Antifibrinolytic drugs for acute traumatic injury (Review)

Roberts I, Shakur H, Ker K, Coats T, on behalf of the CRASH-2 Trial collaborators

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[Intervention Review]

Antifibrinolytic drugs for acute traumatic injury

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ABSTRACT

Background

Uncontrolled bleeding is an important cause of death in trauma victims. Antifibrinolytic treatment has been shown to reduce blood loss following surgery and may also be effective in reducing blood loss following trauma.

Objectives

To quantify the effects of antifibrinolytic drugs on mortality, vascular occlusive events, surgical intervention and receipt of blood transfusion after acute traumatic injury.

Search methods

We searched the PubMed, Science Citation Index, National Research Register, Zetoc, SIGLE, Global Health, LILACS, and Current Controlled Trials to March 2004 and the Cochrane Injuries Group Specialised Register, CENTRAL, MEDLINE and EMBASE to July 2010.

Selection criteria

We included all randomised controlled trials of antifibrinolytic agents (aprotinin, tranexamic acid [TXA] and epsilon-aminocaproic acid) following acute traumatic injury.

Data collection and analysis

The titles and abstracts identified in the electronic searches were screened by two independent authors to identify studies that had the potential to meet the inclusion criteria. The full reports of all such studies were obtained. From the results of the screened electronic searches, bibliographic searches, and contacts with experts, two authors independently selected trials meeting the inclusion criteria.

Main results

Four trials met the inclusion criteria, including 20,548 randomised patients. Two trials with a combined total of 20,451 patients assessed the effects of TXA on mortality; TXA reduced the risk of death by 10% (RR=0.90, 95% CI 0.85 to 0.97; P=0.0035). Data from one trial involving 20,211 patients found that TXA reduced the risk of death due to bleeding by 15% (RR=0.85, 95% CI 0.76 to 0.96; P=0.0077). There was evidence that early treatment (≤3 hours) was more effective than late treatment (>3 hours). There was no evidence that TXA increased the risk of vascular occlusive events or need for surgical intervention. There was no substantial difference in the receipt of blood transfusion between the TXA and placebo groups. The two trials of aprotinin provided no reliable data.

Authors' conclusions

Tranexamic acid safely reduces mortality in bleeding trauma patients without increasing the risk of adverse events. TXA should be given as early as possible and within three hours of injury, as treatment later than this is unlikely to be effective. Further trials are needed to determine the effects of TXA in patients with isolated traumatic brain injury.

PLAIN LANGUAGE SUMMARY

Blood-clot promoting drugs for acute traumatic injury

Injury is the second leading cause of death for people aged five to 45 years. Over three million people worldwide die of injuries every year, often because of extensive blood loss. Antifibrinolytic drugs promote blood clotting by preventing blood clots from breaking down. Some examples of antifibrinolytic drugs are aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid. Doctors sometimes give these drugs to patients having surgery to prevent blood loss. They appear to have few complications. These drugs might also stop blood loss in seriously injured patients and, as a result, save lives.

The authors of this review searched for randomised trials assessing the effects of antifibrinolytics in trauma patients. When the review was first done in 2004 the results of the research were inconclusive. Since then, two new trials of TXA, one involving over 20,000 patients, have been completed. The results of this new research show that when given early, TXA reduces the risk of death compared to patients who do not receive TXA without increasing the risk of side events. The review now includes data from 20,548 people who took part in four trials.

Two small trials of aprotinin were also found although they provided no reliable data.

The authors conclude that TXA can safely reduce death in bleeding trauma patients. They suggest that future trials should explore the effects of TXA in patients with traumatic brain injury with no other trauma.

BACKGROUND

Description of the condition

For people aged five to 45 years, trauma is second only to HIV/AIDS as a cause of death. Each year, worldwide, about three million people die as a result of trauma (Murray 1996), many after reaching hospital. Among trauma patients who do survive to reach hospital, exsanguination is a common cause of death, accounting for nearly half of in-hospital trauma deaths in some settings (Sauaia 1995). Central nervous system injury and multi-organ failure account for most of the remainder, both of which can be exacerbated by severe bleeding (BTF 2000).

Clotting helps to maintain the integrity of the circulatory system after vascular injury, whether traumatic or surgical in origin (Lawson 2004). Major surgery and trauma trigger similar haemostatic responses and the consequent massive blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma in any patient, is stimulation of clot breakdown (fibrinolysis) which may become pathological (hyper-fibrinolysis) in some cases. Antifibrinolytic agents have been shown to reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, without apparently increasing the risk of post-operative complications.

Description of the intervention

Antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and reduce surgical blood loss. A recent systematic review (Henry 2011) of randomised controlled trials of antifibrinolytics (mainly aprotinin or tranexamic acid [TXA]) in elective surgical patients showed that antifibrinolytics reduced the numbers needing transfusion by one third, reduced the volume needed per transfusion by one unit, and halved the need for further surgery to control bleeding. These differences were all statistically significant at the P<0.01 level. Specifically, aprotinin reduced the rate of blood transfusion by 34% (relative risk [RR]=0.66; 95% confidence interval [CI] 0.60 to 0.72) and TXA by 39% (RR=0.61; 95% CI 0.53 to 0.70). Aprotinin use saved 1.02 units of red blood cells (RBCs) (95% CI 0.79 to 1.26) in those requiring transfusion,

and TXA use saved 0.87 units (95% CI 0.53 to 1.20). There was a non-significant reduction in mortality with both aprotinin (RR= 0.81; 95% CI 0.63 to 1.06) and TXA (RR=0.60; 95% CI 0.33 to 1.10).

How the intervention might work

Because the coagulation abnormalities that occur after injury are similar to those after surgery, it is possible that antifibrinolytic agents might also reduce blood loss and mortality following trauma. A simple and widely practicable intervention that reduced blood loss following trauma might prevent tens of thousands of premature deaths. A reduction in the need for transfusion would also have important public health implications. Blood is a scarce and expensive resource and major concerns remain about the risk of transfusion-transmitted infection. Trauma is particularly common in parts of the world where the safety of blood transfusion cannot be assured. A recent study in Uganda estimated the population-attributable fraction of HIV acquisition as a result of blood transfusion to be around two percent (Kiwanuka 2004) although some estimates are much higher (Heymann 1992).

OBJECTIVES

To quantify the effect of antifibrinolytic drugs on mortality, vascular occlusive events, surgical intervention and receipt of blood transfusion after acute traumatic injury.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT), as per the following definition.
RCT: A study involving at least one intervention and one control treatment, concurrent enrolment and follow-up of the intervention and control groups, and in which the interventions to be tested are selected by a random process, such as the use of a random numbers table (coin flips are also acceptable). If the study author(s) state explicitly (usually by using some variant of the term 'random' to describe the allocation procedure used) that the groups compared in the trial were established by random allocation, then the trial is classified as an 'RCT'.

Types of participants

People of any age following acute traumatic injury.

Types of interventions

The interventions considered are the antifibrinolytic agents: aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA).

Types of outcome measures

Primary outcomes

- Mortality at the end of the follow up.

Secondary outcomes

- Number of patients experiencing an adverse event, specifically vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism).
- Number of patients undergoing surgical intervention.
- Number of patients receiving blood transfusion.
- Volume of blood transfused (units).

Search methods for identification of studies

Searches were not restricted by date, language or publication status.

Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group's Specialised Register (searched July 2010)
- Cochrane Central Register of Controlled Trials Issue 3, 2010 (*The Cochrane Library*)
- MEDLINE (1966 to July week 2, 2010)
- PubMed (searched March 17, 2004)
- EMBASE (1980 to week 28, July 2010)
- Science Citation Index (searched March 17, 2004)
- National Research Register (issue 1, 2004)
- Zetoc (searched March 17, 2004)
- SIGLE (searched March 17, 2004)
- Global Health (searched March 17, 2004)
- LILACS (searched March 17, 2004)
- Current Controlled Trials (searched March 17, 2004)

The search strategies used in the latest update are listed in full in Appendix 1.

Searching other resources

All references in the identified trials and background papers were checked and study authors contacted to identify relevant published and unpublished data. Pharmaceutical companies were contacted in 2004 to obtain information on ongoing trials.

Data collection and analysis

Selection of studies

The titles and abstracts identified in the electronic searches were screened by two independent authors to identify studies that had the potential to meet the inclusion criteria. The full reports of all such studies were obtained. From the results of the screened electronic searches, bibliographic searches and contacts with experts, two authors independently selected trials meeting the inclusion criteria. There were no disagreements on study inclusion.

Data extraction and management

Two authors independently extracted information on the following: number of randomised participants, types of participants and types of interventions. The outcome data sought were: numbers of deaths in each group, numbers with vascular occlusive events, numbers requiring surgical intervention, and the amount of blood transfused. Information on loss to follow-up, blinding, and whether an intention-to-treat analysis was performed was also extracted. The authors were not blinded to the authors or journal when doing this. Results were compared and differences would have been resolved by discussion had there been any. Where there was insufficient information in the published report, we attempted to contact the authors for clarification.

Assessment of risk of bias in included studies

Two authors assessed the risk of bias for allocation concealment. Each trial was assessed as being at high, low or unclear risk of bias according to the criteria presented in Higgins 2008.

Assessment of heterogeneity

The presence of heterogeneity of the observed treatment effects were assessed using the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity; substantial heterogeneity is considered to exist when I^2 >50% (Higgins 2008). The following were specified a-priori as factors that could explain any observed heterogeneity: adequacy of allocation concealment; injury severity based on the injury severity score (an ISS of greater than or equal to 16 defines the severely injured strata); and according to whether the study population included predominantly blunt or penetrating trauma.

Assessment of reporting biases

We planned to investigate the presence of reporting (publication) bias using funnel plots, however there were too few included studies to enable meaningful analysis.

Data synthesis

Risk ratios (RR) and 95% confidence intervals (95% CI) were calculated. The risk ratio was chosen because it is more readily applied to the clinical situation. For transfusion volumes, the mean difference (MD) in the units of blood transfused were calculated with 95% CI.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses to explore whether effect sizes vary according to the type of antifibrinolytic agent and the dosing regimen. However there were too few trials for such analyses.

RESULTS

Description of studies

Searches conducted in April 2004 identified a total of 819 records. These were screened by two authors and the full texts of nine potentially eligible reports were obtained for closer examination. Of the nine potentially eligible reports, two trials met the inclusion criteria. Two further trials were identified in an updated search conducted in July 2010. In summary, four randomised controlled trials including 20,548 randomised patients have been identified as meeting the inclusion criteria and are included in this review.

Tranexamic acid

Two trials compared TXA with placebo in trauma patients. The CRASH-2 2010 recruited 20,211 trauma patients with, or at risk of, significant haemorrhage. A trial in Thailand (Yutthakasemsunt 2010) recruited 240 trauma patients with moderate to severe traumatic brain injury. As of November 2012, the Thai trial Yutthakasemsunt 2010 was only available as an abstract with publication of the full trial report pending. The trial has been included based on the data reported in the abstract. The full trial data will be incorporated into this systematic review once the full trial report is available.

Aprotinin

Two trials compared the effects of aprotinin with placebo in trauma patients. One trial (Auer 1979) involved 20 patients with severe head injury, and one (McMichan 1982) involved 77 patients with a combination of hypovolaemic shock and major fractures of either the lower limb, pelvis or both.
See 'Characteristics of included studies' for further details.

Risk of bias in included studies

The CRASH-2 2010 trial was judged to be at low risk of bias. It was a large randomised controlled trial involving 20,211 adult trauma patients who were randomly allocated to receive TXA or placebo. TXA and placebo were packaged in identical ampoules. Hospitals with reliable telephone access used a telephone randomisation service, hospitals without used a local pack system; allocation concealment was adequate. Participants and trial staff were blinded to treatment allocation. Over 99% of patients were followed up.
There was insufficient information presented in the abstract to assess the risk of bias of the trial by Yutthakasemsunt 2010.
The trial by Auer 1979 was described as double blind. The adequacy of allocation concealment was unclear. However, after randomly allocating the first 20 patients, five patients were added to the aprotinin group. Because it was not possible to separate the outcome data for the 20 randomised and the five non-randomised patients, this study provided no useable outcome data.
In the randomised controlled trial by McMichan 1982 the aprotinin and placebo were prepared in "similar ampoules". All ampoules were in boxes of 50, with a code number assigned to each box. The nature of the content of the ampoules was not known to any of the investigators nor to the attending physicians. The codes were not broken until the end of the study. There were seven post-randomisation exclusions from the study in which there were three deaths. These three deaths were excluded because they occurred within the first 24 hours (it is not clear whether or not this was specified in the study protocol). Three patients refused the trial investigations, and one patient was transferred to another hospital for specialist treatment of quadriplegia and later died.

Effects of interventions

Tranexamic acid versus placebo

Mortality

Both the CRASH-2 2010 trial and the trial by Yutthakasemsunt 2010 reported mortality data.

All-cause mortality was significantly reduced with tranexamic acid (pooled risk ratio (RR) 0.90, 95% CI 0.85 to 0.97; P=0.003: Analysis 1.1). There was no evidence of statistical heterogeneity (Chi^2=0.77, df=1 (P=0.38); I^2=0%).
The CRASH-2 2010 also presented mortality data by cause. The risk of death due to bleeding and myocardial infarction were significantly reduced with TXA. There were no statistically significant differences in the risk of death from other causes:

- Bleeding: RR 0.85, 95% CI 0.76 to 0.96; P=0.0077
- Myocardial infarction: RR 0.32, 95% CI 0.14 to 0.75; P=0.0053
- Vascular occlusion: RR 0.69, 95% CI 0.44 to 1.07; P=0.096
- Stroke: RR 1.60, 95% CI 0.52 to 4.89; P=0.40
- Pulmonary embolism: RR 0.86, 95% CI 0.46 to 1.61; P=0.63
- Multi-organ failure: RR 0.90, 95% CI 0.75 to 1.08; P=0.25
- Head injury: RR 0.97, 95% CI 0.87 to 1.08; P=0.60
- 'Other' causes: RR 0.94, 95% CI 0.74 to 1.20; P=0.63

Although not prespecified subgroup analyses of this review, the effects of TXA on death due to bleeding by time to treatment, severity of haemorrhage, Glasgow coma score, and type of injury were assessed in the CRASH-2 trial (CRASH-2 2011). The results are presented below.
Analysis of the risk of death due to bleeding indicated that the effect of TXA varied by time to treatment. Treatment within one hour of injury was associated with a 32% relative reduction in risk of death due to bleeding (RR 0.68, 95% CI 0.57 to 0.82; P<0.0001) and treatment between 1 and 3 hours after injury was associated with a 21% reduction (RR 0.79, 95% CI 0.64 to 0.97; P=0.03). Treatment with TXA after three hours of injury was associated with a 44% relative increase in risk of death due to bleeding (RR 1.44, 95% CI 1.12 to 1.84; P=0.004). Test for subgroup differences: Chi^2=23.51, P<0.00001.
There was no evidence that the effect of TXA on death due to bleeding varied by the severity of haemorrhage, Glasgow coma score, or type of injury:

- Severity of haemorrhage (as assessed by systolic blood pressure): >89 mm Hg (RR 0.88, 95% CI 0.71 to 1.10); 76-89 (RR 1.01, 95% CI 0.79 to 1.30); ≤75 (RR 0.81, 95% CI 0.69 to 0.95). Test for subgroup differences: Chi^2=2.24, P=0.33.
- Glasgow coma score: severe (RR 0.92, 95% CI 0.76 to 1.13); moderate (RR 0.77, 95% CI 0.59 to 0.99); mild (RR 0.86, 95% CI 0.72 to 1.02). Test for subgroup differences: Chi^2=1.28, P=0.53.
- Type of injury: blunt (RR 0.89, 95% CI 0.77 to 1.04); penetrating (RR 0.79, 95% CI 0.66 to 0.96). Test for subgroup differences: Chi^2=0.92, P=0.34.

Vascular occlusive events

The CRASH-2 2010 trial reported data on vascular occlusive events. There was no difference in the risk of experiencing one

or more vascular occlusive events (fatal or non-fatal; myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) between the TXA and placebo groups (RR 0.84, 95% CI 0.68 to 1.02; P=0·084). TXA reduced the risk of myocardial infarction (RR 0.64, 95% CI 0.42 to 0.97; P=0.035). There was no difference in the risk of stroke (RR 0.86, 95% CI 0.61 to 1.23; P=0.42), pulmonary embolism (RR 1.01, 95% CI 0.73 to 1.41; P=0.93) or deep vein thrombosis (RR 0.98, 95% CI 0.63 to 1.51; P=0.91).

Surgical intervention

Data from the CRASH-2 2010 trial suggest that there is no statistically significant difference in the risk of receiving one or more surgical interventions (neurosurgery, chest, abdominal or pelvic surgery) (RR 1.00, 95% CI 0.97 to 1.03; P=0.79) Analysis 1.2.

Receipt of blood transfusion

Of the patients allocated to TXA in the CRASH-2 2010 trial, 5067 (50.4%) received a blood product transfusion versus 5160 (51.3%) of the patients allocated to placebo (RR 0.98, 95% CI 0.96 to 1.01; P=0.21) Analysis 1.3. There was no difference in the average number of blood units transfused (MD -0.17; 95% CI -0.39 to 0.05; P=0.13) Analysis 1.4.

Aprotinin versus placebo

The study by Auer 1979, with 20 randomised patients, provided no useable outcome data for the reasons outlined above. The study by McMichan 1982, with 77 randomised patients (seven post-randomisation exclusions), was reported in four separate reports (Rosengarten 1977; Rosengarten 1979 and McMichan 1977 in 'included studies' reference McMichan 1982).

Mortality

McMichan 1982 reported mortality data; there was no difference in the risk of death between the aprotinin or placebo groups (RR 0.14, 95% CI 0.01 to 2.67; P=0.19) Analysis 2.1.

Vascular occlusive events

Data on vascular occlusive events were not reported.

Surgical intervention

McMichan 1982 reported data on the number of patients undergoing a surgical intervention; there was no difference between the aprotinin or placebo groups (RR 1.07, 95% CI 0.87 to 1.33; P= 0.53) Analysis 2.2.

Receipt of blood transfusion

Data on the number of patients receiving a blood transfusion were not reported. The volume of blood transfused was reported, there was no difference between groups (MD -0.40 units; 95% CI -0.91, 0.11; P=0.12) Analysis 2.3.

DISCUSSION

Summary of main results

Tranexamic acid reduces all-cause mortality in bleeding trauma patients, with no apparent increase in the risk of vascular occlusive events. This conclusion is based on the results of the CRASH-2 2010 trial which recruited 20,211 bleeding trauma patients from 274 hospitals in 40 countries.

Overall completeness and applicability of evidence

The large numbers of patients in a wide range of different health care settings around the world studied in the CRASH-2 2010 trial help the result to be widely generalised. The treatment is effective in patients with blunt and penetrating trauma. Because TXA is inexpensive and easy to administer, it could readily be added to the normal medical and surgical management of bleeding trauma patients in hospitals around the world.

Each year, worldwide, about four million people die as a result of traumatic injuries and violence. Approximately 1.6 million of these deaths occur in hospital and about one third of these deaths (480,000) are from haemorrhage. The CRASH-2 2010 trial has shown that TXA reduces mortality from haemorrhage by about one sixth. If this widely practicable intervention was used worldwide in the treatment of bleeding trauma patients, it could prevent over 70,000 deaths each year (see Table 1).

Many trauma patients suffer a brain injury. Traumatic brain injury (TBI) is commonly accompanied by intracranial bleeding which can develop or worsen after hospital admission. Traumatic intracranial haemorrhage is associated with an increased risk of death and disability, and regardless of location, haemorrhage size is strongly correlated with outcome. If TXA reduced intracranial bleeding after isolated TBI then this could improve patient outcomes. Although, many of the bleeding trauma patients included in the CRASH-2 2010 trial also suffered a brain injury, it is possible that the effects of TXA may differ in patients with isolated TBI. The trial by Yutthakasemsunt 2010 provides some promising evidence for the beneficial effect of TXA on mortality in patients with isolated TBI; however, further evidence is required from larger trials which also assess the effect on disability.

There is no evidence for the effect of aprotinin for trauma.

Quality of the evidence

The quality of the evidence supporting the use of tranexamic acid for trauma is high. The findings of this review are based primarily on the results of the CRASH-2 2010 trial. This was a large, high quality randomised trial with low risk of bias. Sequence generation was appropriately randomised, allocation was concealed and participants, trial personnel and outcome assessors were all blinded. Furthermore, there were minimal missing data with over 99% of patients followed up.

Potential biases in the review process

This systematic review addresses a focused research question and uses pre-defined inclusion criteria and methodology to select and appraise eligible trials.

As with all systematic reviews, the possibility of publication bias should be considered as a potential threat to validity. However, in light of our extensive and sensitive searching we believe that the risk of such a bias affecting the results is minimal.

Agreements and disagreements with other studies or reviews

A systematic review of randomised trials assessing the effects of TXA in patients undergoing elective surgery has been conducted (Henry 2011). This review found that compared to control, TXA reduced the need for blood transfusion without any apparent increase in the risk of adverse events. Unlike the Henry 2011 review, we found no evidence of any substantial reduction in the receipt of a blood transfusion or the amount of blood transfused in trauma patients. One possible explanation is that in the CRASH-2 2010 trial, following the loading dose, TXA was infused over a period of eight hours, whereas decisions about transfusion are made very soon after hospital admission. The absence of any large effect on blood transfusion may also reflect the difficulty of accurately estimating blood loss in trauma patients when assessing the need for transfusion. Finally, the absence of any substantial reduction in transfusion requirements in patients treated with TXA acid may reflect the fact that there were fewer deaths in patients allocated to TXA acid than to placebo and patients who survive as a result of TXA administration would have had a greater opportunity to receive a blood transfusion (competing risks).

AUTHORS' CONCLUSIONS

Implications for practice

Tranexamic acid (TXA) safely reduces mortality in bleeding trauma patients. As there is evidence that the effect on death due to bleeding depends on the time interval between the injury and treatment, TXA should be given as early as possible and within three hours of the injury as treatment later than this is unlikely to be effective.

Implications for research

The knowledge that TXA safely reduces the risk of death from traumatic bleeding raises the possibility that it might also be effective in other situations where bleeding can be life threatening or disabling and further research is warranted to explore this potential. Randomised trials involving patients with isolated traumatic brain injury that assess both mortality and disability outcomes are required before TXA can be recommended for use in these patients. The ongoing CRASH-3 trial with a planned sample size of 10,000 patients with traumatic brain injury, will contribute to resolving the uncertainty about the effects of TXA in this group.

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REFERENCES

References to studies included in this review

Auer 1979 *{published data only}*

* Auer LM, Marth E, Heppner F, Holasek A. Proteolytic enzyme activity in patients with severe head injury and the effect of a proteinase inhibitor. *Acta Neurochirurgica* 1979; **49**(3-4):207–17.

CRASH-2 2010 *{published data only}*

CRASH-2 trial collaborators, Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, 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.

* CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, 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**:23–32.

McMichan 1982 *{published data only}*

McMichan JC, Rosengarten DS, McNeur JC, Philipp

E. Posttraumatic lung syndrome. Definition, diagnosis, and therapy [Das Posttraumatische Lungen–Syndrom Defintion, Diagnose und Therapie]. *Med Welt* 1976;**76** (48):2331–9.

McMichan JC, Rosengarten DS, McNeur JC, Philipp E. Pulmonary failure after major trauma and shock. *Intensive Care Medicine* 1977;**3**:Abstract no. 37.

* McMichan JC, Rosengarten DS, Philipp E. Prophylaxis of post-traumatic pulmonary insufficiency by protease-inhibitor therapy with aprotinin: a clinical study. *Circulatory Shock* 1982;**9**(2):107–16.

Rosengarten DS, McMichan JC, McNeur JC, Philipp E. Platelet and pulmonary insufficiency after bony trauma. *Intensive Care Medicine* 1977;**3**:Abstract no. 327.

Rosengarten DS, McMichan JC, Philipp E. The effect of prophylactic proteinase inhibitor therapy on post-traumatic pulmonary insufficiency and platelet counts. *Advances in Experimental Medicine and Biology* 1979;**120B**:349–60.

Yutthakasemsunt 2010 ***{published data only}***

Yutthakasemsunt S, Kittiwattanagul W, Piyavechvirat P, Thinkhamrop B, Phuenpathom N, Lumbiganon P. Tranexamic Acid for preventing progressive intracranial hemorrhage in adults with traumatic brain injury; a preliminary report. National Neurotrauma Symposium. 14–17 July 2010.

References to studies excluded from this review

Gierhake 1971 ***{published data only}***

Gierhake FW, Grabow L, Spitzer G, Muller C, Braun R, Hessler C, Orth HD, Skibbe G, Zimmerman K. Protease inhibitors and wound healing. Results of a double blind study. *Der Chirurg* 1979;**42**(8):360–3.

Husted 2003 ***{published data only}***

Husted H, Blond L, Sonne Holm S, Holm G, Jacobsen TW, Gebuhr P. Tranexamic acid reduces blood loss and blood transfusions in primary hip arthroplasty: a prospective randomized double blind study in 40 patients. *Acta Orthopaedica Scandinavica* 2003;**74**(6):665–9.

Klobow 1977a ***{published data only}***

Klobow H, Barthels M, Oestern HJ, Sturm J, Wannske M, Schaps D. Early changes of the coagulation system in multiple injuries and their modification with heparin and Trasyolol. *Chirurgisches forum fur experimentelle und klinishe forschung* 1977;**April**:119–23.

Klobow 1977b ***{published data only}***

Klobow H, Barthels M, Oestern HJ, Sturm J, Trentz O, Wannske M. Early changes in the coagulation and fibrinolytic system in patients receiving heparin or trasylol after massive trauma. *Intensive Care Medicine* 1977;**3**: Abstract no 324.

Kuiian 1999 ***{published data only}***

Kuiian SM, Pogosov VS, Kokliaeva NV, Tiukov VL, Riazanov VB, Gur'ianov VA, Akopian RG, Daikhes N, Davudov KhSh, Nazhmudinov I. The use of tranexamic acid as an anesthetic component in ENT surgeries in patients with high surgical-anesthetic risk and in hemorrhagic shock intensive therapy. *Vestnik Otorinolaringologii* 1999;**1**:47–51.

Loew 1970 ***{published data only}***

Loew D. Pathophysiologic importance of kinins in traumatic shock. *Langenbecks Archiv Fur Chirurgie* 1970; **327**:1042–6.

Nissen 1989 ***{published data only}***

Nissen R, Loeschke S, Peters A. Pharmacological treatment of post-traumatic oedema to allow early functional exercise. *Langenbecks Archiv fur Chirurgie* 1989;**Supplement II**: 475–8.

Schneider 1976 ***{published data only}***

Schneider B. Results of a field study on the therapeutic value of aprotinin in traumatic shock. *Arzneimittel Forshung* 1976;**26**:1606–10.

References to ongoing studies

CRASH-3 ***{published data only}***

Dewan Y, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H, on behalf CRASH-3 Collaborators. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials* 2012;**13**:87.

Additional references

BTF 2000

The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Hypotension. *Journal of Neurotrauma* 2000;**17**(6-7):591–5.

CRASH-2 2011

CRASH-2 collaborators, Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, 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.

Henry 2011

Henry DA, Moxey AJ, Carless PA, O'Connell D, Henderson KM, Fergusson D, et al.Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2011, Issue 1. [DOI: 10.1002/14651858.CD001886.pub2]

Heymann 1992

Heymann SJ, Brewer TF. The problem of transfusion associated acquired immunodeficiency syndrome in Africa: a quantitative approach. *American Journal of Infection Control* 1992;**20**:256–62.

Higgins 2008

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0.* The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2008.

Kiwanuka 2004

Kiwanuka N, Gray RH, Serwadda D, et al.The incidence of HIV-1 associated with injections and transfusions in a prospective cohort, Raki, Uganda. *AIDS* 2004;**18**:343–3.

Lawson 2004

Lawson JH, Murphy MP. Challenges for providing effective hemostasis in surgery and trauma. *Seminars in Hematology* 2004;**41**(1 Suppl 1):55–64.

Murray 1996

Murray CJL, Lopez AD. *Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions.* Harvard School of Public Health, 1996.

Sauaia 1995

Sauaia A, Moore FA, Moore E, Moser K, Brennan R, Read RA, Pons PT. Epidemiology of trauma deaths: a reassessment. *Journal of Trauma* 1995;**38**:185–93.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Auer 1979

Methods	Probable RCT: "Twenty patients were included in a double-blind study; nine patients were treated with Trasylol. Eleven received a placebo drug." Five additional (non-randomly allocated) patients were added to the study and received aprotinin treatment. These patients were not separated out in the analysis
Participants	Patients with severe head injury who had remained comatose for seven days. Most of them had clinical brain stem signs
Interventions	Aprotinin group: 500,000 IE initially thereafter 200,000 IV every four hours
Outcomes	Death. Range of biochemical end points.
Notes	Because it was not possible to separate the 5 non-randomised patients from the 20 probably randomised patients, this study provides no useable outcome data

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear.

CRASH-2 2010

Methods	RCT: Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Participants and study staff were blind to treatment allocation
Participants	20,211 adult (>16 years) trauma patients with, or at risk of, significant bleeding
Interventions	Tranexamic acid group: loading dose 1g over 10 minutes then infusion of 1g over 8 hours Matching placebo.
Outcomes	Death. Vascular occlusive events. Blood transfusion requirements. Disability.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Allocation concealment (selection bias)	Low risk	TXA and placebo were packaged in identical ampoules. Hospitals with a reliable telephone access used a telephone randomisation service, hospitals without used a local pack system

McMichan 1982

Methods	RCT: Aprotinin and placebo were supplied in identical coded ampoules. Ampoules were in boxes of 50 with a code number assigned to each box. These numbers were randomised in groups of 20 and each batch was assigned in numerical order. The codes were not broken until the end of the study Patients excluded after randomisation were those who died within the first 24 hours or refused continuing investigation
Participants	Patients with a combination of hypovolaemic shock and major fractures of the lower limb and or pelvis. Patients seen 12 or more hours after injury and those with major head or chest injuries were excluded
Interventions	Aprotinin group: 500,000 Kallikrein Inhibitor Units (KIU) IV statim followed by 300,000 KIU at 6-hour intervals for 96 hours
Outcomes	Death. Mean blood transfusion. Respiratory function.
Notes	77 patients were randomised but there were 7 post-randomisation exclusions. Among the 7 excluded patients, there were 3 deaths within the first 24 hours of injury. One patient was transferred to another hospital because of quadriplegia and died later, and three patients refused investigation. It was noted in the results that the data on transfusion requirement was found to have a non-normal distrubution. Nevertheless, the mean and standard deviation were presented

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Aprotinin and placebo were prepared in "similar ampoules". All ampoules were in boxes of 50, with a code number assigned to each box. The nature of the content of the ampoules was not known to any of the investigators nor to the attending physicians. The codes were not broken until the end of the study

Yutthakasemsunt 2010

Methods	RCT
Participants	240 adults patients (>16 years) with moderate to severe traumatic brain injury (Glasgow Coma Scale 4 to 12) within 8 hours of injury
Interventions	Tranexamic acid group: 2g. Matching placebo.
Outcomes	Death. Progressive intracranial haemorrhage. Disability (GOS). Thromboembolic events.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

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

Study	Reason for exclusion
Gierhake 1971	Types of patients: general surgery patients not trauma.
Husted 2003	Types of patients: orthopaedic patients not trauma.
Klobow 1977a	Types of interventions: trasylol compared with heparin.
Klobow 1977b	Types of interventions: trasylol compared with heparin.
Kuiian 1999	Types of studies: After Dr Vasiliy Vlassov, Director of the Russian Branch of the Nordic Cochrane Centre kindly translated the methods section it was clear that this study was not randomised
Loew 1970	Types of studies: alternation used not random allocation.
Nissen 1989	Types of studies: review article not randomised controlled trial
Schneider 1976	Types of studies: randomisation in this trial was by allocating patients to the treatment group according to the day of admission. However, this procedure was subverted for large numbers (813) of patients in which case the study cannot be considered to be a randomised controlled trial

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

CRASH-3

Trial name or title	Clinical Randomisation of an Antifibrinolytic in Significant Head Injury (CRASH-3)
Methods	Large, international, randomised, placebo controlled trial.
Participants	Adults with traumatic brain injury, who are within eight hours of injury, with any intracranial bleeding on CT scan or who have a GCS of 12 or less, and have no significant extra-cranial haemorrhage, are eligible for inclusion, except those for whom antifibrinolytic agents are thought to be clearly indicated or clearly contra-indicated
Interventions	Loading dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. Maintenance dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given after the loading dose is finished
Outcomes	Primary outcome is death in hospital within 28 days of injury. Secondary outcomes are vascular occlusive events (myocardial infarction, pulmonary embolism, clinical evidence of deep vein thrombosis), stroke, disability, seizures, neurosurgical intervention, days in intensive care, other adverse events
Starting date	July 2012
Contact information	crash@Lshtm.ac.uk
Notes	Current Controlled Trials ISRCTN15088122; Clinicaltrials.gov NCT01402882 The JP Moulton Charitable Trust, UK, is funding the run-in costs for the trial and up to 500 patients' recruitment. Full funding is being sought from public funding organisations for the main trial

DATA AND ANALYSES

Comparison 1. Tranexamic acid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	20367	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.85, 0.97]
2 Proportion undergoing surgical intervention	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Proportion receiving blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Volume of blood transfused	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 2. Aprotinin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Proportion undergoing surgical intervention	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Volume of blood transfused	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Tranexamic acid versus placebo, Outcome 1 All-cause mortality.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 1 Tranexamic acid versus placebo

Outcome: 1 All-cause mortality

Study or subgroup	TXA n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CRASH-2 2010	1463/10060	1613/10067		98.9 %	0.91 [0.85, 0.97]
Yutthakasemsunt 2010	12/120	18/120		1.1 %	0.67 [0.34, 1.32]
Total (95% CI)	**10180**	**10187**		**100.0 %**	**0.90 [0.85, 0.97]**

Total events: 1475 (TXA), 1631 (Placebo)

Heterogeneity: $Chi^2 = 0.77$, df = 1 (P = 0.38); $I^2 = 0.0\%$

Test for overall effect: Z = 3.02 (P = 0.0025)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Tranexamic acid versus placebo, Outcome 2 Proportion undergoing surgical intervention.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 1 Tranexamic acid versus placebo

Outcome: 2 Proportion undergoing surgical intervention

Study or subgroup	TXA n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
CRASH-2 2010	4814/10060	4836/10067		1.00 [0.97, 1.03]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 4814 (TXA), 4836 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 1.3. Comparison 1 Tranexamic acid versus placebo, Outcome 3 Proportion receiving blood transfusion.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 1 Tranexamic acid versus placebo

Outcome: 3 Proportion receiving blood transfusion

Study or subgroup	TXA n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
CRASH-2 2010	5067/10060	5160/10067		0.98 [0.96, 1.01]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 5067 (TXA), 5160 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

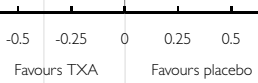
Analysis 1.4. Comparison 1 Tranexamic acid versus placebo, Outcome 4 Volume of blood transfused.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 1 Tranexamic acid versus placebo

Outcome: 4 Volume of blood transfused

Study or subgroup	Tranexamic acid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
CRASH-2 2010	10060	3.05 (7.7)	10067	3.22 (8.02)		-0.17 [-0.39, 0.05]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 2.1. Comparison 2 Aprotinin versus placebo, Outcome 1 Death.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 2 Aprotinin versus placebo

Outcome: 1 Death

Study or subgroup	Aprotinin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
McMichan 1982	0/35	3/35		0.14 [0.01, 2.67]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Aprotinin), 3 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

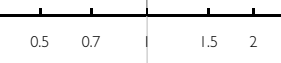
Analysis 2.2. Comparison 2 Aprotinin versus placebo, Outcome 2 Proportion undergoing surgical intervention.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 2 Aprotinin versus placebo

Outcome: 2 Proportion undergoing surgical intervention

Study or subgroup	Aprotinin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
McMichan 1982	30/35	28/35		1.07 [0.87, 1.33]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 30 (Aprotinin), 28 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



Analysis 2.3. Comparison 2 Aprotinin versus placebo, Outcome 3 Volume of blood transfused.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 2 Aprotinin versus placebo

Outcome: 3 Volume of blood transfused

Study or subgroup	Aprotinin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
McMichan 1982	35	1.2 (0.8)	35	1.6 (1.3)		-0.40 [-0.91, 0.11]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Deaths that could be avoided by the administration of TXA to bleeding trauma patients (ten countries with the highest numbers of avoided deaths shown)

Country	Trauma deaths	Haemorrhage deaths	Deaths averted with TXA
India	714,730	85,768	12,865
China	667,277	80,073	12011
Indonesia	279,499	33,534	5030
Russia	246,836	29,620	4443
Brazil	122,953	14,754	2206
USA	122,529	14,703	2206
Iraq	99,968	11,996	1799
Nigeria	87,811	10,537	1581
Bangladesh	76,938	9233	1385
DRC	73,579	8829	1324

Table 1. Deaths that could be avoided by the administration of TXA to bleeding trauma patients (ten countries with the highest numbers of avoided deaths shown) (*Continued*)

World	4,100,645	492,077	73,812

Trauma and haemorrhage death estimates taken from the WHO Global Burden of Disease Study: http://www.who.int/healthinfo/global˙burden˙disease/en/

APPENDICES

Appendix 1. Search strategy

Cochrane Injuries Group Specialised Register (searched July 2010)
(Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren) or (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA) or (aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan)
Cochrane Central Register of Controlled Trials 2010, Issue 3 (*The Cochrane Library)*
#1 MeSH descriptor Antifibrinolytic Agents explode all trees
#2 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin*):ab,ti or ((plasmin or fibrinolysis) near3 inhibitor*):ab,ti
#3 MeSH descriptor Aprotinin explode all trees
#4 (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren or midran):ab,ti or ((Kunitz near3 inhibitor*) or (pancrea* near3 antitrypsin) or (pancrea* near3 trypsin next inhibitor*)):ab,ti
#5 MeSH descriptor Tranexamic Acid explode all trees

#6 (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA):ab,ti
#7 MeSH descriptor Aminocaproic Acids explode all trees
#8 MeSH descriptor 6-Aminocaproic Acid explode all trees
#9 (epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan):ab,ti
#10 (aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic):ab,ti
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)

MEDLINE(Ovid) 1950 to July Week 2 2010

1.exp Antifibrinolytic Agents/
2.(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.
3.exp Aprotinin/
4.(Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.
5.exp Tranexamic Acid/
6.(tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.
7.exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/
8.(((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).ab,ti.
9.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10.randomi?ed.ab,ti.
11.randomized controlled trial.pt.
12.controlled clinical trial.pt.
13.placebo.ab.
14.clinical trials as topic.sh.
15.randomly.ab.
16.trial.ti.
17.10 or 11 or 12 or 13 or 14 or 15 or 16
18.(animals not (humans and animals)).sh.

19.17 not 18
20.9 and 19

EMBASE (Ovid) 1980 to 2010 (Week 28)

1.exp Antifibrinolytic Agent/
2.(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.
3.exp Aprotinin/
4.(Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker? 52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.
5.exp Tranexamic Acid/
6.(tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.
7.exp Aminocaproic Acid/
8.(((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd? 177or neocaprol or nsc?26154 or tachostyptan).ab,ti.
9.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10.exp Randomized Controlled Trial/
11.exp controlled clinical trial/
12.randomi?ed.ab,ti.
13.placebo.ab.
14.*Clinical Trial/
15.randomly.ab.
16.trial.ti.
17.10 or 11 or 12 or 13 or 14 or 15 or 16
18.exp animal/ not (exp human/ and exp animal/)
19.17 not 18
20.9 and 19

WHAT'S NEW

Last assessed as up-to-date: 14 July 2010.

Date	Event	Description
5 November 2012	New search has been performed	Additional data from the CRASH-2 trial of the effects of tranexamic acid on death due to bleeding according to time to treatment, severity of haemorrhage, Glasgow coma scale and type of injury, have been incorporated The conclusions have been edited to emphasise the importance of early administration (≤3 hours of injury) of tranexamic acid

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 4, 2004

Date	Event	Description
22 November 2010	New citation required and conclusions have changed	Two new trials (CRASH-2 2010 - 20,211 bleeding trauma patients) and Yutthakasemsunt 2010 2010 - 240 patients with traumatic brain injury) have been included The objectives of the review have been amended. The Results, Discussion and Conclusions sections have been amended accordingly

CONTRIBUTIONS OF AUTHORS

TC helped design the protocol, identified the included trials, extracted data and drafted the final version of the review.

IR helped design the protocol, identified the included trials, extracted data and drafted the final version of the review.

HS helped design the protocol and draft the final version of the review.

KK helped identify the included trials, extract data and revised the text of the review for the November 2010 and 2012 updates.

DECLARATIONS OF INTEREST

Tim Coats, Haleema Shakur and Ian Roberts were investigators in the CRASH-2 trial.

Haleema Shakur and Ian Roberts are investigators in the ongoing CRASH-3 trial.

Ian Roberts: LSHTM has received funds from pharmaceutical companies to pay for the drug and placebo used in RCTs of tranexamic acid in acute severe bleeding. These funds are delared in the relevant publications.

Haleema Shakur: I am an investigator and grant holder for the WOMAN Trial of tranexamic acid for the treatment of postpartum hemorrhage, the CRASH-3 trial of tranexamic acid for the treatment of traumatic brain injury and the Halt-it trial of tranexamic acid for the treatment of gastrointestinal bleeding.

Katharine Ker: none known.

SOURCES OF SUPPORT

Internal sources

- London School of Hygiene & Tropical Medicine, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The objectives of the review have changed. Reducing blood loss has been removed, and vascular occlusive events and surgical intervention have been added as outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminocaproic Acid [therapeutic use]; Antifibrinolytic Agents [*therapeutic use]; Aprotinin [therapeutic use]; Blood Loss, Surgical [prevention & control]; Blood Transfusion [*utilization]; Hemorrhage [*drug therapy; etiology; mortality]; Randomized Controlled Trials as Topic; Tranexamic Acid [therapeutic use]; Wounds and Injuries [*complications; mortality]

MeSH check words

Humans