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Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer (Review)

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TABLE OF CONTENTS

[Intervention Review]

Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

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ABSTRACT

Background

Ovarian cancer is the third most common gynaecological cancer worldwide, with an age-standardised incidence rate of 6.1 per 10,000 women. Standard therapy for advanced epithelial ovarian cancer (EOC) includes a combination of cytoreductive surgery and platinum-based chemotherapy. Cytoreductive surgery aims to remove as much of the visible tumour as possible. As extensive intraperitoneal metastases are typical of advanced EOC, cytoreductive surgery is usually an extensive procedure with the risk of excessive bleeding. Tranexamic acid given perioperatively is effective in reducing blood loss and allogeneic blood transfusion requirements in a variety of surgical settings. Therefore, tranexamic acid seems to be a promising agent for minimising blood loss and the need for blood transfusion among women with advanced EOC undergoing cytoreductive surgery.

Objectives

To assess the effects of tranexamic acid for reducing blood loss associated with cytoreductive surgery in women with advanced EOC (stage III to IV).

Search methods

We searched the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Trial Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 5, 2015), MEDLINE, EMBASE and conference proceedings to May 2015. We also checked registers of clinical trials, citation lists of included studies, key textbooks and previous systematic reviews for potentially relevant studies.

Selection criteria

We included randomised controlled trials (RCTs) comparing tranexamic acid given during surgery versus placebo or no treatment, in adult women diagnosed with advanced EOC.

Data collection and analysis

Two review authors (CK, AS) independently selected potentially relevant trials, extracted data, assessed risk of bias, compared results and resolved disagreements by discussion.

Main results

We found only one study that met our inclusion criteria. This was a randomised double blind, placebo-controlled multicentre study conducted to evaluate the effectiveness of a single dose of intravenous tranexamic acid (15 mg/kg body weight) versus placebo, given

immediately before surgery for reducing blood loss and the need for red blood cell transfusion. The mean total estimated blood loss was 668.34 mL and 916.93 mL for participants assigned to tranexamic acid and placebo groups, respectively. The mean difference (MD) of total estimated blood loss between the groups did not show a clinically important effect (MD − 248.59 mL; 95% confidence interval (CI) − 550.9 to 53.79; one study, 100 participants; moderate quality evidence). The mean number of transfused units of blood components was not different between the two groups (low quality evidence). There were no noted differences in the incidence of reoperation, readmission or thromboembolic events (very low quality evidence). We considered the methodology of the included study to be at low risk of selection, detection, and reporting biases. However, we were concerned about an imbalance of some baseline characteristics between the groups, and as there was no protocol for blood transfusion, the rate of blood transfusion may vary depending on the practice of each participating hospital.

Authors' conclusions

Currently, there is insufficient evidence to recommend the routine use of tranexamic acid for reducing blood loss in women undergoing cytoreductive surgery for advanced EOC, as only limited data are available from a single, low quality RCT at low overall risk of bias.

PLAIN LANGUAGE SUMMARY

Does tranexamic acid given before an operation reduce blood loss for women with advanced ovarian cancer?

The issue:
Cytoreductive surgery (also called debulking) is a standard surgical procedure for advanced epithelial ovarian cancer. During surgery, the aim is to remove not only the ovaries, but also the uterus, fallopian tubes, and as much of the visible tumour as possible. Blood loss during cytoreductive surgery has long been recognised as a contributor to prolonged recovery time.

The aim of the review:
We evaluated the effectiveness and safety of tranexamic acid for reducing blood loss during cytoreductive surgery in women with advanced epithelial ovarian cancer. We searched for scientific research studies up to May 2015 and found only one randomised controlled trial – considered the gold standard for study design – that assessed a single dose of tranexamic acid given intravenously before the start of surgery versus a placebo in women undergoing cytoreductive surgery for clinically suspected advanced advanced epithelial ovarian cancer.

What are the main findings and conclusion?
Although tranexamic acid did numerically reduce blood loss, there was no clinical benefit, as the difference in blood loss was minimal, and there was no difference in need for blood transfusion, suggesting that this level of blood loss did not make a difference to the patient's well-being. Additionally, there was incomplete and limited evidence regarding tranexamic acid-related adverse events, so we can say little about whether tranexamic acid is safe for women with advanced ovarian cancer. The evidence we found from a single study was therefore insufficient to support routinely giving prophylactic tranexamic acid for cytoreductive surgery. This review indicates the need for future good quality, well-designed randomised controlled trials to provide more evidence on the effectiveness, safety and appropriate administration of tranexamic acid.

Quality of evidence:
The quality of the evidence was variable; therefore the overall the strength of the evidence reported in this review is low, as it is based on only one small randomised controlled study.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer

Patient or population: adult women with advanced EOC undergoing cytoreductive surgery (one randomised trial available)

Settings: 2 university hospitals and 2 central hospitals in the southeast health region of Sweden

Intervention: a single dose of tranexamic acid (15 mg/kg body weight, 100 mg/mL tranexamic acid) immediately before the start of surgery

Comparison: placebo prepared in the identical package

Note: The trial protocol allowed the use of supplemental tranexamic acid (20% of participants of each group received supplemental tranexamic acid during surgery.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Tranexamic acid				
Estimated total blood loss (mL)	Mean 916.93	Mean 248.59 lower (95% CI, 550.9 lower to 53.8 higher)	MD -248.59 (−550.97 to 53.79)	100 (1 study)	⊕⊕⊖⊖ low[1,2]	Trial authors provided additional data. See Table 1.
Number of transfused units of red blood cell (RBC)	Mean 0.76	Mean 0.30 lower (95% CI, 0.88 lower to 0.28 higher)	MD − 0.30 (−0.88 to 0.28)	100 (1 study)	⊕⊕⊖⊖ low[1,3]	38 units and 53 units of RBC were transfused to women in the tranexamic acid and placebo groups, respectively. Trial authors provided additional data regarding to mean number of transfused units . See Table 1
Number of transfused units of plasma	Mean 0.28	Mean 0.12 lower (95% CI, 0.41 lower to 0.17 higher)	MD − 0.12 (−0.41 to 0.17)	100 (1 study)	⊕⊕⊖⊖ low[1,3]	Trial authors provided additional data. See Table 1.

Rate of RBC transfusion (total number of participants who required at least one unit of red blood cell transfusion) Time: perioperative and postoperative periods	**44 per 100**	**30 per 100** (18 to 51)	**RR 0.68** (0.40 to 1.15)	100 (1 study)	⊕⊕⊖⊖ low[1,3]	
Rate of plasma transfusion (total number of participants who required at least one unit of plasma transfusion) Time: perioperative and postoperative periods	**18 per 100**	**8 per 100** (3 to 24)	**RR 0.44** (0.15 to 1.35)	100 (1 study)	⊕⊕⊖⊖ low[1,3]	—
Reoperation (Number of participants with at least one reoperation) Time: perioperative periods	**12 per 100**	**10 per 100** (3 to 31)	**RR 0.83** (0.27 to 2.55)	100 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	—
Readmission (Number of participants with at least one readmission) Time: perioperative periods)	**8 per 100**	**22 per 100** (7 to 64)	**RR 2.75** (0.94 to 8.06)	100 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	—
Venous thromboembolic events (number of participants with at least one venous thromboembolic events) Time: 5-week follow-up visit	**8 per 100**	**4 per 100** (1 to 21)	**RR 0.50** (0.10 to 2.61)	100 (1 study)	⊕⊖⊖⊖ very low[1,2,4,5]	—
Arterial thromboembolic events (number of participants with at least one venous thromboembolic events) Time: 5-week follow-up visit)	**2 per 100**	**1 per 100** (0 to 16)	**RR 0.33** (0.01 to 7.99)	100 (1 study)	⊕⊖⊖⊖ very low[1,2,4,5]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD**: mean difference; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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[1]Based on the high risk of attrition bias and baseline imbalance in allocation.
[2]Wide confidence interval.
[3]The included study had no well-defined criteria or protocol for blood transfusion.
[4]Small number of events in the analysis.
[5]Only about 60% of participants in both arms underwent duplex ultrasound examination to evaluate lower extremity venous thrombosis.

BACKGROUND

Description of the condition

Ovarian cancer is the third most common gynaecological cancer worldwide, with an age-standardised incidence rate of 6.1 per 10,000 women (GLOBOCAN 2012). Epithelial ovarian cancer (EOC), arising from the surface layer of the ovary, accounts for more than 90% of all ovarian cancer and is, in the developed world, the leading cause of death among women with gynaecological cancer, with a mortality rate of more than 60%. This is largely because most women with EOC are diagnosed when the cancer is already at an advanced stage (Jemal 2008). Extensive intraperitoneal metastases are typical of advanced EOC.

Standard therapy for advanced EOC consists of cytoreductive surgery and platinum-based chemotherapy. During cytoreductive surgery (also called debulking), the aim is to remove not only the ovaries but also the uterus, fallopian tubes, and as much of the visible tumour as possible. Studies have noted that the volume of residual disease after cytoreductive surgery is an important independent prognostic factor for survival in women with EOC (Chi 2012; Vergote 2010). The median overall survival of women with advanced EOC, stratified by volume of residual disease following surgery, is 78 months for women with no macroscopic disease, 50 months when the residual disease is less than 1 cm, and 36 months when the residual disease is more than 1 cm (Chi 2012). Therefore, cytoreductive surgery, with the aim of complete resection of all visible tumour, is central to the treatment of EOC. Cytoreductive surgery can be an extensive procedure, and approximately 4.1% to 7.4% of women with advanced EOC experience excessive bleeding during the intervention, with a red blood cell transfusion rate of 30% to 40% (Lundin 2014; Vergote 2010).

Description of the intervention

Tranexamic acid, a 4-aminomethyl cyclohexane-carbolic acid, is a synthetic lysine amino acid derivative that exerts an antifibrinolytic effect through the reversible blockade of the lysine-binding sites on the plasminogen molecule to fibrin, thereby inhibiting clot degradation. Compared to other synthetic lysine analogues, tranexamic acid has a higher antifibrinolytic efficacy in peripheral tissue and a longer half-life at 3.1 hours (McCormack 2012). Tranexamic acid can be administered orally, intravenously and topically. Its role for preventing and treating excessive blood loss continues to receive attention in various surgical and trauma settings (Ker 2013; Kongnyuy 2014; Novikova 2015; Perel 2013; Roberts 2015).

How the intervention might work

Tissue injury triggers the activation of the blood clotting (haemostatic) system. Initially, the formation of thrombin stimulates the conversion of fibrinogen into fibrin. The fibrinolytic processes are subsequently activated to degrade (break down) the fibrin clot in order to maintain vascular patency (when blood vessels are unblocked or unobstructed). Fibrinolysis begins after the conversion of plasminogen into plasmin, an enzyme necessary in the breakdown of fibrin. It is stimulated by tissue plasminogen activator (t-PA) and urokinase plasminogen activator, endogenous activators of plasminogen. Plasmin activity is also modulated by various naturally occurring plasminogen activator inhibitors to achieve equilibrium between clot formation and breakdown (McCormack 2012).

Although fibrinolysis is a part of a normal physiological response to tissue damage, any disturbance in the balance between activators and inhibitors of the fibrinolytic system may result in excessive bleeding. During surgical procedures, increased activity of plasminogen activators also increases the consumption of the plasminogen activator inhibitor and in turn the premature breakdown of fibrin. In procedures that result in extensive tissue damage, this process may be excessive and result in hyperfibrinolysis. Tranexamic acid works by preventing the breakdown of blood clots and so reduces bleeding. As a result of inhibiting fibrinolysis, there is a theoretical possibility of an increased risk of thromboembolic events (blood clots that block vessels (thrombus) can break loose and be carried by the blood stream to other organs (embolism)). However, these adverse events are relatively rare. More common adverse events of tranexamic acid include nausea, vomiting, diarrhoea, dyspepsia and headache (McCormack 2012).

A number of Cochrane systematic reviews in a variety of surgical settings have reported on the perioperative administration of tranexamic acid with the aim of reducing blood loss and the need for blood transfusion (Kongnyuy 2014: Novikova 2015; Perel 2013; Roberts 2015).

In trauma patients, tranexamic acid reduced the risk of death due to bleeding by 15% (risk ratio (RR) 0.85, 95% confidence interval (CI) 0.76 to 0.96; Roberts 2015). In the emergency and urgent surgery setting, tranexamic acid reduced the probability of receiving a blood transfusion by 30% (RR 0.70, 95% CI 0.52 to 0.94; Perel 2013). The amount of postpartum blood loss also decreased in women receiving tranexamic acid compared to women receiving placebo (mean difference 75.17 mL; 95% CI 108.23 to 42.12 mL), regardless of route of delivery (Novikova 2015). Additionally, compared with placebo, tranexamic acid is an effective intervention to reduce blood loss during myomectomy for fibroids (mean difference (MD) 243 mL 95% CI 460.02 to 25.98 mL; Kongnyuy 2014). As a topical application, tranexamic acid reduces blood transfusion rates in surgical patients by 45% (RR 0.55, 95% CI 0.55 to 0.46; Ker 2013).

Why it is important to do this review

Excessive blood loss during extensive surgery puts women at risk of death and increases recovery times. Blood products are a scarce resource and are not without risks. Some previous studies have reported an independent association between receiving a perioperative blood transfusion and a higher risk of cancer recurrence (De Oliveira 2012; Schiergens 2015). As blood loss during cytoreductive surgery for ovarian cancer can be high, tranexamic acid seems to be a promising agent to reduce both it and the need for transfusion.

We hypothesise that tranexamic acid effectively reduces blood loss and blood transfusion requirements in women undergoing cytoreductive surgery for advanced EOC. However, to date there has been no systematic review evaluating the effectiveness of tranexamic acid to reduce blood loss and allogeneic blood transfusion requirements in cytoreductive surgery for advanced EOC.

OBJECTIVES

To assess the effects of tranexamic acid for reducing blood loss associated with cytoreductive surgery in women with advanced EOC (stage III to IV).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

Women aged 18 years or older undergoing cytoreductive surgery for advanced ovarian cancer. We present details of the staging classification of ovarian cancer in Appendix 1 (Prat 2015).

Types of interventions

We planned to include studies comparing tranexamic acid given during surgery versus placebo or no treatment.

Types of outcome measures

Primary outcomes

- Estimated blood loss (mL)

Secondary outcomes

- Units of blood components transfused (e.g. red blood cell and plasma)
- Length of surgery (min)
- Postoperative haemoglobin (g/L)
- Incidence of reoperation
- Incidence of readmission
- Length of hospital stay (days)
- Incidence of venous thromboembolic events (e.g. venous thrombosis, pulmonary embolism)
- Incidence of arterial thromboembolic events (e.g. arterial thrombosis, myocardial infarction, stroke)
- Incidence of nausea/vomiting/diarrhoea
- Incidence of neurological events (e.g. headache, seizure, eye or eyesight problems)
- The severity of tranexamic acid-related adverse events, as categorised according to Common Terminology Criteria for Adverse Events (CTCAE 2010)

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- Cochrane Central Register of Controlled Trial (CENTRAL) (2015, Issue 5)
- MEDLINE (1946 to May week 5, 2015)
- EMBASE (1980 to 2015 week 23)

We present the CENTRAL, MEDLINE and EMBASE search strategies in Appendix 2, Appendix 3 and Appendix 4, respectively.

Searching other resources

Unpublished and grey literature

We searched the following for ongoing trials.

- Metaregister (http://www.controlled-trials.com/rct).
- Physicians Data Query (http://www.nci.nih.gov).
- http://www.clinicaltrials.gov.
- http://www.cancer.gov/clinicaltrials.
- World Health Organization (WHO) International Clinical Trial Registry (http://apps.who.int/trialsearch/Default.aspx).

We searched electronic databases including Greynet.org (http://www.greynet.org) and the Ohio College Library Center (OCLC) WorldCat Dissertations and Theses (WorldCatDissertations) (https://www.oclc.org/support/services/firstsearch/documentation/dbdetails/details/WorldCatDissertations.en.html) to identify the possible relevant conference abstracts and proceedings.

Handsearching

We handsearched reports of conferences from the following sources.

- *Gynecologic Oncology* (Annual Meeting of the Society of Gynecologic Oncology).
- *International Journal of Gynecological Cancer* (Annual Meeting of the International Gynecologic Cancer Society).
- British Cancer Research Meeting.
- American Association for Clinical Research (AACR) Meeting.
- Annual Meeting of the European Society of Medical Oncology (ESMO).
- Annual Meeting of the American Society of Clinical Oncology (ASCO).
- Annual Meeting of the British Gynaecological Cancer Society (BGCS).
- Biennial Meeting of the Asian Society of Gynecologic Oncology (ASGO).
- Biennial Meeting of Asia and Oceania Federation of Obstetrics and Gynaecology (AOFOG).
- Biennial Meeting of the European Society of Gynaecologic Oncology (ESGO).

We also checked the citation lists of the included study and key textbooks for potentially relevant references.

We searched for papers in all languages and would have had them translated, if necessary.

Data collection and analysis

Selection of studies

Before examining the identified trials for possible inclusion, we developed and piloted a data collection form. We downloaded all titles and abstracts retrieved by electronic searching to a reference management database (EndNote) and removed duplicates. Two review authors (CK and AS) examined the remaining references independently. We excluded studies that clearly did not meet the inclusion criteria. We obtained full-text copies of potentially relevant references. Two review authors (CK and AS) independently

assessed the eligibility of the retrieved reports/publications. We resolved any disagreement through discussion or, if required, we consulted a third person (PL). We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Two review authors (CK and AS) independently extracted study characteristics and outcome data from included studies onto a pre-piloted data collection form. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We also noted the details of trial method, participant characteristics, intervention, and outcomes in the Characteristics of included studies table. We resolved disagreements by consensus or by involving a third person (PL). One review author (ML) transferred data into the Review Manager (RevMan) file (RevMan 2014). We double checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (PL) spot checked study characteristics for accuracy against the trial report.

For included studies, we extracted the following data.

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population.
  - Total number enrolled.
  - Patient characteristics.
  - Age.
  - Comorbidities.
  - Other baseline characteristics.
  - Histopathological type of ovarian cancer (according to World Health Organization classification system; Kaku 2003).
  - Stage of ovarian cancer.
  - Completeness of debulking and diameter of residual tumour deposits, if present (cm).
- Intervention details: tranexamic acid.
  - Dose of tranexamic acid.
  - Administration route and frequency, i.e. intravenous (single dose, multiple dose), oral or topical administration.
  - Timing of administration in relation to the start of the operation (knife-to-skin).
- Comparison: usual care or placebo.
  - Definition/details.
  - Additional information if appropriate.
- Outcomes: For each outcome, we extracted the outcome definition and unit of measurement (if relevant).
- Results: We extracted the number of participants allocated to each intervention group, the total number analysed for each outcome, and the missing participants. For adjusted estimates, we recorded adjusted results in analyses.
- Notes: funding of the trial, and notable conflicts of interest of the trial authors.

Results were extracted as follows.

- For dichotomous outcomes (e.g. readmission, reoperation and adverse events): We extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at the endpoint in order to estimate a risk ratio.
- For continuous outcomes (e.g. amount of blood loss and unit(s) of blood component transfused): We extracted the mean and standard deviation (SD) of the outcome of interest and the number of participants assessed in order to estimate the mean difference (MD) between treatment arms.

Where possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned.

Assessment of risk of bias in included studies

We assessed and reported on the methodological risk of bias of the included studies according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which recommends the explicit reporting of the following individual elements for RCTs.

1. Selection bias: random sequence generation and allocation concealment.
2. Performance bias: blinding of participants and personnel (participants and treatment providers).
3. Detection bias: blinding of outcome assessment.
4. Attrition bias: incomplete outcome data.
5. Reporting bias: selective reporting of outcomes.
6. Other bias.

Two review authors (CK, AS) applied the 'Risk of bias' tool independently, and we resolved differences by discussion or by appeal to a third review author (PL or ML). We judged each item as being at high, low or unclear risk of bias as set out in the criteria shown in Appendix 5 (Higgins 2011). We provided a quote from the study report or a statement as justification for our judgement. We summarised results in a 'Risk of bias' summary figure.

Measures of treatment effect

We used the following measures of the effect of treatment:

- For dichotomous outcomes, such as incidence of re-admission, we used number of events and number of participants assessed in both the intervention and comparison groups to calculate the risk ratio (RR) and 95% confidence interval (CI).
- For continuous outcomes, such as estimated blood loss, we used the mean, standard deviation (SD), and number of participants assessed in both the intervention and comparison groups to calculate the mean difference (MD) with a 95% CI.

Dealing with missing data

We did not impute missing outcome data and attempted to contact trial authors to obtain missing data if necessary.

Data synthesis

We identified only one included trial, so it was not possible to perform meta-analyses. Therefore it was not relevant to carry out the following procedures: assessing heterogeneity between the results of trials, assessing reporting biases using funnel plots, or conducting any subgroup analyses or sensitivity analyses. In future updates of the review, we will employ the methods stated in the Differences between protocol and review if we identify additional studies.

RESULTS

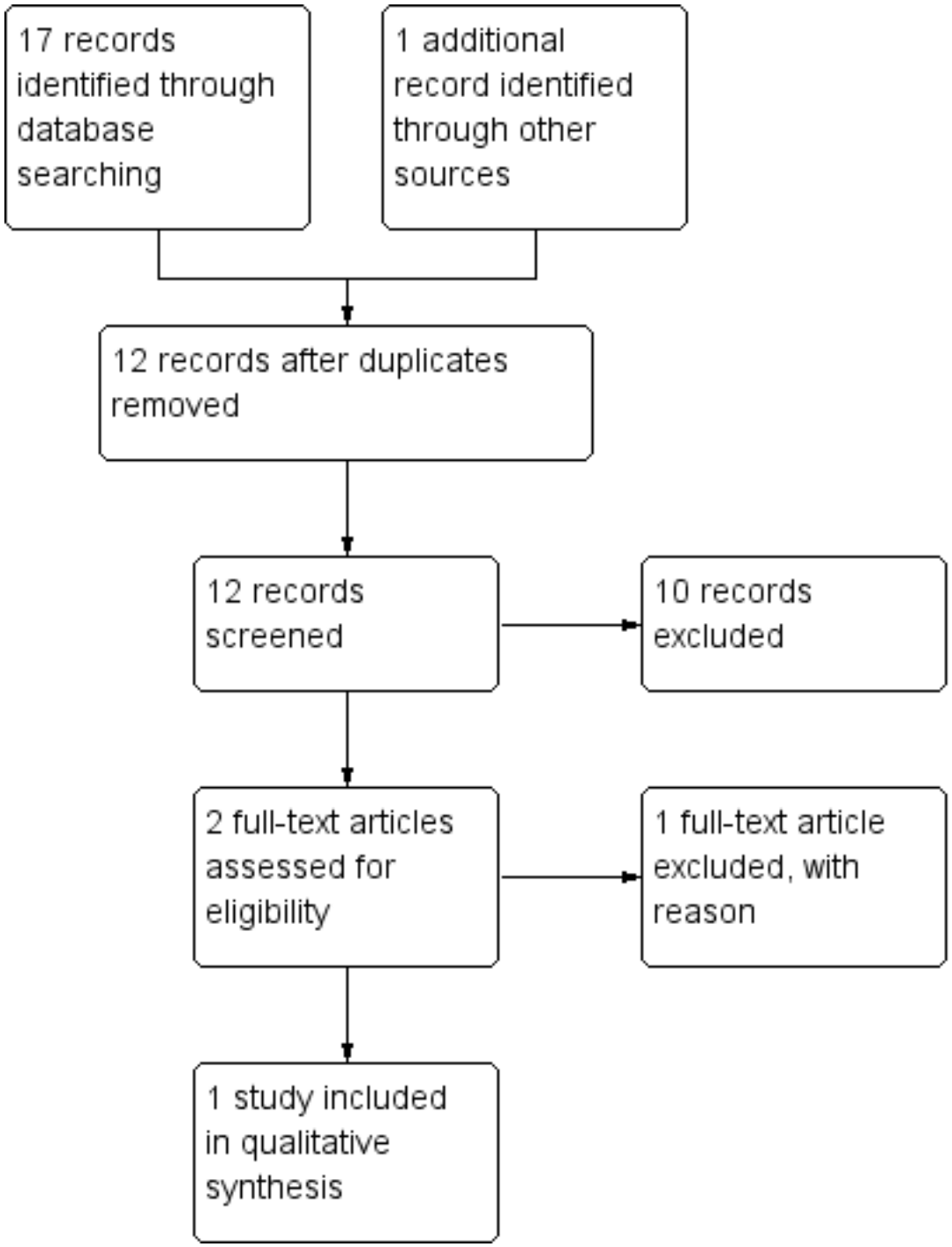
Description of studies

Results of the search

The Cochrane Central Register of Controlled Trials (CENTRAL) search yielded 2 studies; theMEDLINE search, another 2 studies; and the EMBASE search, 13 studies. We checked the reference lists and handsearched journals and congress abstracts, identifying one additional potentially relevant study. We did not identify any ongoing trials.

After excluding non-relevant and duplicated records, we retrieved two possibly eligible randomised controlled trials (RCTs) for more detailed evaluation (Celebi 2006; Lundin 2014). Only one study met the review inclusion criteria (Lundin 2014). We excluded Celebi 2006 because it was conducted in women with cervical cancer. See study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

We found one RCT that met the inclusion criteria (Lundin 2014) and present full details in 'Characteristics of included studies'.

Study design and setting

The included study was a randomised double blind, placebo-controlled multicentre study that took place in two university hospitals and two central hospitals in the southeast health region of Sweden between March 2008 and May 2012.

Participants

The included study recruited 100 participants with clinically advanced ovarian cancer scheduled for cytoreductive surgery who complied with inclusion and exclusion criteria. Fifty participants were randomly allocated to receive tranexamic acid and 50 to receive placebo. Inclusion criteria were as follows: women 18 years of age or over; having an American Society of Anesthesiologists score of less than 3 and speaking Swedish fluently. Exclusion criteria were: allergic to tranexamic acid; receiving anticoagulants

within the past month; having past or current laboratory results suggesting bleeding disorders, coagulopathy or thromboembolic events; having a history of myocardial infarction within the last year; presenting with unstable angina or severe coronary disease; having reduced renal function, and diagnosed with severe psychiatric or mental disorders.

Sample size

The trial authors considered a 500 mL reduction in total blood loss and a reduction in the requirement for RBC transfusions from 37% to 10% to be a clinical meaningful threshold, and they calculated the need for a sample size of 100 participants to demonstrate a difference at a 5% significance level (two-sided test) with an 80% power and an expected dropout rate of 25%.

Intervention

In the included study, participants assigned to the intervention arm received a single dose of tranexamic acid (15 mg/kg body weight, 100 mg/mL tranexamic acid) intravenously before the start of surgery. Those in the placebo arm received an identical package containing normal saline (0.9% NaCl) by the same method.

Compliance and follow-up

Investigators collected complete data on perioperative clinical characteristics, outcomes of blood loss and transfusion for all participants. At the five-week follow-up visit, seven participants (two (4%) in the tranexamic acid group and five (10%) in the placebo group) were lost to follow-up. However, only 56 participants (56%) in both arms (26 or 52% in the tranexamic acid group and 30 or 60% in the placebo group) underwent lower extremity duplex ultrasound examination to evaluate venous thrombosis at five weeks.

Outcomes

Primary endpoints were the total amount of perioperative blood loss and the rate of red blood cell (RBC) transfusion. Secondary endpoints were the incidences of readmission, reoperation and thromboembolic events. Investigators performed analyses according to intention-to-treat principles.

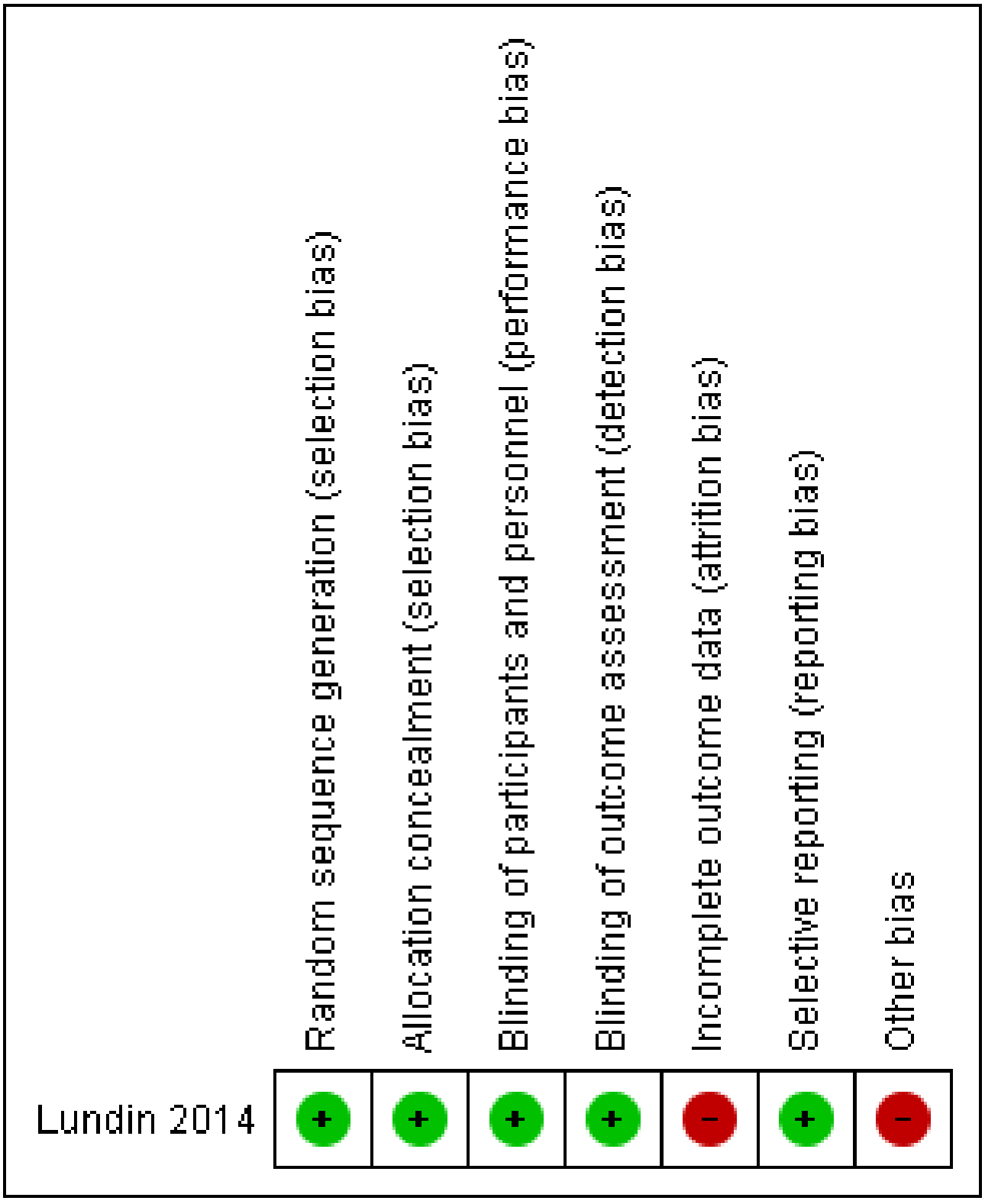
Excluded studies

Of the two potentially eligible studies that we assessed in full-text form(Lundin 2014; Celebi 2006), we excluded one because it was conducted in women who had undergone type III hysterectomy for cervical cancer; the trial did not recruit any women with advanced ovarian cancer (Celebi 2006). See 'Characteristics of excluded studies'.

Risk of bias in included studies

Overall, Lundin 2014 was at low risk of bias, since it satisfied five criteria used to determine risk of bias; (see Figure 2).

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



Allocation

The trial used stratified randomisation to balance allocations among the four participating centres. Each individual assignment from the computer-generated sequence was numbered sequentially. We confirmed via personal correspondence that allocation concealment was adequate. Overall, we deemed this domain to have a low risk of bias (Figure 2).

Blinding

The authors of the included study stated that all hospital staff and participants involved in the included study were blinded to the treatment assigned (verified by personal correspondence). The local hospital pharmacy prepared the study medications containing either tranexamic acid or saline (0.9% NaCl) as placebo with the same appearance and packaging. We determined this to indicate low risk of bias (Figure 2).

Incomplete outcome data

After randomisation, 50 participants were assigned to receive a single dose of tranexamic acid (15 mg/kg body weight) and the remaining 50 to receive placebo. Investigators collected complete data on perioperative clinical characteristics, outcomes of blood loss and transfusion from all participants. In addition, at the five-week follow-up visit, only seven participants in both arms (two (4%) in the tranexamic acid group and five (10%) in the placebo group) were lost to follow-up. However, only 56 participants (56%) in both arms had undergone lower extremity duplex ultrasound examination to evaluate lower extremity venous thrombosis (26 (52%) in the tranexamic acid group and 30 (60%) in the placebo group). As the protocol stated that incidence of thromboembolic events was one of the outcomes of interest, we therefore determined this domain to be at high risk of bias (Figure 2).

Selective reporting

Primary endpoints of the included study consisted of the amount of perioperative blood loss and the rate of red blood cell (RBC) transfusion. Secondary endpoints were the incidence of readmission, reoperation, infection and thromboembolic events. The trial did report all of these outcomes, so we judged this domain to be at a low risk of bias (Figure 2).

Other potential sources of bias

There were baseline imbalances in preoperative clinical characteristics between the two comparison groups with regard to the stage distribution of EOC and the types of surgical procedure carried out. In addition, the included study had no well-defined criteria or protocol for transfusion of blood components. We determined this to confer a high risk of other bias because these parameters are likely to have a significant impact on the outcomes of interest (Figure 2).

Effects of interventions

See: **Summary of findings for the main comparison**

We found only one study in 100 women that met our inclusion criteria, reporting perioperative blood loss and the rate of blood component transfusion (Lundin 2014).

Primary outcome

Tranexamic acid given preoperatively was associated with a reduction in blood loss compared to placebo. Means of total blood loss were 668.34 mL and 916.93 mL (520 ml and 730 ml median values) for participants assigned to the tranexamic acid and placebo groups, respectively. However, this difference did not constitute a clinically important benefit (mean difference (MD) − 248.59; 95% CI, − 550.9 to 53.79). We judged the quality of the evidence on this issue as low. See Table 1, Summary of findings for the main comparison, Analysis 1.1,

Secondary outcomes

Number of transfused units of blood components

Compared to participants in the placebo group, the total number of transfused units of red blood cells (RBC) was lower in the participants receiving preoperative tranexamic acid (18 units versus 53 units). The mean number of transfused units of RBC among women allocated to the tranexamic acid and placebo groups were 0.76 and 1.06 units, respectively. This difference was did not reach the threshold for clinically important effect (MD − 0.30; 95% CI, − 0.09 to 0.28). The mean number of transfused units of plasma was also lower in women enrolled to the tranexamic acid group compared to those in the placebo group. Again, this difference was not clinically important (MD − 0.12, 95% CI, − 0.41 to 0.17). We judged the quality of the evidence on this issue to be low. See Table 1; Summary of findings for the main comparison; Analysis 2.1; Analysis 2.2.

Rate of RBC transfusion

See 'Differences between protocol and review'.

Although tranexamic acid did not confer a clinically important benefit on the need for RBC transfusion, the rate of RBC transfusion was lower in women receiving tranexamic acid (22% versus 30%, respectively; RR, 0.68; 95% CI, 0.40 to 1.15). We judged the quality of the evidence on the effect of tranexamic acid on the need for blood transfusion as low (see Table 1; Summary of findings for the main comparison; Analysis 3.1.

Rate of plasma transfusion

(see Differences between protocol and review)

Women assigned to the tranexamic acid group had a lower rate of plasma transfusion compared to those in the placebo group (8% versus 18%, respectively) (Table 1). However, this difference was not clinically important (RR, 0.44; 95% CI, 0.15 to 1.35; low quality evidence, see Summary of findings for the main comparison; Analysis 3.2.

Incidence of reoperation

The incidence of reoperation in women receiving prophylactic tranexamic acid was 10%, which was comparable to the 12% reported for women in the placebo arm (RR, 0.83; 95% CI, 0.27 to 2.55; very low quality evidence, see Table 1; Summary of findings for the main comparison; Analysis 4.1.

Incidence of readmission

Women receiving prophylactic tranexamic acid had a higher incidence of readmission compared to those who were assigned to placebo group (22% versus 8%, respectively;Table 1). However, this difference was not clinically important (RR, 2.75; 95% CI 0.94 to 8.06; very low quality evidence, see Summary of findings for the main comparison; Analysis 5.1.

Incidence of venous thromboembolic events

Two participants assigned to tranexamic acid group developed either superficial (n = 1) or deep venous thrombosis (n = 1) in the leg, while four participants receiving placebo experienced muscle vein

thrombosis (n = 3) or deep vein thrombosis (n = 1) in the leg (Table 1).This difference did not reach a clinically important effect (RR, 0.50; 95% CI, 0.10 to 2.61; very low quality evidence, see Summary of findings for the main comparison; Analysis 6.1.

Incidence of arterial thromboembolic events

Arterial thromboembolic events were rare (Table 1). Only one participant assigned to the placebo group experienced arterial thrombosis in the popliteal artery. No participants in the intervention group developed arterial thromboembolic events (RR, 0.33, 95% CI, 0.01 to 7.99) (very low quality evidence, see Summary of findings for the main comparison; Analysis 6.2.

The included trial did not report other secondary outcomes (see Differences between protocol and review).

DISCUSSION

Summary of main results

In the single included study, there were no clinically important differences between women receiving tranexamic acid and those receiving a placebo in terms of mean total estimated blood loss and mean number of transfused units of blood components. The number of adverse events, including incidence of reoperation, readmission and thromboembolic events, did not differ between the two comparison groups (see Summary of findings for the main comparison).

Overall completeness and applicability of evidence

This review included one RCT evaluating preoperative tranexamic acid in 100 women with clinically advanced EOC in Sweden. The intervention that was evaluated in the included study was the same one that this review aims to address. Primary outcomes were blood loss and the blood transfusion rate. Secondary outcomes included RBC transfusion, reoperation, readmission and thromboembolic events. Due to incomplete data and limited evidence obtained from a single RCT, we consider that the evidence for the effectiveness and safety of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer is inconclusive.

The study included in the review took place in a developed country, and experienced gynaecologic oncologists carried out all operations. Therefore, generalisation of the results to different settings might be limited.

Quality of the evidence

The greatest threat to the validity of the included study is likely to be the risk of bias, since the study had no well-defined criteria or protocol for transfusion of blood components. Thus, the rate of blood transfusion may vary depending on the practice of each participating centre. In addition, only 56% of participants in both arms underwent lower extremity duplex ultrasound examination to evaluate lower extremity venous thrombosis. The other potential bias was the imbalance of baseline clinical characteristics between the two comparison groups in the included study, particularly with regard to the stage distribution of EOC and the types of surgical procedure carried out, which were likely to have had an impact on the outcomes of interest.

We assessed the quality of evidence using the GRADE approach for each outcome. Based on the concerns regarding the risk of the potential bias and imprecision, we downgraded the evidence to low quality for the amount of estimated blood loss, number of transfused units of blood components and rate of blood component transfusion. We downgraded the evidence to very low quality for adverse events due to sparseness of data. Overall, we determined that the evidence for the effectiveness and safety of a single dose tranexamic acid given immediately prior to surgery to reduce blood loss during cytoreduction for advanced ovarian cancer was inconclusive.

Potential biases in the review process

With support from the Cochrane Gynecological Cancer Group, the authors of this review carried out a comprehensive search, including a thorough search of the grey literature. Two review authors independently screened all potentially relevant studies and extracted data. The review authors also carefully assessed risk of bias in the included trial (Figure 2). We restricted studies to RCTs, as they provide the best evidence. However, as there was only one study that met the review inclusion criteria, we cannot definitively rule out the possibility of publication bias. None of the review authors have any links to drug companies or a financial interest in the prescription of the drug under assessment, nor were they involved in the conduct of the included study. Thus, there were no issues related to bias due to conflicts of interests in this review.

Agreements and disagreements with other studies or reviews

We are not aware of any studies or reviews that have determined the effectiveness and safety of tranexamic acid given perioperatively with the aim of reducing haemorrhage during cytoreductive surgery for advanced ovarian cancer.

Tranexamic acid given perioperatively has proven to be an effective intervention in reducing blood loss and the need for allogeneic blood transfusion in a number of Cochrane systematic reviews in a variety of surgical settings (acute trauma, Roberts 2015; urgent and emergency surgery, Perel 2013) and in different patient groups (pregnant women giving birth, Novikova 2015; women with uterine fibroids undergoing myomectomy, Kongnyuy 2014). This review, which identified only one RCT that met the review inclusion criteria, found that participants assigned to tranexamic acid tended to have lower volume of estimated total blood loss and a lower rate of blood transfusion requirement. However, the difference in volume of blood loss was low (median difference of 210 mL) and did not lead to a difference in the need for blood transfusion, suggesting the treatment did not confer a clinically meaningful benefit (see Summary of findings for the main comparison).

Findings of this review should be considered with caution. Firstly, the mean reduction in estimated total blood loss and the decrease in the rate of RBC transfusion (250 mL, and 14%, respectively) were far lower than originally expected. Trial investigators set a sample size to detect a 500 mL reduction in total amount of blood loss and a 20% reduction in the requirement for RBC transfusion. Given the low power of the included study, we cannot rule out a smaller magnitude of reduction in estimated amount of blood loss and rate of RBC transfusion of tranexamic acid than those set out in the included study.

Secondly, people with cancer commonly have bleeding tendencies arising from various cancer-specific conditions, either due to

localised bleeding from local tumour invasion or as systemic bleeding secondary to loss of haemostatic factors in enlarged extravascular space, hypoproteinaemia, reduced synthesis of coagulation factors, platelet dysfunctions or increased fibrinolysis (Kvolik 2010). Studies have reported associations between ovarian cancer and several enhanced fibrinolysis as a result of elevated levels of D-dimer and other fibrin degradation products (FDPs), and decreased antithrombin III levels (Gadducci 1994; Koh 2006; Sitalakshmi 2008). These abnormal coagulation parameters appear to be more pronounced in people with an advanced stage of disease (Koh 2006; Sitalakshmi 2008). Based on these findings, women with advanced ovarian cancer may be at an increased risk of excessive bleeding during surgery compared to people in other surgical settings. A smaller magnitude of effect of tranexamic acid in lowering blood loss in women with advanced ovarian cancer undergoing cytoreductive surgery could therefore be expected.

As currently limited data are available from just one study, further well-designed RCTs with adequate study power are warranted.

AUTHORS' CONCLUSIONS

Implications for practice

The limited evidence obtained from a single RCT presented in this review suggests that the beneficial effects of a single dose tranexamic acid given before cytoreductive surgery for advanced ovarian cancer did not reach a clinically important level. In addition, evidence for the safety of tranexamic acid used in this surgical setting is inconclusive due to a small number of tranexamic acid-related adverse events and incomplete data collection. At present the evidence does not support the routine administration of tranexamic acid in women undergoing cytoreductive surgery for advanced ovarian cancer.

Implications for research

There is a need for an adequately sized, placebo-controlled trial with a well-defined protocol for blood transfusion and a protocol for evaluating tranexamic acid-related adverse events to shed more light on the effectiveness of tranexamic acid given perioperatively to reduce blood loss during cytoreductive surgery for advanced ovarian cancer.

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CHARACTERISTICS OF STUDIES

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

Lundin 2014

Methods	A randomised double blind, placebo-controlled multicentre study conducted in 2 university hospitals and 2 central hospitals in the southeast health region of Sweden Study duration: March 2008 to May 2012
Participants	100 women with presumed advanced EOC scheduled for cytoreductive surgery and complying with inclusion/exclusion criteria; 50 were randomly allocated to receive tranexamic acid and 50 to receive placebo. Median age of participants in tranexamic acid and those in placebo groups were 63 years and 64.5 years, respectively. Approximately 20.5% and 7.5% of participants assigned to tranexamic acid and placebo groups, respectively, had stage IV ovarian cancer. Approximately 22% and 12% of participants in tranexamic acid and placebo groups, respectively, underwent retroperitoneal lymphadenectomy. Inclusion criteria: women ≥ 18 years of age with an American Society of Anesthesiologists score of ≤3; fluent in Swedish Exclusion criteria: allergy to tranexamic acid; received anticoagulants within the past month; with previous or current laboratory results suggesting bleeding disorders, coagulopathy or thromboembolic

Lundin 2014 *(Continued)*

	events; a history of myocardial infarction within the last year; presenting with unstable angina or severe coronary disease; reduced renal function; severe psychiatric or mental disorder
Interventions	Intervention arm: participants received a single dose of tranexamic acid (15 mg/kg body weight, 100 mg/mL tranexamic acid) immediately before the start of surgery. Control arm: participants received the same volume of normal saline (0.9% NaCl) prepared in identical packaging and given in the same fashion.
Outcomes	Primary endpoints: amount of blood loss and rate of red blood cell (RBC) transfusion Secondary endpoints: readmission, reoperation, and thromboembolic events. Data regarding amount of blood loss and rate of RBC transfusion were collected after operation. At the 5-week postoperative visit, participants were interviewed about postoperative complications and underwent lower extremity duplex ultrasound for evaluating venous thrombosis regardless of symptoms.
Notes	The included study had no well-defined criteria or protocol for transfusion of blood components. The authors of the included study broadly stated that "perioperative bleeding was managed according to clinical practice and blood transfusion was usually given when the haemoglobin level measured during the surgery or postoperatively was below 90 g/L" and "postoperative blood transfusion was given according to the patient's clinical well being and haemoglobin level." In addition, participants were optionally referred to lower extremity duplex ultrasound to look for venous thrombosis regardless of symptoms at the time of 5-weeek follow-up visit. Imbalance of participant allocation was observed. Relative to participants assigned to placebo group, a higher proportion of participants receiving tranexamic acid were diagnosed with stage IV ovarian cancer (20.5% versus 7.5%), had undergone extensive surgery (82% versus 70%) and were overweight or obese (62% versus 38%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified according to each individual centre among the four centres participating in the trial. Each individual assignment from the computer-generated sequences was numbered sequentially.
Allocation concealment (selection bias)	Low risk	Trial authors confirmed adequate allocation concealment by correspondence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Hospital staff and participants involving in this trial were blinded to the treatment assigned. The local hospital pharmacy prepared the study medications containing either tranexamic acid or saline (0.9% NaCl) as placebo with the same appearance and packaging.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to treatment allocation (data additionally provided by the trial authors).
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 56 participants (56%) in both arms underwent lower extremity duplex ultrasound examination to evaluate lower extremity venous thrombosis (26 or 52% in the tranexamic acid group and 30 or 60% in the placebo group).
Selective reporting (reporting bias)	Low risk	All potential relevant outcomes were reported.
Other bias	High risk	There were several imbalances in baseline preoperative clinical characteristics between the two groups, including participants' body mass index, the distribution of stage of disease and types of surgical procedure carried out. In addi-

Lundin 2014 *(Continued)*

	tion, the included trial had no well-defined criteria or protocol for transfusion of blood components. Thus, the rate of blood transfusion may vary depending on the practice of each participating centre.

EOC: epithelial ovarian cancer.

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

Study	Reason for exclusion
Celebi 2006	This randomised study, entitled "The role of antifibrinolytic agents in gynaecologic cancer surgery" was conducted to determine the effectiveness of crystalloid and colloid solutions, tranexamic acid, and epsilon-aminocaproic acid for reducing the need for allogenic blood transfusion and for coagulation and fibrinolysis. This trial randomly assigned 105 participants into 4 groups, receiving: crystalloid solution, colloid solution, 10 mg/kg of tranexamic acid, or 100 mg/kg of epsilon-aminocaproic acid. The reason for exclusion was that it was carried out solely in women who had undergone type 3 hysterectomy for early stage cervical cancer. The study recruited no women with advanced ovarian cancer.

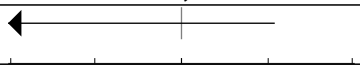
DATA AND ANALYSES

Comparison 1. Estimated total blood loss (mL)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Estimated total blood loss (mL)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Estimated total blood loss (mL), Outcome 1 Estimated total blood loss (mL).

Study or subgroup	Tranexamic acid N	Tranexamic acid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lundin 2014	50	668.3 (755.4)	50	916.9 (787)		0%	-248.59[-550.97,53.79]



Comparison 2. Number of transfused units of blood components

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of transfused units of RBC	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of transfused units of plasma	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2 Number of transfused units of blood components, Outcome 1 Number of transfused units of RBC.

Study or subgroup	Tranexamic acid N	Tranexamic acid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lundin 2014	50	0.8 (1.5)	50	1.1 (1.5)		0%	-0.3[-0.88,0.28]

Analysis 2.2. Comparison 2 Number of transfused units of blood components, Outcome 2 Number of transfused units of plasma.

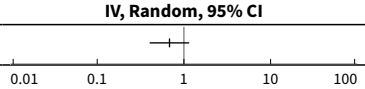
Study or subgroup	Tranexamic acid N	Tranexamic acid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lundin 2014	50	0.2 (0.7)	50	0.3 (0.8)		0%	-0.12[-0.41,0.17]

Comparison 3. Rate of blood component transfusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Red blood cell transfused women	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2 Plasma transfused women	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 3.1. Comparison 3 Rate of blood component transfusion, Outcome 1 Red blood cell transfused women.

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lundin 2014	15/50	22/50		0%	0.68[0.4,1.15]



Analysis 3.2. Comparison 3 Rate of blood component transfusion, Outcome 2 Plasma transfused women.

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lundin 2014	4/50	9/50		0%	0.44[0.15,1.35]

Favours [Tranexamic acid] 0.01 0.1 1 10 100 Favours [Placebo]

Comparison 4. Incidence of reoperation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reoperation	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 4.1. Comparison 4 Incidence of reoperation, Outcome 1 Reoperation.

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lundin 2014	5/50	6/50		0%	0.83[0.27,2.55]

Favours [Tranexamic acid] 0.01 0.1 1 10 100 Favours [Placebo]

Comparison 5. Incidence of readmission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Readmission	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 5.1. Comparison 5 Incidence of readmission, Outcome 1 Readmission.

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lundin 2014	11/50	4/50		0%	2.75[0.94,8.06]

Favours [Tranexamic acid] 0.01 0.1 1 10 100 Favours [Placebo]

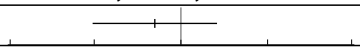
Comparison 6. Incidence of thromboembolic events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Venous thromboembolic events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Arterial thromboembolic events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 6.1. Comparison 6 Incidence of thromboembolic events, Outcome 1 Venous thromboembolic events.

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lundin 2014	2/50	4/50		0%	0.5[0.1,2.61]



Favours [Tranexamic acid] Favours [Placebo]

Analysis 6.2. Comparison 6 Incidence of thromboembolic events, Outcome 2 Arterial thromboembolic events.

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lundin 2014	0/50	1/50		0%	0.33[0.01,7.99]

Favours [Tranexamic acid] Favours [Placebo]

ADDITIONAL TABLES

Table 1. Extracted data

Extracted data[a]	Tranexamic acid group (n = 50)	Placebo (n = 50)
Median total blood loss (mL), IQR	520, 211 to 870[b]	730, 411 to 1278[b]
Mean total blood loss (mL), SD	668, 755[b]	916, 787[b]
Mean number of units of transfused RBC, SD	0.76, 1.45[b]	1.06, 1.49[b]
Mean number of units of transfused plasma, SD	0.16, 0.68[b]	0.28, 0.81[b]
Number of RBC transfused participants	15 (30%)	22 (44%)
Number of plasma transfused participants	4 (8%)	9 (18%)
Number of participants who experienced reoperation	5 (10%)	6 (12%)
Number of participants who had to be readmitted	11 (22%)	4 (8%)
Number of participants who developed venous thromboembolic events	1 (2%)	4 (8%)
Number of participants who developed arterial thromboembolic events	1 (2%)	1 (2%)

IQR: interquartile range; **RBC**: red blood cell; **SD**: standard deviation.
[a]Data extracted from only one available randomised trial.
[b]Additional data provided by the trial authors (Kjølhede 2015 [pers comm]).

APPENDICES

Appendix 1. 2014 the International Federation of Gynecology and Obstetrics (FIGO) ovarian cancer staging system

Stage		Findings
I		Tumor confined to ovaries
	IA	Tumor limited to one ovary (capsule intact), no tumor on ovarian surface, no malignancy cells in the ascites or peritoneal washings
	IB	Tumor limited to both ovaries (capsule intact), no tumor on ovarian surface, no malignancy cells in the ascites or peritoneal washings
	IC	Tumor limited to one or both ovaries with any of the following: surgical spill intraoperatively, capsule rupture before surgery or tumor on ovarian surface, or malignancy cells present in the ascites or peritoneal washings
II		Tumor involves one or both ovaries with pelvic extension
	IIA	Extension and/or implants on the uterus and/or fallopian tubes
	IIB	Extension to other pelvic intraperitoneal tissues
III		Tumor involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal nodes
	IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis
	IIIB	Macroscopic peritoneal metastases beyond the pelvic brim ≤ 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
	IIIC	Macroscopic peritoneal metastases beyond the pelvic brim >2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IV		Distant metastasis excluding peritoneal metastases
	IVA	Pleural effusion with positive cytology
	IVB	Metastases to extra-abdominal organs or parenchymal metastases

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2 ovar* near/5 (cancer* or tumor* or tumour* or neoplasm* or carcinoma* or adenocarcinoma* or malignan*)
#3 #1 or #2
#4 Any MeSH descriptor with qualifier(s): [Surgery - SU]
#5 MeSH descriptor: [Gynecologic Surgical Procedures] explode all trees

#6 cytoreduct* or debulk*
#7 #4 or #5 or #6
#8 MeSH descriptor: [Tranexamic Acid] this term only
#9 tranexamic acid or amchafibrin or anvitoff or cyclokapron or cyklokapron or exacyl or kabi 2161 or lysteda or spotof or t-amcha or tranhexamic acid or transamin or ugurol or xp12b
#10 #8 or #9
#11 #3 and #7 and #10

Appendix 3. MEDLINE Ovid search strategy

1. exp Ovarian Neoplasms/
2. (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3. 1 or 2
4. surgery.fs.
5. exp Gynecologic Surgical Procedures/
6. (cytoreduct* or debulk*).mp.
7. 4 or 5 or 6
8. Tranexamic Acid/
9. (tranexamic acid or amchafibrin or anvitoff or cyclokapron or cyklokapron or exacyl or kabi 2161 or lysteda or spotof or t-amcha or tranhexamic acid or transamin or ugurol or xp12b).mp
10. 8 or 9
11. 3 and 7 and 10

key: mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
fs= floating subheading

Appendix 4. EMBASE search strategy

1. exp ovary tumor/˜
2. (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3. 1 or 2
4. su.fs.
5. exp gynecologic surgery/
6. (cytoreduct* or debulk*).mp
7. 4 or 5 or 6
8. tranexamic acid/
9. (tranexamic acid or amchafibrin or anvitoff or cyclokapron or cyklokapron or exacyl or kabi 2161 or lysteda or spotof or t-amcha or tranhexamic acid or transamin or ugurol or xp12b).mp.
10. 8 or 9
11. 3 and 7 and 10

Key: mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Appendix 5. Risk of bias assessment

Risk of bias assessment based on chapter 8 of Higgins 2011:

- Random sequence generation
  a. Low risk of bias e.g. participants assigned to treatments on the basis of a computer-generated random sequence or a table of random numbers
  b. High risk of bias e.g. participants assigned to treatments on the basis of date of birth, clinic id-number or surname, or no attempt to randomise participants
  c. Unclear risk of bias e.g. not reported, information not available
- Allocation concealment
  a. Low risk of bias e.g. where the allocation sequence could not be foretold
  b. High risk of bias e.g. allocation sequence could be foretold by patients, investigators or treatment providers
  c. Unclear risk of bias e.g. not reported.
- Blinding of participants and personnel
  a. Low risk of bias if participants and personnel were adequately blinded
  b. High risk of bias if participants were not blinded to the intervention that the participant received
  c. Unclear risk of bias if this was not reported or unclear

- Blinding of outcomes assessors
  a. Low risk of bias if outcome assessors were adequately blinded
  b. High risk of bias if outcome assessors were not blinded to the intervention that the participant received
  c. Unclear risk of bias if this was not reported or is unclear
- Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:
  a. Low risk of bias e.g.if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
  b. High risk of bias e.g. if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms
  c. Unclear risk of bias e.g. if loss to follow-up was not reported
- Selective reporting of outcomes
  a. Low risk of bias e.g. review reports all outcomes specified in the protocol
  b. High risk of bias e.g. the study is suspected that outcomes have been selectively reported
  c. Unclear risk of bias e.g. it is unclear whether outcomes have been selectively reported
- Other bias
  a. Low risk of bias e.g. the review authors do not suspect any other source of bias and the trial appears to be methodologically sound
  b. High risk of bias e.g. the review authors suspect that the trial was prone to an additional bias
  c. Unclear risk of bias e.g. the review authors are uncertain whether an additional bias may have been present

WHAT'S NEW

Date	Event	Description
16 January 2019	Amended	No potentially relevant new studies identified after a scoping search in January 2019. The conclusions of this Cochrane review are therefore still considered to be up to date for this topic. A further search of the literature will be carried out in 2022, 5 years after the review was first published.

CONTRIBUTIONS OF AUTHORS

CK conceived the review question, developed, coordinated and completed the review.
AM developed and completed the draft of the review.
ML performed part of the editing of the review and advised on part of the review.
PL developed and coordinated the development of the review, edited the review, and advised on the review.
All authors approved the final version of the review prior to submission.

DECLARATIONS OF INTEREST

Chumnan Kietpeerakool: none known.
Amornrat Supoken: none known.
Malinee Laopaiboon: none known.
Pisake Lumbiganon: none known.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand.
- Thai Cochrane Network of The Australasian Cochrane Centre, Thailand.

External sources

- Thailand Research Fund (Distinguished Professor Awards), Thailand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Type of outcome measures

The included study did not report several outcomes of interest stated in the review protocol, including length of surgery, length of hospital stay, postoperative haemoglobin, incidence of nausea/vomiting/diarrhoea and incidence of neurological adverse events.

We added two new secondary outcomes that reflect the amount of blood loss: rate of red blood cell transfusion (number of participants who required at least one unit of red blood cell transfusion) and rate of plasma transfusion (number of participants who required at least one unit of plasma transfusion).

Searches

In the protocol, we stated: "If ongoing trials that have not been published are identified through these searches, we plan to approach the principal investigators, and major co-operative groups active in this area, to ask for relevant data" However, we did not find any relevant ongoing trials or particularly active trial groups, so we did not make these contacts.

In the review, we added the lists of databases used for searching conference abstracts and proceedings (grey literature). We also added the WHO International Clinical Trial Registry (http://apps.who.int/trialsearch/Default.aspx) as a source of registers of clinical trials to be searched.

Considerations for future updates of the review

Data extraction and management

If a study with multiple intervention groups is identified, we intend to combine all relevant experimental intervention groups into a single group to create a single pair-wise comparison (Higgins 2011).

Assessment of risk of bias in included studies

When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the table.

Measure of treatment effect

Combining intervention groups to create a single pair-wise comparison, as stated in the protocol, was not necessary for this review since the included trial had only two comparison groups. However, we will take this step in future updates if appropriate.

Data collection and analysis

As there was only one trial that met our inclusion criteria, we were unable pool the results in meta-analyses, so it was not feasible to assess heterogeneity between the results of trials, reporting biases or conduct any subgroup or sensitivity analyses. In future update of this review, we will employ the following methods for data analysis.

Assessment of heterogeneity

We will assess clinical heterogeneity by considering the characteristics of the participants included in the studies. We will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistic (Higgins 2003). We will regard heterogeneity as substantial if I^2 is greater than 50% and either Tau^2 is greater than zero or the P value is less than 0.10 in the Chi^2 test (Deeks 2001).

Assessment of reporting biases

We will construct funnel plots corresponding to meta-analyses of the primary outcome to assess the possibility of publication bias if we identify a sufficient number of included studies (i.e. more than 10). We will also carry out sensitivity analyses to investigate the effect on the pooled results if the funnel plots are asymmetrical (Sterne 2011).

Data synthesis

We will perform statistical analysis using RevMan 2014.

- For dichotomous outcomes, we intend to calculate the risk ratio for each study as well as for the pooled outcome.
- For continuous outcomes, we intend to pool the mean difference between the treatment arms if all trials measured the outcome on the same scale; otherwise we will pool the standardised mean differences.

We will use the random-effects model with inverse variance weighting for all meta-analyses if feasible (DerSimonian 1986). We will prepare a 'Summary of findings' table to present the results of the meta-analysis, based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We will present the results of the meta-analysis for the primary outcome and adverse events as outlined in the 'Types of outcome measures' section.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses for the following factors if we identify substantial heterogeneity.

1. Route of administration of tranexamic acid (intravenous, oral or topical administration).
2. Dose of tranexamic acid (single dose versus multiple doses).
3. Largest preoperative tumour size, excluding ovarian mass (≤ 5 cm versus > 5 cm).

We will assess subgroup differences by interaction tests available within RevMan 2014. We will report the results of subgroup analyses using the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will perform a sensitivity analysis in order to determine the impact of the following factors.

1. Repeating the analysis excluding unpublished studies (if any).
2. Repeating the analysis excluding studies judged to be at high or unclear risk of bias for allocation concealment.

NOTES

Parts of the methods section of this protocol are based on a standard template established by the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Antifibrinolytic Agents [*therapeutic use]; Blood Loss, Surgical [*prevention & control] [statistics & numerical data]; Blood Transfusion [statistics & numerical data]; Cytoreduction Surgical Procedures [adverse effects] [*methods]; Erythrocyte Transfusion [*statistics & numerical data]; Incidence; Ovarian Neoplasms [pathology] [*surgery]; Patient Readmission [statistics & numerical data]; Plasma; Randomized Controlled Trials as Topic; Reoperation [statistics & numerical data]; Thromboembolism [epidemiology]; Tranexamic Acid [*therapeutic use]

MeSH check words

Adult; Female; Humans