71, 0.76]
Subtotal (95% CI)	**226**	**230**			**65.0 %**	**0.74 [0.73, 0.76]**
Heterogeneity: Chi^2 = 1.93, df = 1 (P = 0.16); I^2 =48%						



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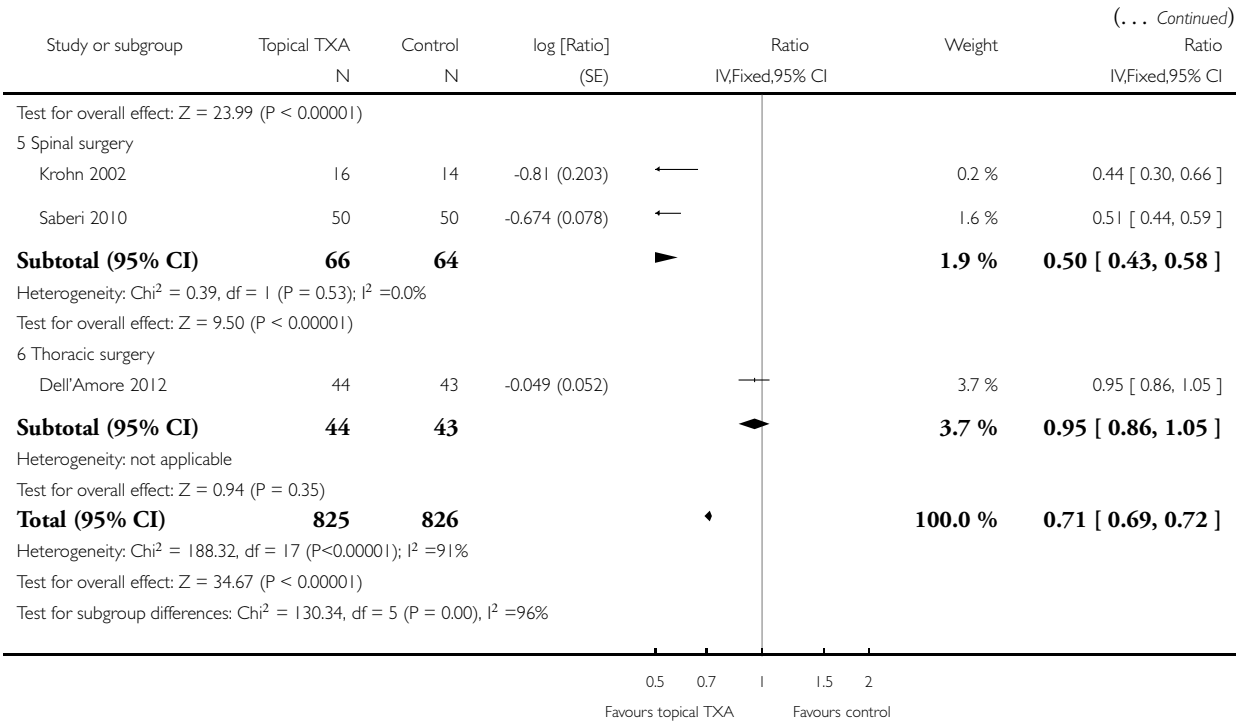


Analysis 1.2. Comparison 1 Topical tranexamic acid versus control, Outcome 2 Estimated blood loss.

Estimated blood loss

Study	Blood loss (ml) in topical TXA gp (mean, sd)	Blood loss (ml) in control gp (mean, sd)	Mean difference (95% CI)	Test for effect (P value)
Alshryda 2013	297(196); n=64	465(298); n=65	-168.00 (-254.91 to -81.09)	0.0002
Georgiadis 2013	940.2(327.1); n=50	1293.1(532.7); n=51	-352.90 (-524.93 to 180.87)	<0.0001
Wong 2010	1g: 1295(349); n=31 3g: 1208(367); n=33	1610(378); n=35	-315.00 (-490.43 to -139.57) -402.00 (-579.09 to -224.91)	0.0004 <0.0001

Analysis 1.3. Comparison 1 Topical tranexamic acid versus control, Outcome 3 Mortality.

Review: Topical application of tranexamic acid for the reduction of bleeding

Comparison: 1 Topical tranexamic acid versus control

Outcome: 3 Mortality

Study or subgroup	Topical TXA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abul-Azm 2006	1/50	4/50		57.0 %	0.25 [0.03, 2.16]
Alshryda 2013	0/79	0/78			Not estimable
Baric 2007	1/97	3/96		43.0 %	0.33 [0.03, 3.12]
De Bonis 2000	0/20	0/20			Not estimable
Dell'Amore 2012	0/44	0/43			Not estimable
Fawzy 2009	0/19	0/19			Not estimable
Nouraei 2013	0/40	0/40			Not estimable
Seo 2012	0/50	0/50			Not estimable
Wong 2010	0/64	0/35			Not estimable
Total (95% CI)	**463**	**431**		**100.0 %**	**0.28 [0.06, 1.34]**

Total events: 2 (Topical TXA), 7 (Control)

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 1.59 (P = 0.11)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Topical tranexamic acid versus control, Outcome 4 Myocardial infarction.

Review: Topical application of tranexamic acid for the reduction of bleeding

Comparison: 1 Topical tranexamic acid versus control

Outcome: 4 Myocardial infarction

Study or subgroup	Topical TXA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Bonis 2000	0/20	1/20		49.7 %	0.33 [0.01, 7.72]
Dell'Amore 2012	0/44	1/43		50.3 %	0.33 [0.01, 7.79]
Fawzy 2009	0/19	0/19			Not estimable
Nouraei 2013	0/40	0/40			Not estimable
Roy 2012	0/25	0/25			Not estimable
Van Elst 2013	0/41	0/26			Not estimable
Total (95% CI)	**189**	**173**		**100.0 %**	**0.33 [0.04, 3.08]**

Total events: 0 (Topical TXA), 2 (Control)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Topical tranexamic acid versus control, Outcome 5 Stroke.

Review: Topical application of tranexamic acid for the reduction of bleeding

Comparison: 1 Topical tranexamic acid versus control

Outcome: 5 Stroke

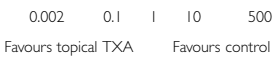
Study or subgroup	Topical TXA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alshryda 2013	0/79	1/78		100.0 %	0.33 [0.01, 7.96]
Dell'Amore 2012	0/44	0/43			Not estimable
Nouraei 2013	0/40	0/40			Not estimable
Roy 2012	0/25	0/25			Not estimable
Van Elst 2013	0/41	0/26			Not estimable
Total (95% CI)	**229**	**212**		**100.0 %**	**0.33 [0.01, 7.96]**

Total events: 0 (Topical TXA), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.49)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Topical tranexamic acid versus control, Outcome 6 Deep vein thrombosis.

Review: Topical application of tranexamic acid for the reduction of bleeding

Comparison: 1 Topical tranexamic acid versus control

Outcome: 6 Deep vein thrombosis

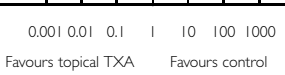
Study or subgroup	Topical TXA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alshryda 2013	2/79	0/78		3.8 %	4.94 [0.24, 101.22]
Dell'Amore 2012	0/44	0/43			Not estimable
Georgiadis 2013	4/50	9/51		67.5 %	0.45 [0.15, 1.38]
Nouraei 2013	0/40	0/40			Not estimable
Roy 2012	0/25	0/25			Not estimable
Sa-Ngasoongsong 2011	0/24	0/24			Not estimable
Seo 2012	0/50	2/50		18.9 %	0.20 [0.01, 4.06]
Van Elst 2013	0/41	0/26			Not estimable
Wong 2010	3/64	1/35		9.8 %	1.64 [0.18, 15.19]
Total (95% CI)	**417**	**372**		**100.0 %**	**0.69 [0.31, 1.57]**

Total events: 9 (Topical TXA), 12 (Control)

Heterogeneity: $Chi^2 = 3.41$, df = 3 (P = 0.33); $I^2 = 12\%$

Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Topical tranexamic acid versus control, Outcome 7 Pulmonary embolism.

Review: Topical application of tranexamic acid for the reduction of bleeding

Comparison: 1 Topical tranexamic acid versus control

Outcome: 7 Pulmonary embolism

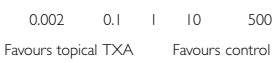
Study or subgroup	Topical TXA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Georgiadis 2013	1/50	2/51		60.5 %	0.51 [0.05, 5.45]
Wong 2010	1/64	1/35		39.5 %	0.55 [0.04, 8.48]
Roy 2012	0/25	0/25			Not estimable
Alshryda 2013	0/79	0/78			Not estimable
Dell'Amore 2012	0/44	0/43			Not estimable
Nouraei 2013	0/40	0/40			Not estimable
Van Elst 2013	0/41	0/26			Not estimable
Seo 2012	0/50	0/50			Not estimable
Total (95% CI)	**393**	**348**		**100.0 %**	**0.52 [0.09, 3.15]**

Total events: 2 (Topical TXA), 3 (Control)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 0.70 (P = 0.48)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Topical tranexamic acid versus control, Outcome 8 Blood transfusion.

Review: Topical application of tranexamic acid for the reduction of bleeding

Comparison: 1 Topical tranexamic acid versus control

Outcome: 8 Blood transfusion

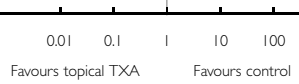
Study or subgroup	Topical TXA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wong 2010	5/64	9/35		5.7 %	0.30 [0.11, 0.84]
Baric 2007	51/97	51/96		25.1 %	0.99 [0.76, 1.29]
Alshryda 2013	1/79	13/78		6.4 %	0.08 [0.01, 0.57]
Sa-Ngasoongsong 2011	1/24	8/24		3.9 %	0.13 [0.02, 0.92]
Roy 2012	2/25	7/25		3.4 %	0.29 [0.07, 1.24]
Georgiadis 2013	0/50	4/51		2.2 %	0.11 [0.01, 2.05]
Fawzy 2009	14/19	13/19		6.4 %	1.08 [0.72, 1.62]
Albirmawy 2013	0/200	2/200		1.2 %	0.20 [0.01, 4.14]
Nouraei 2013	15/40	21/40		10.3 %	0.71 [0.43, 1.17]
De Bonis 2000	3/20	4/20		2.0 %	0.75 [0.19, 2.93]
Seo 2012	10/50	47/50		23.0 %	0.21 [0.12, 0.37]
Saberi 2010	0/50	0/50			Not estimable
Krohn 2002	2/16	9/14		4.7 %	0.19 [0.05, 0.75]
Dell'Amore 2012	8/44	10/43		5.0 %	0.78 [0.34, 1.79]
Ishida 2011	0/50	1/50		0.7 %	0.33 [0.01, 7.99]
Total (95% CI)	**828**	**795**		**100.0 %**	**0.55 [0.46, 0.65]**

Total events: 112 (Topical TXA), 199 (Control)

Heterogeneity: $Chi^2 = 54.48$, df = 13 ($P<0.00001$); $I^2 = 76\%$

Test for overall effect: $Z = 6.55$ ($P < 0.00001$)

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies

Cochrane Injuries Group Specialised Register

(tranexamic or "Cyclohexanecarboxylic Acid*" or Methylamine* or amcha or "trans-4-aminomethyl-cyclohexanecarboxylic acid*" or t-amcha or amca or "kabi 2161" or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or "ugurol oramino methylcyclohexane carboxylate" or "aminomethylcyclohexanecarbonic acid" or "aminomethylcyclohexanecarboxylic acid" or AMCHA or amchafibrin 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) AND (topical* or intra-articular* or intraarticular* or irrigat* or mouthwash* or rins* or intra-nasal* or intranasal* or rectal* or intra-vaginal* or intravaginal* or spray*)

Cochrane Central Register of Controlled Trials (*The Cochrane Library)*

#1MeSH descriptor: [Antifibrinolytic Agents] explode all trees

#2MeSH descriptor: [Tranexamic Acid] explode all trees

#3(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin*):ti,ab,kw (Word variations have been searched)

#4(plasmin or fibrinolysis) near/3 (inhibitor*):ti,ab,kw (Word variations have been searched)

#5#3 or #4

#6(tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin 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):ti,ab,kw (Word variations have been searched)

#7#1 or #2 or #5 or #6

#8MeSH descriptor: [Administration, Topical] explode all trees

#9topical* or intra-articular* or intraarticular* or (local* near/3 appl*) or irrigat* or mouthwash* or rins* or intra-nasal* or intranasal* or rectal* or intra-vaginal* or intravaginal* or spray*:ti,ab,kw (Word variations have been searched)

#10#8 or #9

#11#7 and #10

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R)

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 Acid* or Methylamine* or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin 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).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

Embase Classic + Embase

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 Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin 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).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*).ti,ab.
8. 6 or 7
9. 5 and 8
10. exp Randomized Controlled Trial/
11. exp controlled clinical trial/
12. exp controlled study/
13. comparative study/
14. randomi?ed.ab,ti.
15. placebo.ab.
16. *Clinical Trial/
17. exp major clinical study/
18. randomly.ab.
19. (trial or study).ti.
20. 10 or 11 or 12 or 14 or 15 or 16 or 17 or 18 or 19
21. exp animal/ not (exp human/ and exp animal/)
22. 20 not 21
23. 9 and 22
24. limit 23 to embase

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED)

ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S)

#16 #15 AND #11 AND #6
#15 #14 OR #13 OR #12
#14 TS=(local* near/3 appl*)
#13 TS=(irrigat* or mouthwash* or rins* or intra-nasal* or intranasal* or rectal* or intra-vaginal* or intravaginal* or spray*)

#12 TS= (topical* OR intra-articular* OR intraarticular*)
#11 #10 OR #9 OR #8 OR #7
#10 TS=(AMCHA or amchafibrin 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)
#9 TS=(tranexamic or 'Cyclohexanecarboxylic Acid*' or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or 'kabi 2161' or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or 'ugurol oramino methylcyclohexane carboxylate' or 'aminomethylcyclohexanecarbonic acid' or 'aminomethylcyclohexanecarboxylic acid')
#8 TS=(((plasmin or fibrinolysis) n3 inhibitor*))
#7 TS=(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin*)
#6 #5 AND #4
#5 TS=(human*)
#4 #3 OR #2 OR #1
#3 TS=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))
#2 TS=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)
#1 TS=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial)

PubMed

((((((((((“Comparative Study”[Publication Type]) OR “Randomized Controlled Trial”[Publication Type]) OR “Controlled Clinical Trial”[Publication Type])) OR (((((((randomized[Title/Abstract]) OR randomised[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR study[Title/Abstract]) OR group*[Title/Abstract]))) NOT ((“Animals”[Mesh]) NOT (“Animals”[Mesh] AND “Humans”[Mesh])))) AND ((((((((local[Title/Abstract]) AND application[Title/Abstract])) OR (“local application”[title/abstract])) OR (topical*[title/abstract] OR intra-articular*[title/abstract] OR intraarticular*[title/abstract] OR irrigat*[title/abstract] OR mouthwash*[title/abstract] OR rins*[title/abstract] OR intra-nasal*[title/abstract] OR intranasal*[title/abstract] OR rectal*[title/abstract] OR intra-vaginal*[title/abstract] OR intravaginal*[title/abstract] OR spray*[title/abstract])) OR (“Administration, Topical”[Mesh]))) AND ((((((“Antifibrinolytic Agents”[Mesh]) OR “Tranexamic Acid”[Mesh])) OR (anti-fibrinolytic*[title/abstract] OR antifibrinolytic*[title/abstract] OR antifibrinolysin*[title/abstract] OR anti-fibrinolysin*[title/abstract] OR antiplasmin*[title/abstract] OR anti-plasmin*[title/abstract])) OR (((inhibitor[title/abstract])) AND (plasmin[title] OR fibrinolysis[title/abstract])))) OR (tranexamic[title/abstract] OR “Cyclohexanecarboxylic Acid*”[title/abstract] OR Methylamine*[title/abstract] OR “trans-4-aminomethyl-cyclohexanecarboxylic acid*”[title/abstract] OR t-amcha[title/abstract] OR amca[title/abstract] OR “kabi 2161”[title/abstract] OR transamin*[title/abstract] OR exacyl[title/abstract] OR amchafibrin[title/abstract] OR spotof[title/abstract] OR cyklokapron[title/abstract] OR “ugurol oramino methylcyclohexane carboxylate”[title/abstract] OR “aminomethylcyclohexanecarbonic acid”[title/abstract] OR “aminomethylcyclohexanecarboxylic acid”[title/abstract] OR AMCHA[title/abstract] OR amchafibrin[title/abstract] OR amikapron[title/abstract] OR “aminomethyl cyclohexane carboxylic acid”[title/abstract] OR “aminomethyl cyclohexanecarboxylic acid”[title/abstract] OR “aminomethylcyclohexane carbonic acid”[title/abstract] OR “aminomethylcyclohexane carboxylic acid”[title/abstract] OR “aminomethylcyclohexanecarbonic acid”[title/abstract] OR “aminomethylcyclohexanecarboxylic acid”[title/abstract] OR “aminomethylcyclohexanocarboxylic acid”[title/abstract] OR “aminomethylcyclohexanoic acid”[title/abstract] OR amstat[title/abstract] OR anvitoff[title/abstract] OR cl?65336[title/abstract] OR cl65336[title/abstract] OR cyclocapron[title/abstract] OR cyclokapron[title/abstract] OR cyklocapron[title/abstract] OR exacyl[title/abstract] OR frenolyse[title/abstract] OR hexacapron[title/abstract] OR hexakapron[title/abstract] OR tranex[title/abstract] OR TXA[title/abstract])))))) NOT (MEDLINE[SB])

Clinical trials registries

(randomised or randomized) AND (antifibrinolytic or anti-fibrinolytic or “tranexamic acid”)
AND
Study design: Interventional

CONTRIBUTIONS OF AUTHORS

KK and IR conceived and designed the study. DB designed and conducted the electronic searches. KK and IR screened the search output. KK and DB assessed trials for eligibility, extracted data and assessed risk of bias. KK carried out the analyses. KK wrote the manuscript, incorporating comments from IR and DB into the final draft.

DECLARATIONS OF INTEREST

None known

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Disclaimer:
The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, the UK National Health Service (NHS) or the UK Department of Health.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Antifibrinolytic Agents [*administration & dosage]; Blood Loss, Surgical [*prevention & control]; Epistaxis [*drug therapy]; Hemorrhage [drug therapy]; Randomized Controlled Trials as Topic; Tranexamic Acid [*administration & dosage]

MeSH check words

Humans