

Antifibrinolytics (lysine analogues) for the prevention of bleeding in patients with haematological disorders (Review)

Wardrop D, Estcourt LJ, Brunskill SJ, Doree C, Trivella M, Stanworth S, Murphy MF



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 7

<http://www.thecochranelibrary.com>

WILEY

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	10
Figure 1.	11
Figure 2.	14
DISCUSSION	18
AUTHORS' CONCLUSIONS	20
ACKNOWLEDGEMENTS	20
REFERENCES	21
CHARACTERISTICS OF STUDIES	24
DATA AND ANALYSES	36
ADDITIONAL TABLES	36
APPENDICES	41
CONTRIBUTIONS OF AUTHORS	48
DECLARATIONS OF INTEREST	48
SOURCES OF SUPPORT	48

[Intervention Review]

Antifibrinolytics (lysine analogues) for the prevention of bleeding in patients with haematological disorders

Douglas Wardrop¹, Lise J Estcourt², Susan J Brunskill³, Carolyn Doree³, Marialena Trivella⁴, Simon Stanworth², Michael F Murphy⁵

¹Oxford Cancer and Haematology Centre, Haematology, Oxford, UK. ²Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK. ³Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. ⁴Centre for Statistics in Medicine, University of Oxford, Oxford, UK. ⁵NHS Blood and Transplant, John Radcliffe Hospital, Oxford, UK

Contact address: Lise J Estcourt, Haematology/Transfusion Medicine, NHS Blood and Transplant, Level 2, John Radcliffe Hospital, Headington, Oxford, OX3 9BQ, UK. lise.estcourt@nhsbt.nhs.uk. lestcourt@doctors.org.uk.

Editorial group: Cochrane Haematological Malignancies Group.

Publication status and date: New, published in Issue 7, 2013.

Review content assessed as up-to-date: 10 January 2013.

Citation: Wardrop D, Estcourt LJ, Brunskill SJ, Doree C, Trivella M, Stanworth S, Murphy MF. Antifibrinolytics (lysine analogues) for the prevention of bleeding in patients with haematological disorders. *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No.: CD009733. DOI: 10.1002/14651858.CD009733.pub2.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Patients with haematological disorders are frequently at risk of severe or life-threatening bleeding as a result of thrombocytopenia. This is despite the routine use of prophylactic platelet transfusions (PITx) to prevent bleeding once the platelet count falls below a certain threshold. PITx are not without risk and adverse events may be life-threatening. A possible adjunct to prophylactic PITxs is the use of antifibrinolytics, specifically the lysine analogues tranexamic acid (TXA) and epsilon aminocaproic acid (EACA).

Objectives

To determine the efficacy and safety of antifibrinolytics (lysine analogues) in preventing bleeding in patients with haematological disorders.

Search methods

We searched for randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (CENTRAL Issue 12, 2012), MEDLINE (1948 to 10 January 2013), EMBASE (1980 to 10 January 2013), CINAHL (1982 to 10 January 2013), PubMed (e-publications only) and the Transfusion Evidence Library (1980 to January 2013). We also searched several international and ongoing trial databases to 10 January 2013 and citation-tracked relevant reference lists.

Selection criteria

RCTs involving patients with haematological disorders, who would routinely require prophylactic platelet transfusions to prevent bleeding. We only included trials involving the use of the lysine analogues TXA and EACA.

Data collection and analysis

Two authors independently screened all electronically derived citations and abstracts of papers, identified by the review search strategy, for relevancy. Two authors independently assessed the full text of all potentially relevant trials for eligibility, completed the data extraction and assessed the studies for risk of bias using The Cochrane Collaboration's 'Risk of bias' tool. We requested missing data from one author but the data were no longer available. The outcomes are reported narratively: we performed no meta-analyses because of the heterogeneity of the available data.

Main results

Of 470 articles initially identified, 436 were excluded on the basis of the title and abstract. We reviewed 34 full-text articles from which four studies reported in five articles were eligible for inclusion. We did not identify any RCTs which compared TXA with EACA. We did not identify any ongoing RCTs.

One cross-over TXA study (eight patients) was excluded from the outcome analysis because data from this study were at a high risk of bias. Data from the other three studies were all at unclear risk of bias due to lack of reporting of study methodology.

Three studies (two TXA (12 to 56 patients), one EACA (18 patients)) reported in four articles (published 1983 to 1995) were included in the narrative review. All three studies compared the drug with placebo.

All studies reported bleeding, but it was reported in different ways. All three studies suggested antifibrinolytics reduced the risk of bleeding. The first study showed a difference in average bleeding score of 42 in placebo (P) versus three (TXA). The second study only showed a difference in bleeding episodes during consolidation chemotherapy, with a mean of 2.6 episodes/patient (standard deviation (SD) 2.2) (P) versus a mean of 1.1 episodes/patient (SD 1.4) (TXA). The third study reported bleeding on 50% of days at risk (P) versus bleeding on 31% of days at risk (EACA).

Two studies (68 patients) reported thromboembolism and no events occurred.

All three studies reported a reduction in PITx usage. The first study reported a difference of 222 platelet units (P) versus 69 platelet units (TXA). The second study only showed a difference in total platelet usage during consolidation chemotherapy, with a mean of 9.3 units (SD 3.3) (P) versus 3.7 (SD 4.1) (TXA). The third study reported one PITx every 10.5 days at risk (P) versus one PITx every 13.3 days at risk (EACA).

Two studies reported red cell transfusion requirements and one study found a reduction in red cell transfusion usage.

One study reported death due to bleeding as an outcome measure and none occurred.

Only one study reported adverse events of TXA as an outcome measure and none occurred.

None of the studies reported on the following pre-specified outcomes: overall mortality, adverse events of transfusion, disseminated intravascular coagulation (DIC) or quality of life (QoL).

Authors' conclusions

Our results indicate that the evidence available for the use of antifibrinolytics in haematology patients is very limited. The only available data suggest that TXA and EACA may be useful adjuncts to platelet transfusions so that platelet use, and the complications associated with their use, can be reduced. However, the trials were too small to assess whether antifibrinolytics increased the risk of thromboembolic events. Large, high-quality RCTs are required before antifibrinolytics can be demonstrated to be efficacious and safe in widespread clinical practice.

PLAIN LANGUAGE SUMMARY

Antifibrinolytics (tranexamic acid and epsilon-aminocaproic acid) to prevent bleeding in patients with low platelets due to bone marrow failure

Patients with haematological (blood) cancers and other blood disorders are frequently at risk of severe or life-threatening bleeding from having low platelets (thrombocytopenia). This may be from bone marrow failure due to an underlying blood disorder but also from the toxic effect of treatment (chemotherapy) on the bone marrow. Such patients can be given prophylactic platelet transfusions (from donations) to prevent bleeding if their own platelet counts are too low. These transfusions are not without risks, ranging from mild reactions like fevers to more serious, or even life-threatening, consequences such as infections transmitted to the patient from the transfused platelets, despite stringent attempts to prevent this.

Clearly, ways to safely prevent bleeding in thrombocytopenic patients whilst also minimising exposure to transfused platelets would be welcomed. One possible way of achieving these goals is the use of antifibrinolytics, known as lysine analogues: tranexamic acid (TXA) and epsilon aminocaproic acid (EACA). These medications help to stabilise the clots that form after bleeding, therefore reducing the chances of further bleeding as well as the need for transfusing platelets. There may be risks associated with the use of TXA and EACA;

the most important being an increased risk of forming unwanted blood clots (such as deep vein thrombosis (DVT), which could be potentially life-threatening.

This review has been designed to establish the efficacy and safety of these drugs, specifically in patients with blood disorders, who are at risk of thrombocytopenia and bleeding, either due to the disorder itself, its treatment or both. After searching the available literature up to January 2013, only four trials containing ninety-five patients were eligible for inclusion in our review. Three studies suggested that antifibrinolytics may reduce bleeding and also the need for platelet transfusions. Two studies reported that no blood clots occurred but it was unclear whether these agents reduced the need for other types of transfusions (i.e. red blood cell transfusions to treat and prevent anaemia). The numbers of patients involved were small, and the quality of the evidence was very low, making it difficult to draw conclusions or make recommendations regarding the usefulness and safety of antifibrinolytics. Further, larger trials are needed to determine whether antifibrinolytics can be recommended for widespread use in patients with blood disorders.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antifibrinolytics (lysine analogues) compared to placebo to prevent bleeding in patients with haematological disorders						
Patient or population: patients with haematological disorders Settings: hospital Intervention: antifibrinolytics (lysine analogues) Comparison: placebo						
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	Antifibrinolytics (lysine analogues)				
Number of patients with any bleeding	See comment	See comment	Not estimable	86 (3 studies)	⊕○○○ very low ^{1,2}	Gallardo 1983 saw a reduction in minor bleeding; Avisati 1989 and Shpilberg 1995 saw a reduction in the number of bleeding events
Number of patients with thromboembolism	See comment	See comment	Not estimable	68 (2 studies)	⊕○○○ very low ^{1,2}	No patients within the Avisati 1989 or Shpilberg 1995 studies had an episode of thromboembolism. Gallardo 1983 only reported no deaths due to thrombosis.
Mortality (all-cause)	See comment	See comment	Not estimable	0 (0)	See comment	None of the studies reported all-cause mortality. Shpilberg 1995 reported no deaths due

						to bleeding and Gallardo 1983 reported no deaths due to thrombosis.
Number of platelet transfusions per patient	See comment	See comment	Not estimable	0 (0)	See comment	None of the studies reported the number of platelet transfusions per patient
Adverse events of transfusions	See comment	See comment	Not estimable	0 (0)	See comment	None of the studies reported adverse events due to blood transfusions
Adverse events of anti-fibrinolytic agents	See comment	See comment	Not estimable	74 (2 studies)	⊕○○○ very low ^{1,2}	Shpilberg 1995 reported no side effects were observed and Gallardo 1983 stated side effects were minimal but no further information was provided
<p>*No meta-analyses were performed within this review and therefore no comparative risks could be calculated</p> <p>§One study (Fricke 1991) was included within the review but no data were extracted from this study. This was because Fricke 1991 had significant flaws within the study design (see Risk of bias in included studies and Characteristics of included studies) and no viable data could be extracted from the study report.</p> <p>CI: confidence interval</p>						
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>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.</p> <p>Very low quality: We are very uncertain about the estimate.</p>						
<p>¹ A full assessment of the quality of the evidence was limited by a lack of reporting. However, selective outcome reporting was present in Gallardo 1983.</p> <p>² Within all three studies there were only 86 participants. This is significantly below the optimal information size (OIS) (Pogue 1997).</p>						

BACKGROUND

Description of the condition

Patients with haematological disorders are frequently at risk of severe or life-threatening bleeding as a result of thrombocytopenia. This is commonly a result of the underlying pathology, a side effect of treatment with chemotherapeutic agents, or both. Patients are administered therapeutic platelet transfusions to treat bleeding and prophylactic platelet transfusions to prevent bleeding once the platelet count falls below a certain threshold ($10 \times 10^9/l$, or higher if the risk of haemorrhage is raised, e.g. sepsis or the presence of another bleeding diathesis) (BCSH 2003). A large, recent randomised controlled trial (RCT) of platelet transfusions involving 1272 patients with haematological or solid tumours showed that the baseline level of clinically significant bleeding does not appear to depend on the platelet count once it is above $5 \times 10^9/l$. The risk of bleeding was 17% per day at platelet counts above $5 \times 10^9/l$, compared with 25% per day at counts below this level (Slichter 2010). This confirms earlier work from a large, retrospective observational study of 2942 thrombocytopenic adult patients that showed that the platelet count did not affect the risk of severe or life-threatening bleeding (World Health Organization (WHO) scale 3 or 4) (Friedmann 2002).

Platelet transfusions are not without risks. Adverse events may range from mild reactions, such as fever (one in five transfusions) (Heddle 2009) to more serious and even life-threatening events such as bacterial sepsis from transfusion transmitted infection (one in 10,000 transfusions) (Heddle 2009) or transfusion-related acute lung injury (TRALI) (Popovsky 1985). Patients may also become refractory to platelet transfusions; the incidence increases with the number of platelet transfusions administered (Slichter 2005). Once refractory, the ability to treat bleeding with platelet transfusions becomes more difficult, requiring expensive, specially matched platelets that can be difficult to source. Furthermore, the financial cost of platelet transfusions is considerable. Around 302,000 adult doses of platelets are issued in the UK each year (Bolton-Maggs 2012) at an annual cost of approximately GBP 68.5 million (Llewelyn 2009) and up to two-thirds (67%) of these are given to patients with haematological malignancies (Cameron 2007; Greeno 2007; Pendry 2011).

Clearly interventions that can safely prevent bleeding in thrombocytopenic patients, whilst minimising patient exposure to allogeneic platelets and reducing financial costs, would be welcomed. One possible adjunct, or even an alternative, to prophylactic platelet transfusions is the use of antifibrinolytics, specifically lysine analogues, such as tranexamic acid (TXA) and epsilon aminocaproic acid (EACA).

This systematic review has been designed to establish the safety and efficacy of these agents specifically in patients with haematological disorders who are at risk of thrombocytopenia and bleeding, either due to the disorder itself, its treatment or both.

Description of the intervention

There have been several Cochrane reviews examining the efficacy of antifibrinolytics in preventing bleeding in other patient groups (Gurusamy 2011; Henry 2011; Martin-Hirsch 2010; Novikova 2011; Roos 2008; Tzortzopoulou 2008). The largest of these involved over 25,000 patients, and assessed the use of TXA, EACA, and another type of antifibrinolytic, aprotinin, with respect to the minimisation of perioperative allogeneic blood transfusions (Henry 2011). However, no systematic review has addressed the use of antifibrinolytics to prevent bleeding in haematology patients.

TXA and EACA are effective in surgical patients (Henry 2011; Ker 2012). They have been used widely in both elective and emergency surgery and have been shown to reduce both blood loss and the need for blood transfusions. In the largest Cochrane review, 65 trials compared TXA with control and comprised a total of 4842 patients of whom 2528 were randomised to TXA. TXA versus control showed a relative reduction in the need for allogeneic blood transfusion of 39% (Henry 2011). A significant effect was also observed for EACA; in 16 trials comparing EACA with control (with a total of 1035 patients, of whom 530 were randomised to EACA), there was a relative reduction in the need for allogeneic blood transfusion of 19% (Henry 2011). In the literature there appears to be a paucity of direct comparisons between TXA and EACA but they appear comparable in terms of safety and efficacy. A recent study comparing TXA and EACA in 234 paediatric patients undergoing cardiac surgery found no significant differences between the two in terms of transfusion requirement, rates of revision for re-bleeding, postoperative complications (such as seizures, renal failure and thrombosis) and in-house mortality (Martin 2011).

TXA is effective in trauma patients. In a recent large RCT (CRASH-2), TXA has been shown to significantly reduce the risk of death due to bleeding in trauma patients with significant haemorrhage (Shakur 2010). TXA has also been found to be highly cost-effective: it is relatively inexpensive and its use in preventing bleeding may obviate the need for additional transfusion of blood products and longer stays in hospital. In a recent cost-effectiveness analysis of the CRASH-2 trial, Guerriero 2011 reported that the administration of TXA within three hours of injury to bleeding trauma patients has been estimated to save 755 life years (LYs) per 1000 trauma patients in the UK, and the incremental cost of giving TXA versus not giving TXA was estimated at USD 48,002 in the UK, equivalent of a cost of around USD 64 per life-year saved.

TXA and EACA are commonly used to treat bleeding in patients with haematological disorders (Lozano 2013). They are also used to prevent bleeding in patients who are refractory to platelet transfusions (Lozano 2013). It therefore seems possible that lysine analogues may also be cost-effective in preventing bleeding in patients with haematological disorders with severe thrombocytopenia who are not refractory to platelet transfusions.

TXA and EACA are the only antifibrinolytics in common use. Aprotinin, a naturally occurring serine protease inhibitor, was once commonly used as a blood-sparing agent, particularly in cardiac surgery. However, it is now used rarely due to concerns of an increased risk of cardiovascular complications and death (Henry 2011). This was because the BART (Blood Conservation Using Antifibrinolytics in a Randomized Trial) multi-centre blinded RCT was terminated early when a higher rate of death was seen in patients receiving aprotinin (Fergusson 2008). This study was designed to determine whether aprotinin was superior to either TXA or EACA in decreasing massive postoperative bleeding in patients undergoing high-risk cardiac surgery. A modest and non-significant reduction in the risk of massive bleeding was observed in the aprotinin arm compared to TXA or EACA but the rate of death from any cause at 30 days was 6.0% in the aprotinin group, compared with 3.9% (relative risk 1.55; 95% CI 0.99 to 2.42) and 4.0% (relative risk 1.52; 95% CI 0.98 to 2.36) in the TXA and EACA groups, respectively. The authors concluded the negative mortality trend associated with aprotinin, as compared with the lysine analogues, precluded its use in high-risk cardiac surgery (Fergusson 2008).

Although TXA and EACA have been shown to be effective in other patient groups there is a concern that these drugs may increase the rate of thromboembolism (Henry 2011). This is particularly important in haematology patients, as patients with an underlying malignancy already have a higher rate of thromboembolic disease than the general population. In a retrospective cohort study of thromboembolism in hospitalised neutropenic cancer patients, 4% (593/14,600) of acute leukaemia patients developed venous thromboembolism and 1.9% (279/14,600) of acute leukaemia patients developed arterial thromboembolism (Khorana 2006). Furthermore, TXA and EACA may increase the risk of disseminated intravascular coagulation (DIC). In a subsequent exploratory analysis of the CRASH-2 trial, late treatment with TXA (> 3 hours) seemed to increase the risk of death in trauma patients due to bleeding (Roberts 2011). The mechanism underlying this could not be readily explained, but the authors noted that one possibility related to the evolution of DIC, a condition in which lysine analogues could be contraindicated (Prentice 1980; Roberts 2011; Sawamura 2009). This highlights a serious need for caution in the use of these agents in patients with haematological malignancies as they are at increased risk of DIC (Franchini 2010). Overt cases of DIC are diagnosed in approximately 15% of patients with acute leukaemia and bleeding manifestations tend to prevail over thrombosis (Franchini 2010).

Despite these important concerns, it should be noted that in the recent large Cochrane review of over 25,000 patients (Henry 2011), the use of TXA or EACA was not associated with an increased risk of mortality, myocardial infarction, deep vein thrombosis, stroke, incidence of renal dysfunction or length of hospital stay, although the data were sparse. In addition, there have been small RCTs assessing the efficacy of TXA versus placebo in haematology patients

that did not report an increase in thromboembolic complications, although sample sizes were small (Avvisati 1989; Shpilberg 1995).

How the intervention might work

Tranexamic acid and epsilon aminocaproic acid are synthetic analogues of the amino acid lysine and act by blocking the lysine binding sites on plasminogen. This inhibits the formation of plasmin and therefore prevents fibrinolysis, leading to improved haemostasis (Okamoto 1997). In vitro tranexamic acid is approximately 10 times more potent than aminocaproic acid and binds much more strongly to the sites on the plasminogen molecule (Faught 1998). It is plausible that if these lysine analogues are effective and safe, the bleeding risk in patients with haematological disorders could be reduced, and the requirement for prophylactic platelet transfusions could be minimised.

Why it is important to do this review

Clearly, it is essential to reduce the risk of bleeding in patients with haematological disorders and thrombocytopenia as effectively and as safely as possible. Since the CRASH-2 trial (Roberts 2011) and two large systematic reviews (Henry 2011; Ker 2012) have shown antifibrinolytics to be effective in other patient groups there has been renewed interest in using this drug to prevent bleeding in patients with haematological disorders.

The key questions to address are:

1. What is the efficacy of lysine analogues in preventing bleeding in thrombocytopenic patients with haematological disorders?
2. Can the number of prophylactic platelet transfusions be minimised?
3. Does the use of lysine analogues lead to a significant increase in the incidence of thromboembolism?

If lysine analogues are shown to be effective whilst demonstrating an acceptable safety profile, there would be a strong case for their routine use in patients with haematological disorders at significant risk of severe thrombocytopenia. A systematic review is therefore required before any proposed introduction of these agents in patients with haematological disorders.

OBJECTIVES

To determine the efficacy and safety of antifibrinolytics (lysine analogues) in preventing bleeding in patients with haematological disorders.

METHODS

Criteria for considering studies for this review

Types of studies

We only included RCTs in this review, irrespective of language or publication status.

Types of participants

All patients, of any age, with a haematological disorder (malignant or non-malignant) who were severely thrombocytopenic due to bone marrow failure (secondary to the disease or to its treatment) and required platelet transfusions. We excluded patients with immune thrombocytopenic purpura (ITP) because these patients are not usually treated with platelet transfusions.

Types of interventions

We only reviewed antifibrinolytic agents that act by competitively inhibiting the conversion of plasminogen to plasmin (lysine analogues), i.e. tranexamic acid and epsilon aminocaproic acid. Aprotinin is a serine protease and has a different mechanism of action. We included the following comparisons:

- TXA versus placebo;
- EACA versus placebo;
- TXA versus EACA.

We included any dose of the medication, administered either orally or intravenously.

Types of outcome measures

Primary outcomes

- Number, site and severity of bleeding (i.e. any bleeding, clinically significant bleeding, life-threatening bleeding)
- Thromboembolism (venous and arterial)

Secondary outcomes

- Mortality (all causes)
- Mortality (secondary to bleeding)
- Mortality (secondary to thromboembolism)
- Laboratory assessment of fibrinolysis
- Number of platelet transfusions
- Number of red cell transfusions
- Adverse events of antifibrinolytic agents
- Adverse events of transfusions (e.g. transfusion reactions, antibody development)
- Disseminated intravascular coagulation (DIC)
- Quality of life (QoL)

We listed both primary outcomes in 'Summary of findings' tables, as well as the number of red cell and platelet transfusions.

Search methods for identification of studies

We formulated search strategies in collaboration with the Cochrane Haematological Malignancies Group.

Electronic searches

Our Information Specialist (CD) formulated the search strategies used in collaboration with the Cochrane Haematological Malignancies Group. Relevant RCTs were searched for in the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 12, 2012) ([Appendix 1](#));
- MEDLINE (from 1948 to 10 January 2013) ([Appendix 2](#));
- EMBASE (from 1980 to 10 January 2013) ([Appendix 3](#));
- CINAHL (from 1982 to 10 January 2013) ([Appendix 4](#));
- PubMed (e-publications as of 10 January 2013 only) ([Appendix 5](#));
- LILACS (from 1982 to 10 January 2013) ([Appendix 6](#));
- KoreaMed (from 1982 to 10 January 2013) ([Appendix 6](#));
- PakMediNet (from 2001 to 10 January 2013) ([Appendix 6](#));
- IndMed (from 1985 to 10 January 2013) ([Appendix 6](#));
- UKBTS SRI Transfusion Evidence Library (www.transfusionevidencelibrary.com) (from 1980 to 10 January 2013) ([Appendix 7](#));
- Web of Science, Conference Proceedings Citation Index (from 1990 to 10 January 2013) ([Appendix 8](#)).

Ongoing trial databases (all years) were also searched on 10 January 2013:

- ClinicalTrials.gov ([Appendix 9](#));
- WHO International Clinical Trials Registry Platform (ICTRP) ([Appendix 9](#));
- ISRCTN Register ([Appendix 10](#));
- EU Clinical Trials Register (EUDRACT) ([Appendix 10](#));
- UMIN-CTR Japanese Clinical Trials Registry and the Hong Kong Clinical Trials Registry ([Appendix 10](#)).

Searches in MEDLINE, EMBASE and CINAHL were combined with adaptations of the RCT search filters as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Lefebvre 2011](#)). Searches were not restricted by either date or language.

Searching other resources

We augmented database searching with the following.

- Handsearching of reference lists
 - We checked references of all identified trials, relevant review articles and current treatment guidelines for further literature.
 - We limited these searches to the 'first generation' reference lists.
- Personal contacts

- We contacted authors of relevant studies, study groups and experts worldwide who are known to be active in the field for unpublished material or further information on ongoing studies.

Data collection and analysis

Selection of studies

One author (CD) initially screened all search results for relevance against the eligibility criteria and disregarded all those that were clearly irrelevant. Thereafter, two review authors (DW, LE) independently screened all the remaining hits for relevance against the full eligibility criteria. We retrieved full-text papers for all those references where we were unable to decide on eligibility based on title and abstract alone. We sought further information from the study authors where articles contained insufficient data to make a decision about eligibility. We resolved differences of opinion through discussion and consensus. We tabulated studies which did not meet our eligibility criteria ([Characteristics of excluded studies](#)).

Data extraction and management

Two review authors (DW, SB) conducted data extraction according to the guidelines proposed by The Cochrane Collaboration ([Higgins 2011a](#)). We resolved potential disagreements between the authors by consensus. If an agreement could not be reached, a third author (LE) was asked to give her opinion. We were not blinded to the names of authors, institutions, journals or the outcomes of the trials. We used a standardised data extraction form to record the following items:

1. General information: review author's name, date of data extraction, study ID, first author of study, author's contact address (if available), citation of paper, objectives of the trial.
2. Trial details: trial design, location, setting, sample size, power calculation, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow-up, stratification, stopping rules described, results, conclusion and funding.
3. 'Risk of bias' assessment: sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias.
4. Characteristics of participants: age, gender, ethnicity, total number recruited, total number randomised, total number analysed, types of haematological disease, lost to follow-up numbers, drop outs (percentage in each arm) with reasons, protocol violations, current treatment, previous treatments.
5. Interventions: experimental and control interventions, type of antifibrinolytic given, timing of intervention, compliance to interventions, additional interventions given especially in

relation to platelet and red cell transfusions, any differences between interventions.

6. Outcomes measured: number, site and severity of bleeding episodes; thromboembolism (venous and arterial); mortality (all causes); mortality due to haemorrhage; mortality due to thromboembolism; laboratory assessment of fibrinolysis; number of platelet transfusions; number of red cell transfusions; adverse effects of antifibrinolytic agents; adverse effects of transfusions (e.g. transfusion reactions, development of platelet antibodies); DIC.

We retrieved the data from both full-text and abstract reports of studies. Where these sources did not provide sufficient information, we contacted authors, study groups or companies for additional details.

Assessment of risk of bias in included studies

Three authors (DW, SB, LE) assessed all included studies for possible risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011c](#)). The assessment included information about the design, conduct and analysis of the trial. We evaluated whether the studies are at a low risk, high risk or unclear risk of bias. To assess risk of bias, the following questions were included in the 'Risk of bias' table for each included study:

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was the knowledge of the allocated intervention adequately prevented during the study?
 - Were incomplete outcome data adequately addressed?
 - Are reports of the study free of selective outcome reporting?
 - Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

We performed this according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2011](#)). For dichotomous outcomes we recorded the numbers of outcomes in treatment and control groups.

For continuous outcomes, we recorded the mean and standard deviations.

Dealing with missing data

We performed this according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). We contacted one author by email in order to obtain information that was missing or unclear in the published report. One author responded to our email request but was unable to provide any further information ([Gallardo 1983](#)). We recorded the number of patients lost to follow-up for each trial.

Assessment of heterogeneity

We did not perform a formal assessment of heterogeneity because it was not possible to perform meta-analyses due to the nature of the data reported by the included studies. (Deeks 2011).

Assessment of reporting biases

We did not perform a formal assessment of reporting biases because there were not enough data to support such an assessment and no meta-analyses of outcome data were performed (Sterne 2011).

Data synthesis

We performed a narrative synthesis of the findings from the included studies, structured around the type of antifibrinolytic. No statistical analyses were performed because the studies reported outcomes in different ways and these results could not be integrated.

We used the GRADE profiler to create 'Summary of findings' tables as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

Subgroup analysis and investigation of heterogeneity

We pre-specified three subgroup analyses:

- Age (children/adults);
- Underlying haematological diagnoses;
- Type of treatment (e.g. chemotherapy, autologous and allogeneic transplantation, immunosuppression).

However, we did not perform any subgroup analyses due to a lack of outcome data.

Sensitivity analysis

We did not perform a formal sensitivity analysis because we performed no meta-analyses.

RESULTS

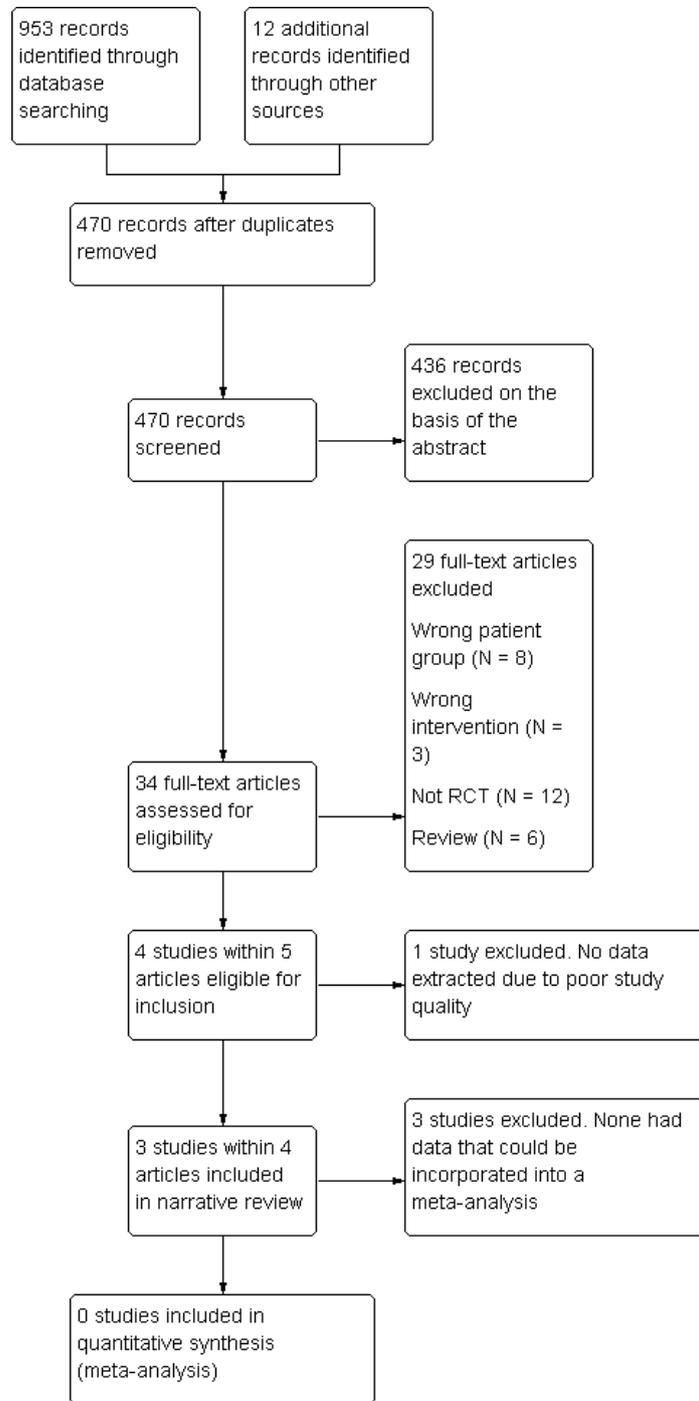
Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#) and [Table 1](#).

Results of the search

See PRISMA diagram [Figure 1](#). The original search identified 953 records through database searching with an additional 12 records identified through other sources (principally the handsearching of reference lists of included studies). After duplicates were removed, we screened 470 records in abstract form for eligibility and excluded 436 records. Of the remaining records, we retrieved and assessed 34 full-text articles for eligibility and excluded 29 due to either: not being an RCT (N = 12), wrong patient group (N = 8), because the article was a review (N = 6) or ineligible intervention (N = 3).

Figure 1. Study flow diagram.



Included studies

There were four studies (within five articles) eligible for inclusion (Avisati 1989; Fricke 1991; Gallardo 1983; Shpilberg 1995). The four studies were published between 1989 and 1995. Two were conducted in the USA, one in Israel, and a further one in Italy and the Netherlands. The studies randomised a total of 95 participants (range 8 to 56). See [Characteristics of included studies](#) for full details of each study and [Table 1](#) for a comparison between studies.

- Three studies evaluated the effect of tranexamic acid (TXA) therapy in the reduction of bleeding during treatment of acute myeloid leukaemia (Avisati 1989; Fricke 1991; Shpilberg 1995). One cross-over TXA study (eight patients) was excluded from the outcome analysis because the data were uninterpretable due to major methodological flaws in the study design (see [Table 1](#) for details of the study design) (Fricke 1991). We included data from this study in the 'Risk of bias' assessment.

- One study evaluated the effect of epsilon aminocaproic acid (EACA) for bleeding control during remission induction for acute leukaemia (Gallardo 1983).

In the remainder of this review, these sub-categories will be reported in separate sections.

Tranexamic acid (TXA) versus placebo

There were three studies evaluating this comparison (Avisati 1989; Fricke 1991; Shpilberg 1995) ([Table 1](#)).

Participants

In total 76 patients were randomised to receive TXA or placebo ([Table 1](#)). The population characteristics varied between the studies. In Avisati 1989, the 12 patients randomised were all diagnosed with acute promyelocytic leukaemia (APML) and were all undergoing induction chemotherapy. In Fricke 1991, seven patients had aplastic anaemia (AA) and one patient had myelodysplastic syndrome (MDS); all were out-patients but no other treatments were reported. In Shpilberg 1995, all 56 patients had acute myeloid leukaemia (AML), however, only one of the patients randomised was diagnosed with APML (consolidation group). Thirty-eight of the patients randomised were undergoing induction chemotherapy and 18 were undergoing consolidation chemotherapy.

Intervention

All three studies compared TXA versus placebo ([Table 1](#)). In Avisati 1989, TXA or placebo began at the same time as the antileukaemic therapy (day 1) and lasted for 14 days. In Fricke

1991, all patients served as their own control and, after a four-day trial period to test drug tolerance (followed by a one-week interval without the drug), each patient began a course of either TXA or placebo that lasted for four weeks or until a platelet transfusion was required to control bleeding. In Shpilberg 1995, TXA or placebo was given when the platelet count was less than $20 \times 10^9/l$ or in a falling trend and less than $50 \times 10^9/l$.

Co-interventions

In Avisati 1989, platelet transfusions (6 to $8U/m^2$) were given routinely during the first seven days and additionally for overt haemorrhage, and packed red cells were administered to maintain the haemoglobin concentration above 9.0 g/dl. In Fricke 1991, each patient's personal physician was permitted to determine the need for platelet transfusion based on "some form of bleeding, such as severe petechiae, blood blisters, and gum or nose bleeding". No red cell transfusion policy was stated. In Shpilberg 1995, platelet transfusions (4 units/ m^2) were given irrespective of the count but only when clinically significant bleeding occurred and packed red cells were given to maintain the haemoglobin concentration above 9.0 g/dl.

Outcomes

Efficacy endpoints in Avisati 1989 were severity of bleeding, thromboembolism, laboratory assessment of fibrinolysis, packed red cell and platelet concentrate transfusion requirement. In Fricke 1991, the endpoints were number of bleeding episodes, severity of bleeding episodes, site of bleeding episodes, red cell and platelet transfusion requirements, and drug side effects. Shpilberg 1995 reported the number of bleeding events and severity of bleeding (using a scoring system), red cell and platelet concentrate transfusion requirement, thromboembolism and adverse events of drug, duration of hospitalisation, duration of significant thrombocytopenia ($< 20 \times 10^9/l$) and days with fever.

Epsilon aminocaproic acid (EACA) versus placebo

There was only one study evaluating this comparison (Gallardo 1983). It was an abstract published in 1983 detailing a randomised two-arm study with patients undergoing remission induction for acute leukaemia.

Participants

In total 19 patients undergoing remission induction for acute leukaemia were randomised to receive EACA or not; 15 with AML and four with acute lymphocytic leukaemia (ALL). One patient

was not evaluable for unstated reasons, leaving nine patients in each study arm.

Intervention

All patients received platelet transfusions (multiple, single donor or HLA-matched) in the event of thrombocytopenia (< 20,000/microlitre) - this count defined the “days at risk of bleeding”. One arm received EACA (100 mg/kg loading dose and 12 to 24 g/day thereafter in divided doses) with the platelet transfusion whilst the other arm did not.

Co-interventions

All patients received platelet transfusions (multiple, single donor or HLA-matched) in the event of thrombocytopenia (< 20,000/microlitre) - this count defined the “days at risk of bleeding”. This study reported no other co-interventions.

Outcomes

Outcomes reported included bleeding; either as capillary bleeding (CB; skin, mucous membranes, conjunctivae, nose, guaiac in gastrointestinal (GI) or genitourinary (GU) tract) or major bleeding (MB; nose bleeding requiring posterior packing, gross GI or GU bleeding and central nervous system (CNS) bleeding), monitoring of antifibrinolytic therapy using I¹²⁵ fibrinogen plasma clot

lysis, platelet transfusion requirement, adverse events of drug and thromboembolism.

Tranexamic acid versus epsilon aminocaproic acid

No RCTs that evaluated this comparison were identified.

Excluded studies

See [Characteristics of excluded studies](#) for further details.

- Twelve studies were not randomised controlled trials.

([Bartholomew 1989](#); [Ben-Bassat 1990](#); [Cattan 1963](#); [Chakrabarti 1998](#); [Dean 1997](#); [Fossa 1978](#); [Gardner 1980](#); [Garewal 1985](#); [Kalmadi 2006](#); [Sanz 2010](#); [Schwartz 1986](#); [Wassenaar 2008](#))

- Eight studies examined different patient groups.

([Amar 2003](#); [Byams 2007](#); [Celebi 2006](#); [McConnell 2011](#); [McConnell 2012](#); [Mevio 1983](#); [Movafegh 2011](#); [Yang 2001](#))

- Six studies were reviews.

([Bates 2011](#); [Breen 2012](#); [Brown 2002](#); [Levy 2005](#); [Marti-Carvajal 2011](#); [Rickles 2007](#))

- Three studies examined a different intervention.

([Bedirhan 2001](#); [Jeserschek 2003](#); [Katzel 1998](#))

Risk of bias in included studies

See [Figure 2](#) and [Characteristics of included studies](#) for further details.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Protocol deviation balanced?
Awisati 1989	?	?	?	?	+	?	+	?
Fricke 1991	?	?	?	?	-	-	-	?
Gallardo 1983	?	?	?	?	?	-	?	?
Shpilberg 1995	?	?	?	?	?	?	?	?

All studies (Avisati 1989; Fricke 1991; Gallardo 1983; Shpilberg 1995) had some threats to validity. The majority of these threats were due to a lack of detail provided on the specific criteria and we therefore judged them as 'unclear' using the Cochrane grading system. However Fricke 1991 had significant flaws in study design which we considered 'high risk', including attrition bias, reporting bias and other sources of bias (see Figure 2 and Characteristics of included studies).

Allocation

None of the studies reported the method of sequence generation or allocation concealment and all were reported in this review as having an unclear risk of bias.

Blinding

We deemed all studies to have an unclear risk of bias (Avisati 1989; Fricke 1991; Gallardo 1983; Shpilberg 1995).

In Avisati 1989, the risk of performance bias and detection bias were unclear as the article states that attending physicians were blinded to the treatment groups and that bleeding assessments were examined by the same investigator, but it is not stated whether the investigator was one of the attending physicians. In Gallardo 1983, the risk of performance and detection bias was unclear as the abstract did not state whether the investigators and or patients were blinded or not and does not state who carried out the bleeding assessments. In Shpilberg 1995, the threat of performance and detection bias was unclear as although the study states that it was double-blinded, no further details were given as to who was blinded. In Fricke 1991, although it was stated that study was double-blinded, the article states that drug levels were obtained during 38 of the 49 courses. It does not state that the investigators or patients were blinded to this information. It also states that the study defined overall success of TXA in a patient as either five failures of placebo and none of drug or seven failures of placebo and one of drug and defined overall failure of TXA as two failed courses of drug. Sequential courses continued until overall success or failure of TXA could be determined. However, it did not state how this assessment of success or failure was performed without un-blinding study personnel.

Incomplete outcome data

There were no missing outcome data in Avisati 1989, so we deemed the article to have a low risk of attrition bias. We deemed Fricke 1991 to have a high risk of bias - the article states that "three [of eight] patients completed the randomised portion of the study ... five of the eight patients did not complete enough courses to determine the efficacy of the drug". The two remaining studies (Gallardo 1983; Shpilberg 1995) were deemed to have an unclear

risk of bias as there were insufficient data to assess incomplete outcome data.

Selective reporting

We deemed two studies to have an unclear risk of bias (Avisati 1989; Shpilberg 1995) and two studies to have a high risk of bias (Fricke 1991; Gallardo 1983).

There were insufficient data to assess the risk of selective reporting (reporting bias) in Avisati 1989 and in Shpilberg 1995 and we deemed these to have an unclear risk of bias. There was a high risk of reporting bias in two studies (Fricke 1991; Gallardo 1983)

In Fricke 1991, one patient died of intracranial haemorrhage four days after starting the first randomised course. Data from this course were not reported. There were two courses of TXA or placebo interrupted in two separate patients; one due to an upper respiratory tract infection and the other in which the patient developed an oesophageal haematoma after starting antibiotic treatment for an infection. Data from these courses were not included in the analysis as the investigators felt that the infection/antibiotic treatment may have compromised haemostasis. Furthermore, in Fricke 1991, the article states that severity of bleeding (as well as number and site) were recorded by the assessor (the patient) but this outcome is not reported in the article. Finally, five of the eight patients were reported as not completing enough sessions to determine the effectiveness of TXA.

In Gallardo 1983, there are data for thromboembolism and death ("no patient died of thrombosis") but no data given on number episodes of thromboembolism or number of deaths. There are also no data reported on the monitoring of antifibrinolytic therapy using I¹²⁵ fibrinogen plasma clot lysis. This may have been because the article was an abstract and there was limited space available.

Other potential sources of bias

We deemed two studies to have a low risk of bias (Avisati 1989; Shpilberg 1995), one an unclear risk of bias (Gallardo 1983) and the remaining one a high risk of bias (Fricke 1991).

Avisati 1989 and Shpilberg 1995 seemed to be free of other sources of bias and we deemed them to be at low risk of bias. In Gallardo 1983, the "at risk of bleeding days" were much higher in the EACA group - 158 versus 80 due to more severe thrombocytopenia and more cycles of chemotherapy for refractory disease. There may be bias in the randomisation procedure but the method of randomisation is not stated and we deemed the study overall to have an unclear risk of bias.

There were other sources of potential bias in Fricke 1991. The overall success of TXA was defined as either five failures of placebo and none of the drug or seven failures of placebo and one of the

drug and overall failure of TXA was defined as two failed courses of drug. Failure of a course was defined as a patient receiving a platelet transfusion for bleeding during a four-week study period. Patients received a variable number of courses of drug/placebo. The three patients who completed the study received between three (two TXA, one placebo) and nine courses (five TXA, four placebo) of treatment. The five patients who did not complete the study received between zero and 20 courses (10 TXA, 10 placebo) of treatment. Of the three patients who completed the study, two did not have any successful courses of treatment. The third patient had 3/5 successful courses with TXA and 1/4 successful courses with placebo, however this was classified by the study as a failure of TXA (two failed courses with TXA). Interim analysis of the data was therefore performed after each course of treatment for each patient, with completion of the study being biased against TXA (only two failures of TXA are required, whereas five failures of placebo and none of TXA for study to be classified as completed). In [Fricke 1991](#), failure of a course of treatment would be classified in the same way whether patient was on study drug for one day before bleeding or 27 days before bleeding that required treatment with a platelet transfusion. More bleeding episodes seen in the TXA arm may have been due to more days on study drug before bleeding requiring a platelet transfusion. Number of days on study drug before bleeding was not reported for individual courses.

No protocol deviations were commented upon in any of the studies. However, in [Fricke 1991](#), one patient began receiving HLA-matched platelet transfusions two months after enrolment and was kept in the study because these platelet transfusions failed to control bleeding. Definition of failure of a course of treatment for this patient was the need for additional platelet transfusions. It is unclear whether this represented a protocol violation but two other patients were withdrawn from the study after they started to receive HLA-matched platelet transfusions.

Effects of interventions

See: [Summary of findings for the main comparison Antifibrinolytics \(lysine analogues\) compared to placebo to prevent bleeding in patients with haematological disorders](#) (See [Table 2](#) and [Table 3](#))

Tranexamic acid (TXA) versus placebo

There were three studies evaluating this comparison ([Avisati 1989](#); [Fricke 1991](#); [Shpilberg 1995](#)).

We extracted no data from the [Fricke 1991](#) study due to major methodological problems in the study design. In addition to the high risk of bias in terms of attrition bias, reporting bias and other bias (see text section above, [Figure 2](#) and the [Risk of bias in included studies](#) table) there were a variable number of study cycles depending on the results of previous cycles of treatment. All these factors meant that it was impossible to fully understand the

data in this trial and we took the decision to not include this trial in the assessment of 'effects of interventions'.

Number, site and severity of bleeding (i.e. any bleeding, clinically significant bleeding, life-threatening bleeding)

Both studies reported bleeding. [Avisati 1989](#) reported bleeding as a cumulative score in the first observation period (days two to seven), second observation period (days eight to 14) and overall cumulative score. The cumulative score when comparing TXA and placebo in the first, second and overall study periods were 2 versus 31, 1 versus 11, and 3 versus 42, respectively. [Shpilberg 1995](#) reported the mean number of bleeding events per patient. During induction chemotherapy, the mean number of bleeding events per patient was 6.2 (2.9) versus 4.5 (3.6) for TXA and placebo respectively. During consolidation chemotherapy, there was a statistically significant difference ($P < 0.5$) comparing TXA with 1.1 (1.4) bleeding events per patient versus 2.6 (2.2) in the placebo arm. There was also a statistically significant difference in the bleeding score during consolidation chemotherapy with 1.3 (1.8) in the TXA arm versus 5.1 (3.6) in the placebo arm.

Thromboembolism (venous and arterial)

Both studies reported thromboembolism but did not distinguish between arterial or venous events. [Shpilberg 1995](#) reported that no thromboembolic events occurred in either group throughout the study. [Avisati 1989](#) reported that there were no thromboembolic complications and there was no evidence of enhanced thrombin generation (as assessed by thrombin-antithrombin-III complexes). TXA was only given for the first six days out of 14 days of observation because of what the authors described as the "known increase of cerebral thromboembolic disease with prolonged therapy".

Mortality (all causes)

Neither study reported all-cause mortality.

Mortality (secondary to bleeding)

Only [Shpilberg 1995](#) reported mortality (secondary to bleeding) and stated that there was no fatal bleeding in either group.

Mortality (secondary to thromboembolism)

Neither study reported mortality secondary to thromboembolism.

Laboratory assessment of fibrinolysis

Only [Avisati 1989](#) reported laboratory assessment of fibrinolysis. There were no statistically significant differences in the coagulation and fibrinolysis indices between the two groups apart from the results for fibrin degradation products. The study stated that

median fibrin degradation products decreased in the TXA arm but increased in the placebo arm during the first week of observation ($P < 0.01$) (Table 4).

Number of platelet transfusions

Both studies reported the number of platelet transfusions. [Avvisati 1989](#) reported that in the first period of observation (days two to seven) 69 units of platelets were transfused in the TXA arm versus 177 units in the placebo arm. In the second period of observation (days eight to 14) 0 units of platelets were transfused in the TXA arm versus 45 units in the placebo arm. Overall, 69 units were transfused in the TXA arm versus 222 units in the placebo arm. During induction chemotherapy in [Shpilberg 1995](#), there was no difference in the mean number of platelet transfusions in the TXA arm (22.1 (13.2)) units versus the placebo arm (23.1 (11.70)). However, there was a significant difference ($P < 0.05$) during consolidation chemotherapy with respect to the mean number of platelet units transfused between the TXA arm (3.7 (4.1)) versus the placebo arm (9.3 (3.3)).

Number of red cell transfusions

Both studies reported number of red cell transfusions. [Avvisati 1989](#) reported a reduction in red cell transfusions given to the TXA arm compared to the placebo arm. During the first observation period (day two to seven) 19 units were transfused in the TXA arm compared to 35 units in the placebo arm. In the second observation period (days eight to 14), nine units were transfused versus 21 units. Overall 21 units were transfused in the TXA arm versus 56 units in the placebo arm. There was no reduction in red cell transfusion requirements in [Shpilberg 1995](#). During induction, the mean number of transfusions in the TXA arm versus the placebo arm was 7.5 (4.7) versus 7.3 (3.3). During consolidation, the mean number was 4.1 (2.8) units versus 4.1 (3.4) units in the TXA and placebo arms, respectively.

Adverse events of antifibrinolytic agents

[Avvisati 1989](#) did not report adverse events of antifibrinolytic agents. [Shpilberg 1995](#) reported that no side effects were observed.

Adverse events of transfusions (e.g. transfusion reactions, antibody development)

Neither study reported the adverse events of transfusions.

Disseminated intravascular coagulation (DIC)

Neither study reported DIC.

Quality of life

Neither study reported quality of life.

Epsilon aminocaproic acid (EACA) versus placebo

There was only one study evaluating this comparison ([Gallardo 1983](#)). It was a randomised two-arm study published in 1983 involving patients undergoing remission induction for acute leukaemia.

Number, site and severity of bleeding (i.e. any bleeding, clinically significant bleeding, life-threatening bleeding)

[Gallardo 1983](#) reported bleeding as the proportion of days at risk of bleeding (defined as where the platelet count was $< 20,000/\text{microlitre}$). This was 158 days for the group on EACA compared to only 80 for the group on no EACA, but the abstract noted that the patients on EACA had more severe thrombocytopenia and more cycles of chemotherapy for refractory disease. Capillary bleeding (i.e. bleeding in skin, mucous membranes, conjunctivae, nose and guaiac in gastrointestinal (GI) or genitourinary (GU) tract) was present in 31% of days at risk with patients on EACA compared to 50% of patients not receiving EACA (P value not reported). There was no difference in major bleeding (defined as nose bleeding requiring posterior packing, gross GI or GU bleeding and bleeds within the CNS) between the two groups (15% versus 19%) (P value not reported).

Thromboembolism (venous and arterial)

There were no reports of thromboembolism although the study stated that no patient died of thrombosis.

Mortality (all causes)

The study did not report all-cause mortality.

Mortality (secondary to bleeding)

The study did not report mortality secondary to bleeding.

Mortality (secondary to thromboembolism)

The study stated that no patient died of thrombosis.

Laboratory assessment of fibrinolysis

The study reported that antifibrinolytic therapy was monitored with the I^{125} fibrinogen plasma clot lysis assay although no further data were described regarding this outcome.

Number of platelet transfusions

The study reported that platelet transfusions per days at risk were decreased in the patients on EACA, one every 13.3 versus one every 10.5 days at risk. However, the authors noted that these were not statistically significant (P value not reported). The abstract detailed a projection that the results would achieve statistical significance at a P value of < 0.05 with 25 patients in each group. However, no subsequent study has since been published. It is therefore important to note that there were insufficient patients within this study to show statistical significance for any clinically meaningful true difference.

Number of red cell transfusions

The study did not report the number of red cell transfusions

Adverse events of antifibrinolytic agents

No specific adverse events were described, although the study stated that side effects were minimal.

Adverse events of transfusions (e.g. transfusion reactions, antibody development)

The study did not report adverse events of transfusions.

DIC

The study did not report DIC.

Quality of life

The study did not report quality of life.

Tranexamic acid versus epsilon aminocaproic acid

No RCTs that evaluated this comparison were identified.

DISCUSSION

The overall aim of this review was to determine the efficacy and safety of antifibrinolytics (lysine analogues) in the prevention of bleeding in patients with haematological disorders.

Specifically, we aimed to address the following questions:

- i) Do lysine analogues help to prevent bleeding in thrombocytopenic patients with haematological disorders?*
- ii) Can the number of prophylactic platelet transfusions be minimised?*
- iii) Do lysine analogues increase the incidence of thromboembolism?*

Our primary outcomes were bleeding and the occurrence of thromboembolism. Our secondary outcomes were mortality, laboratory assessment of fibrinolysis, number of platelet transfusions, number of red cell transfusions, adverse events of antifibrinolytic agents, adverse events of transfusions (e.g. transfusion reactions, antibody development), disseminated intravascular coagulation (DIC) and quality of life.

Summary of main results

Only four studies met our inclusion criteria and one of these studies had to be excluded from the assessment of [Effects of interventions](#) due to major methodological flaws in its design and a high risk of bias across several criteria. Of the remaining three randomised controlled trials (RCTs), a total of 86 patients were investigated. There were two studies comparing tranexamic acid (TXA) and placebo ([Avvisati 1989](#); [Shpilberg 1995](#)) and one study comparing epsilon aminocaproic acid (EACA) with placebo ([Gallardo 1983](#)). There were no studies comparing TXA with EACA.

i) Do lysine analogues help to prevent bleeding in thrombocytopenic patients with haematological disorders?

All three studies suggested antifibrinolytics reduced the risk of bleeding, although one study ([Shpilberg 1995](#)) only demonstrated this effect in patients undergoing consolidation chemotherapy and not during induction chemotherapy.

ii) Can the number of prophylactic platelet transfusions be minimised?

All three studies reported a reduction in platelet usage. However, in [Shpilberg 1995](#), the effect was only noted for patients undergoing consolidation chemotherapy. This is consistent with the finding that it was only this population who seemed to benefit from both reduced bleeding and a reduced need for platelet transfusions. [Gallardo 1983](#) reported one platelet transfusion every 10.5 days at risk in the placebo arm versus one platelet transfusion every 13.3 days at risk in the EACA arm. However, the authors noted that these data were not statistically significant.

iii) Do lysine analogues increase the incidence of thromboembolism?

Two studies reported the presence or absence of thromboembolism and no events occurred in either of these studies ([Avvisati 1989](#); [Shpilberg 1995](#)). It was reported in [Gallardo 1983](#) that no patient died of thrombosis.

Other results

Two of the studies ([Avvisati 1989](#); [Shpilberg 1995](#)) reported red blood cell (RBC) transfusion requirements. There was no significant difference between the TXA and placebo arms in one study ([Shpilberg 1995](#)) but the other found a significant reduction in RBC usage in the TXA arm ([Avvisati 1989](#)).

None of the studies reported on overall (all-cause) mortality. However, one of the studies reported on mortality due to bleeding ([Shpilberg 1995](#)) and only one reported on mortality due to

thromboembolism (Gallardo 1983); none occurred in either category.

Two studies (Gallardo 1983; Shpilberg 1995) reported on the side effects of antifibrinolytics. Gallardo 1983 stated that the side effects of EACA “were minimal” but did not provide any further detail on this within the abstract. Shpilberg 1995 also reported on side effects of TXA and stated that none were observed.

None of the studies reported on several of our outcomes, these included: adverse events of transfusion, presence or development of DIC, and quality of life.

Overall completeness and applicability of evidence

There are a number of limitations that may affect the strength of any conclusions in this review. Only three small studies were included within this review. Two studies (68 patients) compared TXA with placebo and one study (18 patients) compared EACA with placebo. It was not possible to extract data on outcomes for all trials, and due to the age of all three studies only one author could be located. This author no longer had data available because the trial was conducted over 30 years ago (Gallardo 1983).

Do lysine analogues help to prevent bleeding in thrombocytopenic patients with haematological disorders?

All of the three included studies suggested that bleeding was reduced, although in one study (Shpilberg 1995) this effect was limited to patients undergoing consolidation chemotherapy. The authors suggested that this may have been due to the more complex coagulopathy involved during induction chemotherapy and this may be why there was no appreciable benefit of antifibrinolytics. Clearly, the numbers were small and larger RCTs would be required to support this observation.

Can the number of prophylactic platelet transfusions be minimised?

Again, all studies were suggestive of a role of antifibrinolytics in reducing platelet usage, but it is important to note that in Shpilberg 1995 the effect was only seen in the consolidation group and not in the induction group, and in Gallardo 1983, although the number of platelet transfusions required per days at risk was less for the EACA arm, the results were not statistically significant and greater numbers would be required to achieve this. The authors projected that the results would reach statistical significance at a P value of < 0.05 with 25 patients in each group. However, despite an extensive literature search, no further data were published with larger patient groups

Do lysine analogues increase the incidence of thromboembolism?

Two studies (68 patients) reported the presence or absence of thromboembolic events and no events occurred in either study (Avvisati 1989; Shpilberg 1995). It was reported in Gallardo 1983 that no patient died of thrombosis but it is unclear whether any non-fatal thromboembolic events occurred at all. Although there is no evidence within these three studies to suggest that there is an increased risk of thromboembolism with anti-fibrinolytics there are insufficient data to conclude that this risk does not exist.

Other results

None of the studies reported on several of this review’s outcomes, these included: adverse events of transfusion, the presence or development of DIC, and Quality of Life. This highlights the paucity of data in this area.

Quality of the evidence

We assessed the quality of the evidence using the GRADE approach and this was either very low or the outcome had not been reported by any of the studies (Summary of findings for the main comparison). We were unable to gain additional information via direct author contact and therefore could not improve the quality of the data.

One study (Fricke 1991) had significant methodological problems with its design (Risk of bias in included studies and Figure 2). The overall success of TXA was defined as either five failures of placebo and none of the drug, or seven failures of placebo and one of the drug. Overall failure of TXA was defined as two failed courses of the drug. Failure of a course was defined as a patient receiving a platelet transfusion for bleeding during a four-week study period. Patients received a variable number of courses of drug/placebo. The three patients who completed the study received between three (two TXA, one placebo) and nine courses (five TXA, four placebo) of treatment. The five patients who did not complete the study received between zero and 20 courses (10 TXA, 10 placebo) of treatment. Of the three patients who completed the study, two did not have any successful courses of treatment. The third patient had 3/5 successful courses with TXA and 1/4 successful courses with placebo, however this was classified by the study as a failure of TXA (two failed courses with TXA). Interim analysis of the data was therefore performed after each course of treatment for each patient, with completion of the study being biased against TXA (only two failures of TXA are required, whereas five failures of placebo and none of TXA for study to be classified as completed). All of the other three included studies (Avvisati 1989; Gallardo 1983; Shpilberg 1995) had some threats to validity and in most cases this was graded as ‘unclear’ due to lack of detail in the study to determine the level of risk. One of these studies (Gallardo 1983) was at high risk of selective reporting. The data were presented

in an abstract form and the problem was likely to have been due to limited space. However, important data were omitted, most notably number of episodes of thrombosis since the comment “no patient died of thrombosis” is suggestive of the presence of thrombosis in the study. This is clearly of particular importance when considering the safety of antifibrinolytics when thrombosis is a noted side effect of these agents.

[Avisati 1989](#) appeared to be the study most free of bias with low risk when considering attrition bias and other bias. Other than those mentioned, the other parameters for bias were listed as unclear due to a lack of data to determine risk as high or low.

One negative aspect that all the studies had in common was low sample sizes which reduced their statistical power. This means that even if a clinically meaningful true difference was present it may not be detected due to the small number of patients within each study. This could not be overcome via the use of meta-analysis because the data had been reported in different ways. In one study in particular ([Gallardo 1983](#)) the small sample size was insufficient to permit statistical significance for at least one outcome (number of platelet transfusions in each arm)

Potential biases in the review process

There were no clear biases identified in the review process.

The systematic methods of searching, data extraction and result analysis were followed with reference to the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)).

One important consideration was whether our decision not to include [Fricke 1991](#) in the narrative review of the included studies may represent some risk of publication bias. [Fricke 1991](#) was the only study that showed a lack efficacy of the antifibrinolytic (TXA). However, given the methodological flaws and high levels of risk across several criteria as mentioned in [Assessment of risk of bias in included studies](#), it was felt that it should be excluded from the narrative review.

Agreements and disagreements with other studies or reviews

The fact that there were so few RCTs that were suitable for inclusion in our narrative review demonstrates the lack of efficacy and safety data for the use of antifibrinolytics in thrombocytopenic haematology patients.

Comparison to other systematic reviews

To our knowledge, there are no other systematic reviews examining this topic.

Comparison to non-randomised trials

Several small non-randomised studies have used TXA or EACA in haematology patients ([Bartholomew 1989](#); [Ben-Bassat 1990](#); [Chakrabarti 1998](#); [Dean 1997](#); [Gardner 1980](#); [Garewal 1985](#); [Kalmadi 2006](#); [Schwartz 1986](#); [Wassenaar 2008](#)). However, virtually all of these studies did not have a comparator arm, making it difficult to draw any valid conclusions on the effectiveness and safety of antifibrinolytics. One larger study of TXA in patients with acute promyelocytic leukaemia (APL) used an historical control ([Sanz 2010](#)); there was no difference in deaths due to bleeding between those patients who received TXA and those who did not. Death due to bleeding is a rare event and this study may not have had sufficient power to detect a difference. This study ([Sanz 2010](#)) did show a statistically significant increase in the number of patients who developed thromboembolic complications. However, because [Sanz 2010](#) used an historical control there may have been other confounding factors including changes to the chemotherapy regime used that could have also affected the number of thromboembolic events.

AUTHORS' CONCLUSIONS

Implications for practice

Our results indicate that the evidence available for the use of antifibrinolytics in haematology patients is very limited. The only data available suggest that tranexamic acid and epsilon aminocaproic acid may help reduce bleeding and might therefore be useful adjuncts to platelet transfusions but it was not possible to perform a meta-analysis. All the studies showed a reduction in bleeding, although not for all patients; and all studies showed a reduction in platelet usage. However, the trials were too small to assess whether antifibrinolytics increased the risk of thromboembolic events. Although the available evidence from the included studies appears consistent, our review suggests that the data are far too limited to currently recommend the widespread use of antifibrinolytics in patients with haematological disorders.

Implications for research

Due to the renewed interest in the use of antifibrinolytics in haematology patients larger randomised controlled trials are required before antifibrinolytics can be demonstrated to be efficacious and safe in widespread clinical practice.

ACKNOWLEDGEMENTS

Sally Hopewell: protocol development and methodological expert.

REFERENCES

References to studies included in this review

- Avvisati 1989** *{published data only}*
Avvisati G, ten Cate JW, Buller HR, Mandelli F. Tranexamic acid for control of haemorrhage in acute promyelocytic leukaemia. *Lancet* 1989;**2**(8655):122–4.
- Fricke 1991** *{published data only}*
Fricke W, Alling D, Kimble J, Griffith P, Klein H. Lack of efficacy of tranexamic acid in thrombocytopenic bleeding. *Transfusion* 1991;**31**(4):345–8.
- Gallardo 1983** *{published data only}*
Gallardo RL, Gardner FH. Antifibrinolytic therapy for bleeding control during remission induction for acute leukemia. *Blood* 1983;**62**:202a.
- Shpilberg 1995** *{published data only}*
Shpilberg O, Blumenthal R, Sofer O, Eldor A, Ben-Bassat I. A controlled trial of tranexamic acid (TA) treatment for reduction of bleeding during acute myeloid leukemia (AML) induction and consolidation. *Blood* 1993;**82**:547a.
* Shpilberg O, Blumenthal R, Sofer O, Katz Y, Chetrit A, Ramot B, et al. A controlled trial of tranexamic acid therapy for the reduction of bleeding during treatment of acute myeloid leukemia. *Leukemia and Lymphoma* 1995;**19**:141–4.

References to studies excluded from this review

- Amar 2003** *{published data only}*
Amar D, Grant FM, Zhang H, Boland PJ, Leung DH, Healey JA. Antifibrinolytic therapy and perioperative blood loss in cancer patients undergoing major orthopedic surgery. *Anesthesiology* 2003;**98**:337–42.
- Bartholomew 1989** *{published data only}*
Bartholomew J, Salgia R, Bell W. Control of bleeding in patients with immune and non-immune thrombocytopenia with aminocaproic acid. *Archives of Internal Medicine* 1989;**149**:1959–61.
- Bates 2011** *{published data only}*
Bates JS, Buie LW, Woodis CB. Management of menorrhagia associated with chemotherapy-induced thrombocytopenia in women with hematologic malignancy. *Pharmacotherapy* 2011;**11**:1092–110.
- Bedirhan 2001** *{published data only}*
Bedirhan MA, Turna A, Yagan N, Tasci O. Aprotinin reduces postoperative bleeding and the need for blood products in thoracic surgery: results of a randomized double-blind study. *European Journal of Cardio-thoracic Surgery* 2001;**20**:1122–7.
- Ben-Bassat 1990** *{published data only}*
Ben-Bassat I, Douer D, Ramot B. Tranexamic acid therapy in acute myeloid leukemia: possible reduction of platelet transfusions. *European Journal of Haematology* 1990;**45**: 86–9.

- Breen 2012** *{published data only}*
Breen KA, Grimwade D, Hunt BJ. The pathogenesis and management of the coagulopathy of acute promyelocytic leukaemia. *British Journal of Haematology* 2011;**156**:24–36.
- Brown 2002** *{published data only}*
Brown SA, Aledort LM, Lee CA. Haemostasis: from bench to bedside. *Haemophilia* 2002;**8**:685–93.
- Byams 2007** *{published data only}*
Byams VR, Dowling NF, Heit JA, Kouides PA, Philipp CS, Stein SF, et al. Quality of life (QOL) evaluation in women with menorrhagia and abnormal hemostasis testing participating in a cross-over study of intranasal desmopressin and oral tranexamic acid. *Journal of Thrombosis and Hemostasis* 2007;**5**(2):P–S-189.
- Cattan 1963** *{published data only}*
Cattan A, Schwarzenberg L, Schneider M, Amiel J-L, Mathé G. Trial of epsilon-amino-caproic acid in patients with a bleeding disorder, in particular thrombocytopenic disorders [Essai de traitement par l'acide epsilon-amino-caproïque de patients atteints de syndrome hémorragiques, en particulier de syndromes liés a une thrombocytopenie]. *La Presse Medicale* 1963;**71**(43):2037–8.
- Celebi 2006** *{published data only}*
Celebi N, Celebioglu B, Selcuk M, Canbay O, Karagoz AH, Aypar U. The role of antifibrinolytic agents in gynecologic cancer surgery. *Saudi Medical Journal* 2006;**27**(5):637–41.
- Chakrabarti 1998** *{published data only}*
Chakrabarti S. Low dose bolus aminocaproic acid: an alternative to platelet transfusion in thrombocytopenia. *European Journal of Haematology* 1998;**60**:313–4.
- Dean 1997** *{published data only}*
Dean A, Tuffin P. Fibrinolytic inhibitors for cancer-associated bleeding problems. *Journal of Pain and Symptom Management* 1997;**3**(1):20–4.
- Fossa 1978** *{published data only}*
Fossa SD, Solheim OO, Fossa JJ. Cyklokapron (tranexamic acid) in the treatment of patients with advanced neoplasms. *Tidsskr Nor Laegeforen* 1978;**98**(28):1368–70.
- Gardner 1980** *{published data only}*
Gardner FH, Helmer RE. Aminocaproic acid: use in control of hemorrhage in patients with amegakaryocytic thrombocytopenia. *JAMA* 1980;**243**(1):35–7.
- Garewal 1985** *{published data only}*
Garewal HS, Durie BGM. Anti-fibrinolytic therapy with aminocaproic acid for the control of bleeding in thrombocytopenic patients. *Scandinavian Journal of Haematology* 1985;**35**:497–500.
- Jeserschek 2003** *{published data only}*
Jeserschek R, Clar H, Aigner C, Rehak P, Primus B, Windhager R. Reduction of blood loss using high-dose aprotinin in major orthopaedic surgery. *Journal of Bone and Joint Surgery* 2003;**85**(2):174–7.

Kalmadi 2006 *{published data only}*

Kalmadi S, Tiu R, Lowe C, Jin T, Kalaycio M. Epsilon aminocaproic acid reduces transfusion requirements in patients with thrombocytopenic hemorrhage. *Cancer* 2006; **107**(1):136–40.

Katzel 1998 *{published data only}*

Katzel R, Keuper H, Wiedemann B, Brethner L, Viogt B. The effects of intraoperative aprotinin on perioperative haemostasis and fibrinolysis and their effects on blood loss and transfusion requirements in lung surgery [Effekte der intraoperativen Aprotininapplikation auf perioperative Haemostase und Fibrinolyseveränderungen und ihre Auswirkungen auf Blutverlust und Transfusionsbedarf bei lungenchirurgischen Eingriffen]. *Infusionstherapie und Transfusionsmedizin* 1998;**25**:236–45.

Levy 2005 *{published data only}*

Levy JH. Novel concepts in treatment and prevention of bleeding. *IARS Review Course Lectures*. International Anesthesia Research Society, 2005:43–7.

Marti-Carvajal 2011 *{published data only}*

Marti-Carvajal AJ, Simancas D, Cardona AF. Treatment for disseminated intravascular coagulation in patients with acute and chronic leukemia. *Cochrane Database of Systematic Reviews* 2011, Issue 6. [DOI: 10.1002/14651858.CD008562.pub2]

McConnell 2011 *{published data only}*

McConnell JS, Shewale S, Munro NA, Shah K, Deakin AH, Kinninmonth AWG. Reduction of blood loss in primary hip arthroplasty with tranexamic acid or fibrin spray. *Acta Orthopaedica* 2011;**82**(6):660–3.

McConnell 2012 *{published data only}*

McConnell JS, Shewale S, Munro NA, Shah K, Deakin AH, Kinninmonth AWG. Reducing blood loss in primary knee arthroplasty: a prospective randomised controlled trial of tranexamic acid and fibrin spray. *Knee* 2012;**19**(4):295–8.

Mevio 1983 *{published data only}*

Mevio E, Santarelli P. Tranexamic acid in prevention of oropharyngeal radiomucositis [L'acido tranexamico nella prevenzione delle radiomucositi a livello oro-faringeo]. *La Radiologia Medica* 1983;**69**:325–8.

Movafegh 2011 *{published data only}*

Movafegh A, Eslamian L, Dorabadi A. Effects of intravenous tranexamic acid administration on blood loss during and after cesarian delivery. *International Journal of Gynecology and Obstetrics* 2011;**115**:224–6.

Rickles 2007 *{published data only}*

Rickles FR, Falanga A, Montesinos P, Sanz MA, Brenner B, Barbuti T. Bleeding and thrombosis in acute leukemia: what does the future of therapy look like?. *Thrombosis Research* 2007;**120**(2):99–106.

Sanz 2010 *{published data only}*

Sanz MA, Montesinos P. Open issues on bleeding and thrombosis in acute promyelocytic leukemia. *Thrombosis Research* 2010;**125**(2):51–4.

Schwartz 1986 *{published data only}*

Schwartz BS, Williams EC, Conlan MG, Mosher DF. Epsilon-aminocaproic acid in the treatment of patients with acute promyelocytic leukaemia and acquired alpha-2-plasmin inhibitor deficiency. *Annals of Internal Medicine* 1986;**105**:873–7.

Wassenaar 2008 *{published data only}*

Wassenaar T, Black J, Kahl B, Schwartz B, Longo W, Mosher D, et al. Acute promyelocytic leukemia and acquired alpha-2-plasmin inhibitor deficiency: a retrospective look at the use of epsilon-aminocaproic acid (Amicar) in 30 patients. *Hematological Oncology* 2008;**26**:241–6.

Yang 2001 *{published data only}*

Yang H, Zheng S, Shi C. Clinical study on the efficacy of tranexamic acid in reducing postpartum blood loss: a randomized, comparative, multicenter trial. *Chinese Journal of Obstetrics and Gynecology* 2001;**36**(10):590–2.

Additional references**BCSH 2003**

British Committee for Standards in Haematology. Guidelines for the use of platelet transfusions. *British Journal of Haematology* 2003;**122**(1):10–23.

Bolton-Maggs 2012

Bolton-Maggs PHB (editor) and Cohen H on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. *The 2011 Annual SHOT Report*. Serious Hazards of Transfusion (SHOT), 2012.

Cameron 2007

Cameron B, Rock G, Olberg B, Neurath D. Evaluation of platelet transfusion triggers in a tertiary-care hospital. *Transfusion* 2007;**47**(2):206–11.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Faught 1998

Faught C, Wells P, Fergusson D, Laupacis A. Adverse effects of methods for minimizing perioperative allogeneic transfusion: a critical review of the literature. *Transfusion Medicine Reviews* 1998;**12**(3):206–25.

Fergusson 2008

Fergusson DA, Hebert PC, Mazer CD, Frenes S, MacAdams C, Murkin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *New England Journal of Medicine* 2008;**358**(22):2319–31.

Franchini 2010

Franchini M, Dario Di Minno MN, Coppola A. Disseminated intravascular coagulation in hematologic malignancies. *Seminars in Thrombosis and Haemostasis* 2010;**36**(4):388–403.

Friedmann 2002

Friedmann AM, Sengul H, Lehmann H, Schwartz C, Goodman S. Do basic laboratory tests or clinical observations predict bleeding in thrombocytopenic oncology patients? A reevaluation of prophylactic platelet transfusions. *Transfusion Medicine Reviews* 2002;**16**(1): 34–45.

Greeno 2007

Greeno E, McCullough J, Weisdorf D. Platelet utilisation and the transfusion trigger: a prospective analysis. *Transfusion* 2007;**72**(2):201–5.

Guerriero 2011

Guerriero C, Cairns J, Perel P, Shakur H, Roberts I. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS One* 2011;**6**(5):e18987.

Gurusamy 2011

Gurusamy KS, Pissanou T, Pikhart H, Vaughan J, Burroughs AK, Davidson BR. Methods to decrease blood loss and transfusion requirements for liver transplantation. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD009052.pub2]

Heddle 2009

Heddle NM, Webbert K. Chapter 6: Investigation of acute transfusion reactions. In: Murphy MF, Pamphilon DH editor(s). *Practical Transfusion Medicine*. 3rd Edition. Blackwell, 2009:63–89.

Henry 2011

Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD001886.pub4]

Higgins 2011a

Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in Statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011c

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Ker 2012

Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012;**344**:e3054. [PUBMED: 22611164]

Khorana 2006

Khorana AA, Francis CW, Culakova E, Fisher RI, Kuderer NM, Lyman GH. Thromboembolism in hospitalized neutropenic cancer patients. *Journal of Clinical Oncology* 2006;**24**(3):484–90.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Llewelyn 2009

Llewelyn CA, Wells AW, Amin M, Casbard A, Johnson A J, Ballard S, et al. The EASTR study: a new approach to determine the reasons for transfusion in epidemiological studies. *Transfusion Medicine* 2009;**19**(2):89–98.

Lozano 2013

Lozano M, Sweeney JD. Avoiding platelet transfusions. In: Sweeney J, Lozano M editor(s). *Platelet Transfusion Therapy*. Bethesda, Maryland: AABB Press, 2013:567–89.

Martin 2011

Martin K, Gertler R, Sterner A, MacGuill M, Schreiber C, Horer J, et al. Comparison of blood-sparing efficacy of epsilon-aminocaproic acid and tranexamic acid in newborns undergoing cardiac surgery. *The Thoracic and Cardiovascular Surgeon* 2011;**59**(5):276–80.

Martin-Hirsch 2010

Martin-Hirsch PPL, Keep SL, Bryant A. Interventions for preventing blood loss during the treatment of cervical intraepithelial neoplasia. *Cochrane Database of Systematic Reviews* 2010, Issue 6. [DOI: 10.1002/14651858.CD001421.pub2]

Novikova 2011

Novikova N, Hofmeyr GJ. Tranexamic acid for preventing postpartum haemorrhage. *Cochrane Database of Systematic Reviews* 2010, Issue 7. [DOI: 10.1002/14651858.CD007872.pub2]

Okamoto 1997

Okamoto S, Hijikata-Okunomiya A, Wanaka K, Okada Y, Okamoto U. Enzyme-controlling medicines: introduction. *Seminars in Thrombosis and Hemostasis* 1997;**23**(6): 493–501.

Pendry 2011

Pendry K, Davies T. An audit of the use and wastage in the North West of England and North Wales - where have all the platelets gone?. *Blood and Transfusion Matters* 2011;**34**: 17–9.

Pogue 1997

Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for

- cumulative meta-analysis. *Controlled Clinical Trials* 1997; **18**(6):580–93.
- Popovsky 1985**
Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion* 1985;**25**(6):573–7.
- Prentice 1980**
Prentice CR. Basis of antifibrinolytic therapy. *Journal of Clinical Pathology Supplement* 1980;**14**:35–40.
- Roberts 2011**
Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, Dewan Y, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; **377**(9771):1096–101, 1101.e1–2.
- Roos 2008**
Roos YB, Rinkel GJE, Vermeulen M, Algra A, van Gijn J. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: 10.1002/14651858.CD001245]
- Sawamura 2009**
Sawamura A, Hayakawa M, Gando S, Kubota N, Sugano M, Wada T, et al. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. *Thrombosis Research* 2009;**124**(5): 608–13.
- Schünemann 2011**
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011].
- The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Shakur 2010**
Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;**376**(9734):23–32.
- Slichter 2005**
Slichter SJ, Davis K, Enright H, Braine H, Gernsheimer T, Kao KJ, et al. Factors affecting posttransfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. *Blood* 2005;**105** (10):4106–14.
- Slichter 2010**
Slichter SJ, Kaufman RM, Assmann SF, McCullough J, Triulzi DJ, Strauss RG, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *New England Journal of Medicine* 2010;**362**(7):600–13.
- Sterne 2011**
Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Tzortzopoulou 2008**
Tzortzopoulou A, Cepeda MS, Schumann R, Carr DB. Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD006883.pub2]
- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Avvisati 1989

Methods	Parallel RCT. 2 centres (Italy and Netherlands). Enrolment period not stated	
Participants	<p>Inclusion criteria: patients with newly diagnosed APL who met the following criteria: age 15 to 60 yrs; ventricular ejection fraction > 50%; serum alanine aminotransferase (ALT) < 4 x upper limit of normal; creatinine < 177 µmol/l</p> <p>Exclusion criteria: not stated</p> <p>Arm 1 N = 6 (APL N = 6)</p> <p>Arm 2 N = 6 (APL N = 6)</p>	
Interventions	<p>Comparison between TXA and placebo</p> <p>Arm 1 TXA (2 g given as a continuous infusion every 8 h for the first 6 days of antileukaemic treatment)</p> <p>Arm 2 Placebo (equal volume of 5% glucose)</p> <p>RBC transfusion thresholds: packed red cells given to maintain Hb > 9.0 g/dl</p> <p>Platelet transfusion threshold: 6 to 8 U/m² (source not stated) routinely given during first 7 days and additionally for overt haemorrhage</p> <p>Packed red cells and additional platelet concentrates given at the discretion of the attending physician</p>	
Outcomes	<p>Main or primary outcome not stated</p> <p>Outcomes reported:</p> <ul style="list-style-type: none"> • Severity of bleeding • Thromboembolism • Laboratory assessment of fibrinolysis • Packed red cell transfusion requirement • Platelet concentrate transfusion requirement <p>Number of days patients from both arms on study: 14</p>	
Notes	<p>Patients randomised at: not reported</p> <p>Follow-up of patients: for 14 days from start of antileukaemic treatment</p> <p>Stopping guidelines: not reported</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised to either TXA or placebo. The article does not state how patients were randomised
Allocation concealment (selection bias)	Unclear risk	Not stated

Avvisati 1989 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The article states that “Patients and attending physicians were blinded to the treatment groups” and that bleeding assessments were examined by the same investigator but it is not clear whether the investigator was one of the attending physicians
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	“Each patient was examined daily by the same investigator (G.A.) for clinically manifest haemorrhage during the entire study of 14 days”. Unclear whether G.A. was blinded to the treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	The article states that their efficacy endpoints were “severity of bleeding” and the packed red cell and platelet concentrate transfusion requirement but also reports outcome data for laboratory assessment of coagulation and fibrinolysis. It also states that there were no episodes of thromboembolism. We would be concerned as to what other outcomes were measured and not reported
Other bias	Low risk	The study seemed to be free of other sources of bias
Protocol deviation balanced?	Unclear risk	Protocol deviations or violations were not commented on

Fricke 1991

Methods	Cross-over RCT. USA. Enrolment period and centres not stated
Participants	<p>Inclusion criteria: patients with amegakaryocytic thrombocytopenia who met the following criteria: platelet count < 20,000/microlitre (< 20 x 10⁹/l) with no immediate prospect of recovery and absent/rare megakaryocytes in the bone marrow aspirate/biopsy; at least 1 bleeding episode per month (excluding skin bleeding); a history of platelet transfusions for such bleeding episodes</p> <p>Exclusion criteria: patients who had any of the following: active bleeding from an anatomical lesion (e.g. peptic ulcer); personal/family history of hypercoagulopathy; pregnancy; DIC; liver failure; personal history of a congenital bleeding disorder</p> <p>Arms (cross-over RCT): N = 8 (aplastic anaemia N = 7; myelodysplastic syndrome N = 1)</p>

Interventions	<p>Comparison between TXA and placebo</p> <p>Arm 1 TXA (20 mg/kg) 3 x daily for 4 weeks or until a platelet transfusion was required to control bleeding. Followed by a 1-week rest period. Placebo (equivalent number of identical placebo tablets) for 4 weeks or until a platelet transfusion was required to control bleeding. Followed by a 1-week rest period. The method of allocating the randomised patients to further courses of TXA or placebo was not stated</p> <p>Arm 2 Placebo (equivalent number of identical placebo tablets) for 4 weeks or until a platelet transfusion was required to control bleeding. Followed by a 1-week rest period. TXA (20 mg/kg) 3 x daily for 4 weeks or until a platelet transfusion was required to control bleeding. Followed by a 1-week rest period. The method of allocating the randomised patients to further courses of TXA or placebo was not stated</p> <p>Further cycles of TXA and placebo were repeated until TXA was deemed a success or a failure</p> <p>RBC transfusion thresholds: not stated</p> <p>Platelet transfusion thresholds: platelets (dose and source not stated) given in the event of bleeding as each patient's personal physician deemed necessary</p>	
Outcomes	<p>Main or primary outcome not stated</p> <p>Outcomes reported</p> <ul style="list-style-type: none"> • Number of bleeding episodes • Severity of bleeding episodes • Site of bleeding episodes • Platelet transfusion requirement • Red cell transfusion requirement • Drug side effects <p>Number of days patients on study: not stated</p> <p>Defined overall success of TXA in a patient as either 5 failures of placebo and none of drug or 7 failures of placebo and 1 of drug. Defined overall failure of TXA as 2 failed courses of drug. Sequential courses continued until overall success or failure of TXA could be determined</p>	
Notes	<p>Patients randomised at: not reported</p> <p>Follow-up of patients: not reported</p> <p>Stopping guidelines: not reported</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States that patients were randomised but does not state the mechanism of randomisation. Nor does it state whether they were re-randomised after the initial 2 courses of TXA and placebo or what other method was used to allocate them to successive courses of TXA or placebo

Allocation concealment (selection bias)	Unclear risk	States that patients were randomised but does not state the mechanism of allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>States that study was double-blinded (and the interventions were identical)</p> <p>However, the article states that drug levels were obtained during 38 of the 49 courses. It does not state that the investigators or patients were blinded to this information during the study. "Plasma tranexamic acid levels were taken weekly and before each platelet transfusion, if possible"</p> <p>It also states that the study defined overall success of TXA in a patient as either 5 failures of placebo and none of drug or 7 failures of placebo and 1 of drug. Defined overall failure of TXA as 2 failed courses of drug. Sequential courses continued until overall success or failure of TXA could be determined. However, it did not state how this assessment of success or failure was performed without unblinding study personnel</p> <p>It is unlikely that patients were informed of these results and therefore blinding of participants is assumed to be at low risk of bias. However, it is not clear that study personnel were not informed of the results and therefore overall risk of bias was classified as unclear</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>States that study was double-blinded (and the interventions were identical)</p> <p>However, the article states that drug levels were obtained during 38 of the 49 courses. It does not state that the outcome assessors were blinded to this information during the study. "Plasma tranexamic acid levels were taken weekly and before each platelet transfusion, if possible"</p> <p>It also states that the study defined overall success of TXA in a patient as either 5 failures of placebo and none of drug or 7 failures of placebo and 1 of drug. Defined overall failure of TXA as 2 failed courses of drug. Sequential courses continued until overall success or failure of TXA could be determined. However, it did not state how this assessment of success or failure was per-</p>

		formed without unblinding study personnel (including outcome assessors)
Incomplete outcome data (attrition bias) All outcomes	High risk	States that "Three patients completed the randomised portion of the study". "Five of the eight patients did not complete enough courses to determine the efficacy of the drug"
Selective reporting (reporting bias)	High risk	The article states that severity of bleeding (as well as number and site) were recorded by the assessor (the patient) but this outcome was not reported in the article 1 patient died of intracranial haemorrhage 4 days after starting the first randomised course. Data from this course were not included in the analysis There were 2 courses of TXA or placebo interrupted in 2 patients. One due to an upper respiratory tract infection and the other in which the patient developed an oesophageal haematoma after starting antibiotic treatment for an infection. Data from these courses were not included in the analysis as the investigators felt that the infection/antibiotic treatment may have compromised haemostasis
Other bias	High risk	One patient began receiving HLA-matched platelet transfusions 2 months after enrolment and was kept in the study as these transfusions did not completely control the bleeding. This creates bias as the other patients were deemed to have "failed" the course if bleeding necessitating platelet transfusions occurred. 2 other patients were withdrawn after they started to receive HLA-matched platelet transfusions The overall success of TXA was defined as either 5 failures of placebo and none of the drug or 7 failures of placebo and 1 of the drug. Overall failure of TXA was defined as 2 failed courses of the drug. Failure of a course was defined as a patient receiving a platelet transfusion for bleeding during a 4-week study period. Patients received a variable number of courses of drug/placebo. The 3 patients who completed the study received between 3 (2 TXA, 1 placebo) and

Fricke 1991 (Continued)

		<p>9 courses (5 TXA, 4 placebo) of treatment. The 5 patients who did not complete the study received between 0 and 20 courses (10 TXA, 10 placebo) of treatment. Of the 3 patients who completed the study, 2 did not have any successful courses of treatment. The third patient had 3/5 successful courses with TXA and 1/4 successful courses with placebo, however this was classified by the study as a failure of TXA (2 failed courses with TXA)</p> <p>Failure of a course of treatment would be classified in the same way whether patient was on study drug for 1 day before bleeding or 27 days before bleeding that required treatment with a platelet transfusion. More bleeding episodes seen in TXA arm may have been due to more days on study before bleeding requiring a platelet transfusion. Number of days on study drug before bleeding was not reported for individual courses</p>
Protocol deviation balanced?	Unclear risk	Insufficient information to determine

Gallardo 1983

Methods	Parallel RCT. Abstract. Single centre: USA. Enrolment period not stated
Participants	<p>Inclusion criteria: patients undergoing remission induction for acute leukaemia. No other inclusion criteria stated</p> <p>Exclusion criteria: not stated</p> <p>N = 19 were eligible. N = 9 in each arm (AML N = 15; ALL N = 4). N = 1 was not evaluable (reason not stated). Distribution of subtypes in to each arm not stated</p> <p>Arm 1 N = 9</p> <p>Arm 2 N = 9</p>
Interventions	<p>Comparison between EACA therapy and no EACA therapy.</p> <p>Arm 1 N = 9 (to receive EACA 100 mg/kg loading dose and 12 to 24 g/day in divided doses)</p> <p>Arm 2 N = 9 (did not receive EACA)</p> <p>RBC transfusion threshold: not stated</p> <p>Platelet transfusion threshold: patients in both arms were administered platelet transfusion (dose and source not stated) when platelet count < 20,000/microlitre. This threshold defined the “days at risk of bleeding”</p>
Outcomes	<p>Main or primary outcomes not stated.</p> <p>Outcomes reported:</p> <ul style="list-style-type: none"> • Bleeding; either as capillary bleeding (CB; skin, mucous membranes,

	<p>conjunctivae, nose, guaiac in GI or GU tract) or major bleeding (MB; nose bleeding requiring posterior packing, gross GI or GU bleeding and CNS bleeding</p> <ul style="list-style-type: none"> • Monitoring of antifibrinolytic therapy using I¹²⁵ fibrinogen plasma clot lysis • Platelet transfusion requirement • Adverse events of antifibrinolytic • Thromboembolism <p>Number of days patients on study: not reported</p>	
Notes	<p>Patients randomised at: not reported Follow-up of patients: not reported Stopping guidelines: not reported</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit a judgement of 'high' or 'low' risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit a judgement of 'high' or 'low' risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit a judgement of 'high' or 'low' risk. The abstract does not state whether investigators and patients were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit a judgement of 'high' or 'low' risk. The abstract does not state who carried out the bleeding assessments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit a judgement of 'high' or 'low' risk
Selective reporting (reporting bias)	High risk	There are data for thromboembolism and death ("no patient died of thrombosis") but no data given on number episodes of thromboembolism or number of deaths. No data reported monitoring of antifibrinolytic therapy using I ¹²⁵ fibrinogen plasma clot lysis
Other bias	Unclear risk	The "at risk of bleeding days" were much higher in the EACA group - 158 vs. 80 due to more severe thrombocytopenia and more cycles of chemotherapy for refractory disease. There may be bias in the randomisation procedure but method of randomi-

Gallardo 1983 (Continued)

		sation is not stated
Protocol deviation balanced?	Unclear risk	Protocol deviations or violations were not commented on

Shpilberg 1995

Methods	Parallel RCT. Enrolment period 1990 to 1992. 2 centres (Israel)
Participants	<p>Inclusion criteria: de novo AML. All ages.</p> <p>Exclusion criteria: laboratory signs of DIC; recent history of a thromboembolic event; clinical evidence or suspicion of thromboembolism</p> <p>There were 2 parts to the study. The first part investigated patients undergoing induction chemotherapy. The second part investigated patients undergoing consolidation chemotherapy</p> <p>Induction chemotherapy: N = 38 (FAB M1 N = 5; FAB M2 N = 8; FAB M4 N = 25) Arm 1 N = 16 (FAB M1 N = 2; FAB M2 N = 2; FAB M4 N = 12) Arm 2 N = 22 (FAB M1 N = 3; FAB M2 N = 6; FAB M4 N = 13)</p> <p>Consolidation chemotherapy: N = 18 (FAB M2 = 8; FAB M3 = 1; FAB M4 = 9) Arm 1 N = 10 (FAB M2 N = 5; FAB M3 N = 1; FAB M4 N = 4) Arm 2 N = 8 (FAB M2 N = 3; FAB M4 N = 5)</p>
Interventions	<p>Comparison between TXA and placebo in patients receiving (i) induction chemotherapy and (ii) consolidation chemotherapy. Both parts of the investigation had the same intervention</p> <p>Arm 1 TXA 1 g every 6 hours</p> <p>Arm 2 Identically appearing placebo</p> <p>RBC transfusion threshold: administered to maintain > 9 g/dl</p> <p>Platelet transfusion threshold: patients in both arms were administered platelet transfusions. (Random donor pooled; 4 units/m²) in the event of clinically significant bleeding, irrespective of platelet count</p>
Outcomes	<p>Main or primary outcomes not stated</p> <p>Outcomes reported:</p> <ul style="list-style-type: none"> ● Number of bleeding events and severity of bleeding (using a scoring system) ● Platelet concentrate transfusion requirement ● Red cell transfusion requirement ● Thromboembolism ● Adverse events of drug ● Duration of hospitalisation ● Duration of significant thrombocytopenia (< 20 x 10⁹/l) ● Days with fever <p>Number of days patients on study: not stated</p>
Notes	<p>Patients randomised at: not reported</p> <p>Follow-up of patients: not reported</p> <p>Stopping guidelines: not reported</p>

Shpilberg 1995 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study states that the trial was randomised but no further details are given as to how this was done
Allocation concealment (selection bias)	Unclear risk	Study states that the trial was randomised but no further details are given as to how this was done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study states that the trial was double-blind but no further details are given as to who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study states that the patients were carefully examined daily by one of the investigators. The trial was double-blind but no further details are given as to who was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data to assess
Selective reporting (reporting bias)	Unclear risk	Insufficient data to assess
Other bias	Unclear risk	The study seemed to be free of other forms of bias
Protocol deviation balanced?	Unclear risk	Insufficient information to determine

ALL: acute lymphocytic leukaemia

AML: acute myeloid leukaemia

APL: acute promyelocytic leukaemia

CNS: central nervous system

DIC: disseminated intravascular coagulation

EACA: epsilon aminocaproic acid

FAB: French American British Classification

GI: gastrointestinal

GU: genitourinary

QoL: quality of life

RBC: red blood cells

RCT: randomised controlled trial

TXA: tranexamic acid

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

Study	Reason for exclusion
Amar 2003	Wrong patient group - a randomised controlled trial examining the usefulness of antifibrinolytic therapy in patients with non-haematological malignancy undergoing major orthopaedic surgery
Bartholomew 1989	Not a RCT - a non-randomised controlled trial on the control of bleeding in patients with immune and non-immune thrombocytopenia with aminocaproic acid
Bates 2011	Review
Bedirhan 2001	Wrong intervention - a randomised controlled trial investigating the use of aprotinin in postoperative bleeding and the need for blood products in thoracic surgery
Ben-Bassat 1990	Not an RCT - non-randomised and non-controlled study of tranexamic acid therapy in acute myeloid leukaemia
Breen 2012	Review
Brown 2002	Review
Byams 2007	Wrong patient group - a cross-over study evaluating the use of desmopressin and tranexamic acid in women with menorrhagia
Cattan 1963	Not an RCT - non-randomised study of EACA in patients with thrombocytopenia
Celebi 2006	Wrong patient group - a randomised, double-blind prospective study that examined the role of antifibrinolytic agents in gynaecologic cancer surgery
Chakrabarti 1998	Not an RCT - non-randomised and non-controlled trial of EACA in patients with acute leukaemia
Dean 1997	Not an RCT - non-randomised and non-controlled trial of EACA and TXA for cancer-associated bleeding problems
Fossa 1978	Not an RCT - non-randomised, controlled pilot study on the effect of TXA in patients being treated for various advanced malignancies
Gardner 1980	Not an RCT - a series of cases of patients with amegakaryocytic thrombocytopenia treated with EACA to control bleeding
Garewal 1985	Not an RCT - non-randomised and non-controlled trial of EACA for the control of bleeding in thrombocytopenic patients
Jeserschek 2003	Wrong intervention - a randomised controlled trial examining the role of high-dose aprotinin in the reduction of bleeding in major orthopaedic surgery
Kalmadi 2006	Not a RCT - retrospective study of the effect of EACA on transfusion requirements in patients with thrombocytopenic haemorrhage

(Continued)

Katzel 1998	Wrong intervention - a prospective, controlled, double-blind pilot study examining the role of aprotinin during thoracic surgery for malignant lung disease
Levy 2005	Review
Marti-Carvajal 2011	Review
McConnell 2011	Wrong patient group - a randomised controlled trial examining the reduction of blood loss in primary hip arthroplasty with tranexamic acid fibrin spray
McConnell 2012	Wrong patient group - a randomised controlled trial examining the reduction of blood loss in primary knee arthroplasty with tranexamic acid fibrin spray
Mevio 1983	Wrong patient group - a double-blind study examining the role of tranexamic acid in the prevention of radiomucositis in head and neck cancer patients submitted for radiotherapy
Movafegh 2011	Wrong patient group - a randomised, double-blind study examining the effect of intravenous tranexamic acid on blood loss during and after caesarian delivery
Rickles 2007	Review
Sanz 2010	Not an RCT - non-randomised with historical control evaluating the use of tranexamic acid in patients with promyelocytic leukaemia
Schwartz 1986	Not an RCT - a non-randomised, non-controlled trial of the effect of EACA in patients with acute promyelocytic leukaemia and acquired alpha-2-plasmin inhibitor deficiency
Wassenaar 2008	Not an RCT - a retrospective study of the use of EACA in patients with acute promyelocytic leukaemia and acquired alpha-2-plasmin inhibitor deficiency
Yang 2001	Wrong patient group - a randomised, comparative trial examining the efficacy of tranexamic acid in reducing post-partum blood loss in primigravid women

EACA: epsilon aminocaproic acid

RCT: randomised controlled trial

TXA: tranexamic acid

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Study characteristics

Study	Type of study	No. of patients	No. of patients receiving antifibrinolytic	No. of patients platelet refractory/allo-immunisation	Diagnosis of patients	Treatment of underlying disease	Antifibrinolytic dose	Antifibrinolytic frequency	Antifibrinolytic route	Treatment started	Treatment stopped	Platelets given
Tranexamic acid studies												
Avvisati 1989	RCT	12	6	NR	APL	Chemo	2 g	8-hourly	IV in 500 ml 5% glucose	1st day of anti-leukaem Rx	After 6 days	Prophylactic
Fricke 1991	RCT Cross-over	8 Only 3 completed study	8	At least 3	7 AA 1 MDS	NR	20 mg/kg	8-hourly	Oral	After 4-day trial period to assess drug tolerance	Successive 4/52 courses or until grade 2 bleeding	Therapeutic
Shpilberg 1995	RCT	56	26	NR	AML 38 induction 18 consolidation	Chemo	1 g	6-hourly	Oral	Platelets < 20 or rapidly falling and < 50	Platelet count > 20 for 2 consecutive counts	Therapeutic
EACA studies												
Gallardo 1983	RCT	19	9	NR	15 AML 4 ALL (1 patient not)	Chemo	Loading dose 100 mg/kg 12 to 24	NR	NR	Platelet count < 20 x 10 ⁹ /l	Platelet count ≥ 20 x 10 ⁹ /l	Platelet count < 20 x 10 ⁹ /l

Table 1. Study characteristics (Continued)

					evalu- able)		g/day there- after						
--	--	--	--	--	-----------------	--	--------------------------	--	--	--	--	--	--

AA: aplastic anaemia
 ALL: acute lymphocytic leukaemia
 AML: acute myeloid leukaemia
 APL: acute promyelocytic leukaemia
 C: control
 EACA: epsilon aminocaproic acid
 IV: intravenous
 MDS: myelodysplastic syndrome
 NR: not reported
 RCT: randomised controlled trial
 TXA: tranexamic acid

Table 2. Results of studies (primary outcomes of review)

Study	Type of study	Number of patients	Type of patients	Number, site and severity of bleeding	Thromboembolism (venous and arterial)	
Tranexamic acid studies						
Avvisati 1989	RCT	12	APL	Cumulative haemorrhagic scores TXA 3 C 42 (P = 0.0045)	No thromboembolic events observed	
Shpilberg 1995	RCT	56	AML 38 induction 18 consolidation	Mean number of bleeding events per patient : Induction TXA 6.2 ± 2.9 C 4.5 ± 3.6 Consolidation TXA 1.1 ± 1.4 C 2.6 ± 2.2 (P < 0.05)	Cumulative haemorrhagic scores: Induction TXA 8.3 ± 4.8 C 5.6 ± 4.8 Consolidation TXA 1.3 ± 1.8 C 5.1 ± 3.6 (P < 0.05)	No thromboembolic events observed
EACA Studies						
Gallardo 1983	RCT	19	15 AML 4 ALL	Capillary bleeding [†] EACA 31% of days at risk [@] Placebo 50% of	Major bleeding [‡] EACA 15% Placebo 19%	No deaths due to thromboembolic disease

Table 3. Results of studies (secondary outcomes of review) (Continued)

								be- tween the 2 groups apart from FDPs *. FDPs de- creased in TXA arm but in- creased in the placebo arm (P < 0.01)	group: (units) TXA 21 C 56				
Shpil- berg 1995	RCT	56	AML 38 in- duc- tion 18 con- solida- tion	NR	No fa- tal bleed- ing in either group	NR	NR	Induc- tion (units) TXA 22.1 ± 13.2 C 23.1 ± 11.7 Con- solida- tion (units) TXA 3.7 ± 4. 1 C 9.3 ± 3.3 (P < 0. 05)	No re- duc- tion RBC trans- fu- sion re- quire- ments Induc- tion (units) TXA 7.5 ± 4. 7 C 7.3 ± 3.3 Con- solida- tion (units) TXA 4.1 ± 2. 8 C 4.1 ± 3.4	No side ef- fects were ob- served	NR	NR	NR
EACA studies													

Table 3. Results of studies (secondary outcomes of review) (Continued)

Gal-lardo 1983	RCT	19	15 AML 4 ALL	NR	NR	No patient died of thrombosis	Monitored with the I ¹²⁵ fibrinogen plasma clot lysis assay but no further data described	EACA 1 every 13.3 days at risk [@] Placebo 1 every 10.5 days at risk [@]	NR	Side effects were stated as minimal	NR	NR	NR
-----------------------	-----	----	--------------------	----	----	-------------------------------	--	---	----	-------------------------------------	----	----	----

*Blood coagulation tests were prothrombin time, activated partial thromboplastin time, fibrinogen, FDP, antithrombin III activity, thrombin-antithrombin III complexes, protein C activity and α_2 -antiplasmin. These were carried out daily for the first 10 days.

[@]Days at risk defined as days when platelet count fewer than $20 \times 10^9/l$.

⁺Capillary bleeding defined as bleeding in skin, mucous membranes, conjunctivae, nose and guaiac in GI or GU tract.

[‡]Major bleeding defined as nose bleeding requiring posterior packing, gross gastrointestinal or genitourinary tract bleeding and central nervous system bleeding.

ALL: acute lymphocytic leukaemia

AML: acute myeloid leukaemia

APL: acute promyelocytic leukaemia

C: control

DIC: intravascular coagulation

EACA: epsilon aminocaproic acid

FDPs: fibrin degradation products

GI: gastrointestinal

GU: genitourinary

QoL: quality of life

NR: not reported

RBC: red blood cell

RCT: randomised controlled trial

TXA: tranexamic acid

Tx: transfusion

Table 4. Laboratory assessment of fibrinolysis - Avvisati 1989

Coagulation factors	Timing	Treatment groups	
		Median (range)	
		Tranexamic acid	Placebo
Fibrinogen (mg/dl)	Baseline	80 (55 to 395)	70 (50 to 190)

Table 4. Laboratory assessment of fibrinolysis - Avvisati 1989 (Continued)

	Day 3	55 (20 to 125)	62 (45 to 150)
	Day 5	53 (35 to 80)	78 (36 to 150)
	Day 7	60 (50 to 65)	85 (17 to 160)
Thrombin-antithrombin complex (ng/ml)	Baseline	32 (4 to 58)	22 (15 to 26)
	Day 3	50 (20 to 100)	22 (11 to 52)
	Day 5	41 (5 to 51)	17 (5 to 34)
	Day 7	10 (5 to 31)	21 (3 to 37)
α_2-antiplasmin (%)	Baseline	39 (29 to 80)	50 (29 to 58)
	Day 3	27 (17 to 40)	35 (27 to 47)
	Day 5	32 (27 to 34)	36 (29 to 51)
	Day 7	33 (19 to 53)	42 (32 to 59)
Fibrin/fibrinogen degradation products (μg/dl)	Baseline	40 (10 to 80)	80 (40 to 160)
	Day 3	NR	NR
	Day 5	NR	NR
	Day 7	NR	NR

NR: not reported

APPENDICES

Appendix I. CENTRAL search strategy

#1 MeSH descriptor Antifibrinolytic Agents, this term only

#2 MeSH descriptor Tranexamic Acid, this term only

#3 MeSH descriptor Aminocaproic Acids explode all trees

#4 (antifibrinolytic* or anti fibrinolytic* or antiplasmin* or plasmin inhibitor* or tranexamic or cyclohexanecarboxylic acid* or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or kabi 2161 or transamin or exacyl or anvitoff or spotof or cyklokapron or ugurol 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 TXA)

#5 (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Cymin or Dubatran or Examic or Existat or Extam or Fibran or Hemstate or Menogia or Monitex or Nestrans or Nexamic or Nexi-500 or Nexmeff or Nixa-500 or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramix or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Tranxi or Traptic or Traxage or Traxamic or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic)

#6 ((aminocaproic or aminacaproic or aminohehexanoic or aminohehexanoic or epsilon-aminocaproic or E-aminocaproic or amino caproic or amino-n-hexanoic) NEAR/2 acid*)

#7 (epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid)

#8 (cl 10304 or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan)

#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

#10 MeSH descriptor Hematologic Neoplasms explode all trees

#11 MeSH descriptor Leukemia explode all trees

#12 MeSH descriptor Lymphoma explode all trees

#13 MeSH descriptor Multiple Myeloma explode all trees

#14 MeSH descriptor Anemia, Aplastic explode all trees

#15 MeSH descriptor Bone Marrow Diseases explode all trees

#16 MeSH descriptor Thrombocytopenia explode all trees

#17 (thrombocytopeni* or thrombocytopaeni* or leukemia or leukaemia or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythem* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*)

#18 ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) NEAR/3 (malignan* or oncolog* or cancer* or neoplasm*))

#19 MeSH descriptor Antineoplastic Agents explode all trees

#20 MeSH descriptor Stem Cell Transplantation explode all trees

#21 MeSH descriptor Bone Marrow Transplantation, this term only

#22 MeSH descriptor Radiotherapy explode all trees

#23 (chemotherap* or radiotherap* or chemoradiotherap* or stem cell* or bone marrow transplant* or rituximab)

#24 ((haematolog* or hematolog*) NEAR/2 patients)

#25 (malignan* or oncolog* or cancer*):ti

#26 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)

#27 (#9 AND #26)

Appendix 4. CINAHL (EBSCOhost) search strategy

1. (MH Antifibrinolytic Agent)
2. (MH Aminocaproic Acids+)
3. (antifibrinolytic* or "anti fibrinolytic*" or antiplasmin* or "plasmin inhibitor*")
4. TI (tranexamic or "cyclohexanecarboxylic acid*" or "trans-4-aminomethyl-cyclohexanecarboxylic acid*" or "t-amcha" or "kabi 2161" or transamin or exacyl or anvitoff or spotof or cyklokapron or ugurol 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 "aminomethylcyclohexanecarboxylic acid" or "aminomethylcyclohexanoic acid" or amstat or anvitoff or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or TXA) OR AB (tranexamic or "cyclohexanecarboxylic acid*" or "trans-4-aminomethyl-cyclohexanecarboxylic acid*" or "t-amcha" or "kabi 2161" or transamin or exacyl or anvitoff or spotof or cyklokapron or ugurol 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 "aminomethylcyclohexanecarboxylic acid" or "aminomethylcyclohexanoic acid" or amstat or anvitoff or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or TXA)
5. TI (Agretax or "Bio-Stat" or Capiloc or Capitrax or "Clip Inj" or "Clot-XL" or "Clotawin-T" or Cymin or Dubatran or Examic or Existat or Extam or Fibran or Hemstate or Menogia or Monitex or Nestrin or Nexamic or "Nexi-500" or Nexmeff or Nixa-500 or Rheonex or "Sylstep TX" or Synostat or "T-nex" or "T Stat" or "T Stat" or Tanmic or "Temsyl-T" or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or "Trance Inj" or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Tranxi or Trapic or Traxage or Traxamic or Trenaxa or Trexamic or "Trim Inj" or "Tx-1000" or "Tx 500" or Wistran or "X-Tran" or Xamic) OR AB (Agretax or "Bio-Stat" or Capiloc or Capitrax or "Clip Inj" or "Clot-XL" or "Clotawin-T" or Cymin or Dubatran or Examic or Existat or Extam or Fibran or Hemstate or Menogia or Monitex or Nestrin or Nexamic or "Nexi-500" or Nexmeff or Nixa-500 or Rheonex or "Sylstep TX" or Synostat or "T-nex" or "T Stat" or "T Stat" or Tanmic or "Temsyl-T" or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or "Trance Inj" or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Tranxi or Trapic or Traxage or Traxamic or Trenaxa or Trexamic or "Trim Inj" or "Tx-1000" or "Tx 500" or Wistran or "X-Tran" or Xamic)
6. TI ((aminocaproic or amino-caproic or aminohexanoic or amino-hexanoic or epsilon-aminocaproic or E-aminocaproic or amino caproic or amino-n-hexanoic) and acid*) OR AB ((aminocaproic or amino-caproic or aminohexanoic or amino-hexanoic or epsilon-aminocaproic or E-aminocaproic or amino caproic or amino-n-hexanoic) and acid*)
7. TI (epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or acikaprin or afibrin or capracid or capramol or caprogele or caprolest or caprolisine or caprolysin or capromol or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid) OR AB (epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or acikaprin or afibrin or capracid or capramol or caprogele or caprolest or caprolisine or caprolysin or capromol or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid)
8. TI (cl 10304 or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha-aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd-177 or neocaprol or nsc? 26154 or tachostyptan) OR AB (cl 10304 or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha-aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd-177 or neocaprol or nsc-26154 or tachostyptan)
9. S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8
10. (MH Hematologic Neoplasms+)
11. (MH Leukemia+)
12. (MH Lymphoma+)
13. (MH Bone Marrow Diseases+)
14. (MH Thrombocytopenia+)
15. TI (thrombocytopeni* or thrombocytopeni* or leukemia or leukaemia* or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*)
16. TI ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) and (malignan* or oncolog* or cancer* or neoplasm*))

17. (MH Antineoplastic Agents)
18. (MH Chemotherapy, Cancer+)
19. (MH Hematopoietic Stem Cell Transplantation)
20. (MH Bone Marrow Transplantation+)
21. (MH Radiotherapy+)
22. TI (chemotherap* or radiotherap* or chemoradiotherap* or stem cell* or bone marrow transplant* or rituximab)
23. TI ((haematolog* N2 patients) or (hematolog* N2 patients))
24. TI (malignan* or oncolog* or cancer*)
25. S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
26. S9 AND S25

Appendix 5. PubMed (epublications only)

- #1 antifibrinolytic*[tiab] OR "anti fibrinolytic"[tiab] OR antiplasmin*[tiab] OR "plasmin inhibitor"[tiab] OR tranexamic[tiab] OR amcha[tiab] OR transamin[tiab] OR exacyl[tiab] OR amchafibrin[tiab] OR anvitoff[tiab] OR spotoff[tiab] OR cyklokaprone[tiab] OR uguro[tiab] OR amikapron[tiab] OR amstat[tiab] OR anvitoff[tiab] OR OR cyclocapron[tiab] OR cyclokaprone[tiab] OR cyklocapron[tiab] OR exacyl[tiab] OR frenolyse OR hexacapron[tiab] OR hexakapron[tiab] OR TXA[tiab] OR agretax[tiab] OR "Bio-Stat"[tiab] OR Capiloc[tiab] OR Capitrax[tiab] OR "Clip Inj"[tiab] OR "Clot-XL"[tiab] OR "Clotawin-T"[tiab] OR Cymin[tiab] OR Dubatran[tiab] OR Examic[tiab] OR Existat[tiab] OR Extam[tiab] OR Fibran[tiab] OR Hemstate[tiab] OR Menogia[tiab] OR Monitex[tiab] OR Nestran[tiab] OR Nexamic[tiab] OR "Nexi-500"[tiab] OR Nexmeff[tiab] OR Nixa-500[tiab] OR Rheonex[tiab] OR "Sylstep TX"[tiab] OR Synostat[tiab] OR "T-nex"[tiab] OR "T Star"[tiab] OR Tanmic OR "Temsyl-T"[tiab] OR Texakind[tiab] OR Texanis[tiab] OR Texapar[tiab] OR Texid[tiab] OR Thams[tiab] OR Tonopan[tiab] OR Traklot[tiab] OR Tramic[tiab] OR Tramix[tiab] OR Tranarest[tiab] OR "Trance Inj"[tiab] OR Traneceid[tiab] OR Tranee[tiab] OR Tranemic[tiab] OR Tranex[tiab] OR Tranexa[tiab] OR Tranfib[tiab] OR Tranlok[tiab] OR Transtat[tiab] OR Transys[tiab] OR Tranxi[tiab] OR Trapic[tiab] OR Traxage[tiab] OR Traxamic[tiab] OR Trenaxa[tiab] OR Trexamic[tiab] OR "Trim Inj"[tiab] OR "Tx-1000"[tiab] OR "Tx 500"[tiab] OR Wistran[tiab] OR "X-Tran"[tiab] OR Xamic[tiab] OR aminocaproic[tiab] OR aminohexanoic[tiab] OR amino caproic[tiab] OR amino-n-hexanoic[tiab] OR epsikapron[tiab] OR cy-116[tiab] OR cy116[tiab] OR epsamon[tiab] OR amicar[tiab] OR caprocid[tiab] OR acikaprin[tiab] OR afibrin[tiab] OR capracid[tiab] OR capramol[tiab] OR caprogel[tiab] OR caprolest[tiab] OR caprolysine[tiab] OR caprolysin[tiab] OR capromol[tiab] OR hemocaprol[tiab] OR caproamin[tiab] OR EACA[tiab] OR caprolest[tiab] OR capralense[tiab] OR hexalense[tiab] OR hamostat[tiab] OR hemocid[tiab] OR ecapron[tiab] OR ekaprol[tiab] OR epsamon[tiab] OR epsicapron[tiab] OR epsilcapramin[tiab] OR "epsilon amino caproate"[tiab] OR "epsilon aminocaproate"[tiab] OR epsilon-aminocaproic[tiab] OR ethaaminocaproich[tiab] OR emocaprol[tiab] OR hepin[tiab] OR ipsilon[tiab] OR neocaprol[tiab] OR nsc26154[tiab] OR tachostyptan[tiab]
- #2 thrombocytopeni*[tiab] OR thrombocytopaeni*[tiab] OR leukemia[tiab] OR leukaemia[tiab] OR lymphoma*[tiab] OR aplastic anemia[tiab] OR aplastic anaemia[tiab] OR myelodysplas*[tiab] OR myeloproliferat*[tiab] OR multiple myeloma[tiab] OR plasma cell myeloma[tiab] OR thrombocythemi*[tiab] OR thrombocythaemi*[tiab] OR polycythemi*[tiab] OR polycythaemi*[tiab] OR myelofibros*[tiab] OR AML[tiab] OR CLL[tiab] OR CML[tiab] OR Hodgkin*[tiab]
- #3 (haematolog*[tiab] OR hematolog*[tiab] OR blood[tiab] OR red cell*[tiab] OR white cell*[tiab] OR lymphom*[tiab] OR marrow[tiab] OR platelet*[tiab]) and (malignan*[tiab] OR oncolog*[tiab] OR cancer*[tiab] OR neoplasm*[tiab])
- #4 chemotherap*[tiab] OR radiotherap*[tiab] OR chemoradiotherap*[tiab] OR stem cell*[tiab] OR bone marrow transplant*[tiab] OR rituximab[tiab]
- #5 "haematology patients"[tiab] OR "hematology patients"[tiab] OR "haematological patients"[tiab] OR "hematological patients"[tiab]
- #6 malignan*[ti] OR oncolog*[ti] OR cancer*[ti]
- #7 #2 OR #3 OR #4 OR #5 OR #6
- #8 #1 AND #7
- #9 publisher[sb] NOT pubstatusnihms
- #10 #8 AND #9

Appendix 6. LILACS, KoreaMed, IndMed, PakMediNet search strategy

antifibrinolytic OR antifibrinolytics OR “anti fibrinolytic” OR “anti fibrinolytics” OR antiplasmin OR “plasmin inhibitor” OR tranexamic OR cyklokapron OR aminocaproic OR EACA OR amcha

Appendix 7. UKBTS SRI Transfusion Evidence Library search strategy

#1 (antifibrinolytic OR antifibrinolytics OR anti-fibrinolytic OR anti fibrinolytics OR antiplasmin OR plasmin inhibitor OR tranexamic OR amcha OR transamin OR exacyl OR amchafibrin OR anvitoff OR spotof OR cyklokapron OR ugurol OR amikapron OR amstat OR anvitoff OR cyclocapron OR cyclokapron OR cyklocapron OR exacyl OR frenolyse OR hexacapron OR hexakapron OR agretax OR Capiloc OR Capitrax OR Cymin OR Dubatran OR Examic OR Existat OR Extam OR Fibran OR Hemstate OR Monitex OR Nestran OR Nexamic OR Nexmeff OR Nixa-500 OR Rheonex OR Synostat OR aminocaproic OR aminohexanoic OR amino caproic OR EACA OR amino-n-hexanoic OR epsikapron OR epsamon OR amicar OR caprocid OR acikaprin OR afibrin OR capracid OR capramol OR caprogele OR caprolest OR caprolisine OR caprolysin OR capromol OR hemocaprol OR caproamin OR caprolest OR capralense OR hexalense OR hamostat OR hemocid OR ecapron OR ekaprol OR epsamon OR epsicapron OR epsilcapramin OR epsilon amino caproate OR epsilon aminocaproate OR epsilonaminocaproic OR ethaaminocaproich OR emocaprol OR hepin OR ipsilon OR neocaprol OR tachostyptan)

#2 ((haematolog* OR hematolog* OR marrow OR platelet*) AND (malignan* OR oncolog* OR cancer* OR neoplasm*))

#3 (leukemi* or leukaemi* or lymphoma* or chemotherap* OR radiotherap* OR chemoradiotherap* OR stem cell* OR bone marrow transplant* OR rituximab OR “haematology patients” OR “hematology patients” OR “haematological patients” OR “hematological patients”)

#4 (malignan* OR oncolog* OR cancer*) [In Title]

#5 #2 OR #3 OR #4

#6 #1 AND #5

Appendix 8. Web of Science, Conference Proceedings Citation Index search strategy

(malignan* OR oncolog* OR cancer* OR neoplasm* OR chemotherap* OR radiotherap* OR chemoradiotherap* OR stem cell* OR bone marrow transplant* OR rituximab OR “haematology patients” OR “hematology patients” OR “haematological patients” OR “hematological patients”) AND (antifibrinolytic OR antifibrinolytics OR anti-fibrinolytic OR anti fibrinolytics OR tranexamic OR aminocaproic OR EACA)

Appendix 9. ClinicalTrials.gov and ICTRP search strategy

Condition: malignan* OR oncolog* OR cancer* OR neoplasm* OR chemotherap* OR radiotherap* OR chemoradiotherap* OR stem cell* OR bone marrow transplant* OR rituximab OR “haematology patients” OR “hematology patients” OR “haematological patients” OR “hematological patients”

AND

Intervention: antifibrinolytic OR antifibrinolytics OR anti-fibrinolytic OR anti fibrinolytics OR tranexamic OR aminocaproic OR EACA

Appendix 10. ISRCTN, EUDRACT, UMIN and Hong Kong Registry search strategy

antifibrinolytic OR antifibrinolytics OR anti-fibrinolytic OR anti fibrinolytics OR tranexamic OR aminocaproic OR EACA

CONTRIBUTIONS OF AUTHORS

Douglas Wardrop: protocol development and content expert.

Lise Estcourt: protocol development and content expert.

Susan Brunskill: protocol development and methodological expert.

Marialena Trivella: methodological expert.

Carolyn Doree: protocol development and search strategy expert.

Simon Stanworth: protocol development and content expert.

Mike Murphy: protocol development and content expert.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- NHS Blood and Transplant, UK.

External sources

- German Ministry of Education and Research (BMBF) towards support of the Cochrane Haematological Malignancies Group, Germany.
Editorial support