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

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Summary

Background Tranexamic acid can reduce bleeding in patients undergoing elective surgery. We assessed the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients.

Methods This randomised controlled trial was undertaken in 274 hospitals in 40 countries. 20 211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat. This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

Findings 10 096 patients were allocated to tranexamic acid and 10 115 to placebo, of whom 10 060 and 10 067, respectively, were analysed. All-cause mortality was significantly reduced with tranexamic acid (1463 [14·5%] tranexamic acid group *vs* 1613 [16·0%] placebo group; relative risk 0·91, 95% CI 0·85–0·97; p=0·0035). The risk of death due to bleeding was significantly reduced (489 [4·9%] *vs* 574 [5·7%]; relative risk 0·85, 95% CI 0·76–0·96; p=0·0077).

Interpretation Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.

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Introduction

Injuries are major causes of death worldwide.[1,2] Every year, more than a million people die as a result of road traffic injuries around the world. Road traffic injuries are the ninth leading cause of death globally, and such injuries are predicted to become the third leading cause of death and disability by 2020. About 1·6 million people die as a result of intentional acts of interpersonal, collective, or self-directed violence every year. More than 90% of trauma deaths occur in low-income and middle-income countries.[2] Haemorrhage is responsible for about a third of in-hospital trauma deaths and can also contribute to deaths from multiorgan failure.[3]

The haemostatic system helps to maintain circulation after severe vascular injury, whether traumatic or surgical in origin.[4] Major surgery and trauma trigger similar haemostatic responses, and in both situations severe blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma is stimulation of clot breakdown (fibrinolysis), which might become pathological (hyper-fibrinolysis) in some cases.[4] Antifibrinolytic agents reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, and do so without apparently increasing the risk of postoperative complications.[5]

Tranexamic acid is a synthetic derivative of the aminoacid lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen.[6] A systematic review of the randomised trials of tranexamic acid in patients undergoing elective surgery identified 53 studies including 3836 participants.[5] Tranexamic acid reduced the need for blood transfusion by a third (relative risk [RR] 0·61, 95% CI 0·54–0·70), with no significant reduction in mortality (0·61, 0·32–1·12).[5] Because the haemostatic responses to surgery and trauma are similar,[4] tranexamic acid might reduce mortality due to bleeding in trauma patients. However, up until now there have been no randomised trials of this drug in such patients.[7] We assessed the effects of the early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients with or at risk of significant haemorrhage.

Methods

Study design and patients

For the **CRASH-2 trial website** see http://www.crash2.LSHTM.ac.uk

CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2) is a large placebo-controlled trial of the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion. The trial was undertaken in 274 hospitals in 40 countries. The first patient was enrolled in May, 2005. The study aims, methods, and protocol have been reported previously. The trial protocol was peer-reviewed and published on *The Lancet* website in 2005.

For the **CRASH-2 protocol** see http://www.thelancet.com/protocol-reviews/05PRT-1

Adult trauma patients with significant haemorrhage (systolic blood pressure <90 mm Hg or heart rate >110 beats per min, or both), or who were considered to be at risk of significant haemorrhage, and who were within 8 h of injury, were eligible for the trial. Patients were included if the responsible doctor was substantially uncertain about whether or not to treat with tranexamic acid (ie, entry was governed by the uncertainty principle).[8] Patients for whom the responsible doctor considered that there was a clear indication for tranexamic acid were not randomly assigned. Similarly, patients for whom there was considered to be a clear contraindication to tranexamic acid treatment were not randomly assigned. However, when the responsible doctor was substantially uncertain as to whether or not to treat with this agent, these patients were eligible for randomisation.

Consent procedures at participating hospitals were established by local regulation and the appropriate ethics committees. Informed consent was obtained from patients if physical and mental capacity allowed. If patients could not give consent, proxy consent was obtained from a relative or representative. If a proxy was unavailable, then if permitted by local regulation, consent was deferred or waived. When consent was deferred or given by a proxy, the patient was informed about the trial as soon as possible and consent obtained for use of the data collected if needed.

Randomisation and masking

After eligibility had been confirmed and the locally approved consent procedures had been completed, patients were randomly assigned. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. In hospitals in which telephone randomisation was not practicable we used a local pack system that selected the lowest numbered treatment pack from a box containing eight numbered packs. Apart from the pack number, the treatment packs were identical. The pack number was recorded on the entry form which was sent to the international trial coordinating centre in London, UK. Hospitals with reliable telephone access used the University of Oxford Clinical Trial Service Unit (CTSU) telephone randomisation service. The randomisation service used a minimisation algorithm balancing for sex, age, time since injury, type of injury (blunt or penetrating), Glasgow Coma Score, systolic blood pressure, respiratory rate, central capillary refill time, and country, taking into account what packs were available at that hospital. Once the treatment pack number was recorded, the patient was included in the trial whether or not the treatment pack was opened or the allocated treatment started. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation.

Tranexamic acid and placebo ampoules were indistinguishable. Tranexamic acid was manufactured by Pharmacia (Pfizer, Sandwich, UK) and placebo by St Mary's Pharmaceutical Unit, Cardiff, UK. The treatment packs were prepared by an independent clinical trial supply company (Bilcare, Crickhowell, UK). Correct blinding and coding of ampoules was assured by independent random testing of each batch by high performance liquid chromatography to confirm the contents. Emergency unblinding was available by telephoning CTSU.

Procedures

Patients were randomly allocated to receive a loading dose of 1 g of tranexamic acid infused over 10 min, followed by an intravenous infusion of 1 g over 8 h, or matching placebo (0·9% saline). Every patient was assigned a uniquely numbered treatment pack, which contained four ampoules of either tranexamic acid 500 mg or placebo, one 100 mL bag of 0·9% saline (for use with the loading dose), a syringe and needle, stickers with the trial details and randomisation number (for attaching to infusion bags, data forms, and patient medical records), and instructions. Each box contained information leaflets for patients and their representatives, consent forms, and data collection forms. The stickers, instructions, leaflets, and forms were in local languages.

Outcome measures and prespecified subgroup analyses

The primary outcome was death in hospital within 4 weeks of injury. Cause of death was described by the following categories: bleeding, vascular occlusion (myocardial infarction, stroke, and pulmonary embolism), multiorgan failure, head injury, and other. Secondary outcomes were vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis), surgical intervention (neurosurgery, thoracic, abdominal, and pelvic surgery), receipt of blood transfusion, and units of blood products transfused. Dependency was measured at hospital discharge, or on day 28 if still in hospital, with the 5-point Modified Oxford Handicap Scale. The scale was dichotomised into dead or dependent (dead, fully dependent requiring attention day and night, or dependent but not needing constant attention) or independent (some restriction in lifestyle but independent, minor symptoms, or no symptoms).[9] Data for the use of recombinant Factor VIIa and for gastrointestinal bleeding as a complication

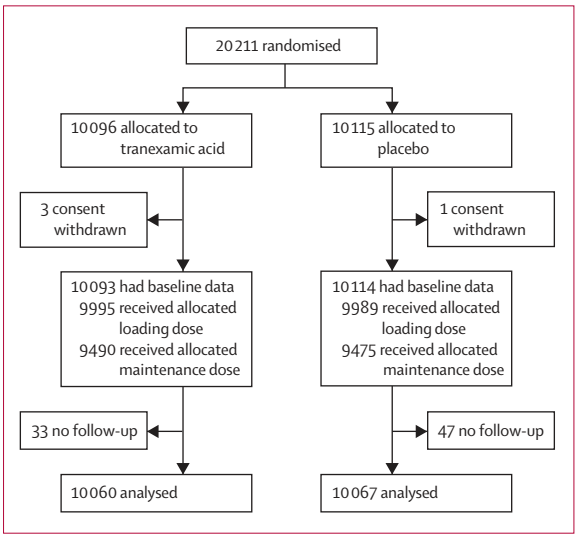


Figure 1: **Trial profile**

Results

Figure 1 shows the trial profile. 20 211 patients were randomly assigned to tranexamic acid or placebo (figure 1), of whom 20 116 were randomly assigned through the local pack system and 95 through telephone randomisation. The data from four patients were removed from the trial because their consent was withdrawn after randomisation. Five patients enrolled in the study were later found to be younger than 16 years. Age was unknown for four patients. 23 patients were enrolled more than 8 h after their injury. Time of injury was not known for 11 patients. Nine patients had haemorrhage from non-traumatic conditions. Three patients were given a pack that differed from that allocated. The planned consent procedures were not fully followed in 34 patients. The relevant ethics committees were informed and approval for use of data was obtained. All the patients, apart from the four in whom consent was withdrawn, were included in the analysis.

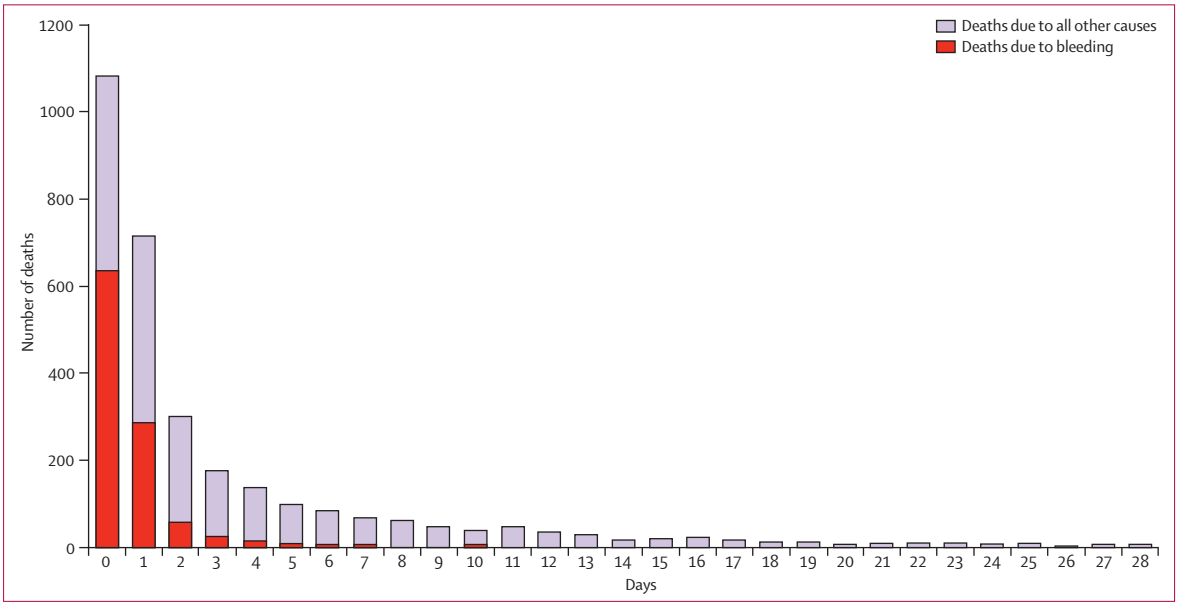
Treatment groups were balanced with respect to all baseline patient characteristics (table 1; the webappendix p 1 shows baseline data of patients with follow-up). Primary outcome data were available for 20 127 (99·6%) randomised patients, 10 060 allocated to tranexamic acid and 10 067 placebo, of whom 19 944 (99·1%) patients were known to have completed the loading dose and 18 965 (94·2%) the 8 h maintenance dose. 3076 (15·3%) patients died, of whom 1086 (35·3%) died on the day of randomisation (figure 2). There were 1063 deaths due to bleeding, of which 637 (59·9%) were on the day of randomisation.

See **Online** for webappendix

	Tranexamic acid (n=10 093)	Placebo (n=10 114)
Sex		
Men	8439 (83·6%)	8496 (84·0%)
Women	1654 (16·4%)	1617 (16·0%)
Not known	0	1 (0·01%)
Time since injury (h)		
Mean (SD)	2·8 (2·2)	2·9 (2·6)
≤1	3756 (37·2%)	3722 (36·8%)
>1–≤3	3045 (30·2%)	3006 (29·7%)
>3†	3287 (32·6%)	3380 (33·4%)
Not known	5 (0·05%)	6 (0·06%)
Systolic blood pressure (mm Hg)		
≤75	1566 (15·5%)	1608 (15·9%)
76–89	1615 (16·0%)	1697 (16·8%)
≥90	6901 (68·4%)	6791 (67·1%)
Not known	11 (0·11%)	18 (0·18%)
Central capillary refill time (s)		
≤2	3432 (34·0%)	3406 (33·7%)
3–4	4665 (46·2%)	4722 (46·7%)
>4	1699 (16·8%)	1672 (16·5%)
Not known	297 (2·9%)	314 (3·1%)
Glasgow Coma Score (total)		
Severe (3–8)	1799 (17·8%)	1839 (18·2%)
Moderate (9–12)	1353 (13·4%)	1351 (13·4%)
Mild (13–15)	6934 (68·7%)	6908 (68·3%)
Not known	7 (0·07%)	16 (0·16%)

Data are number (% of group total), unless otherwise indicated. *Includes five patients younger than 16 years. †Includes 23 patients randomly assigned more than 8 h after injury. ‡Includes patients with both blunt and penetrating and those with only blunt injuries.

Table 1: **Baseline data of participants**



	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14·5%)	1613 (16·0%)	0·91 (0·85–0·97)	0·0035
Vascular occlusion*	33 (0·3%)	48 (0·5%)	0·69 (0·44–1·07)	0·096
Head injury	603 (6·0%)	621 (6·2%)	0·97 (0·87–1·08)	0·60

Data are number (%), unless otherwise indicated. RR=relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

Table 2: Death by cause

Discussion

The results show that the early administration of tranexamic acid to trauma patients with, or at risk of, significant bleeding reduces the risk of death from haemorrhage with no apparent increase in fatal or non-fatal vascular occlusive events. All-cause mortality was significantly reduced with tranexamic acid.

The trial inclusion criteria were clinical and did not depend on the results of laboratory tests. Patients were enrolled if they were judged to have on-going significant haemorrhage, as evidenced by hypotension or tachycardia, or if they were considered to be at risk of significant haemorrhage—eg, patients with compensated haemorrhage and stable vital signs, or those in whom bleeding might have stopped but who might recommence bleeding following volume resuscitation. The use of clinical inclusion criteria is appropriate in the context of traumatic bleeding in which a range of clinical signs need to be assessed when establishing the presence or absence of haemorrhage, while taking into account remedial measures such as fluid resuscitation. The clinical inclusion criteria, and the large numbers of patients studied in a range of different health-care settings, help these results to be generalised widely.

Our study had strengths and limitations. The randomisation methods ensured that participating clinicians did not have foreknowledge of treatment allocation. Baseline prognostic factors were well balanced. All analyses were on an intention-to-treat basis and, because almost all randomised patients were followed up, there was no need to use imputation methods for missing data.[11] The primary endpoint was all-cause mortality, and the observed reduction in mortality with tranexamic acid was both statistically significant and clinically important. The diagnosis of traumatic haemorrhage can be difficult, and some of the included patients might not have been bleeding at the time of randomisation. This misdiagnosis would have reduced the power of the trial to show an effect of tranexamic acid on mortality from bleeding. Nevertheless, we recorded a significant reduction in death due to bleeding.

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value
Vascular occlusive events*				
Need for transfusion and surgery				
Dependency				

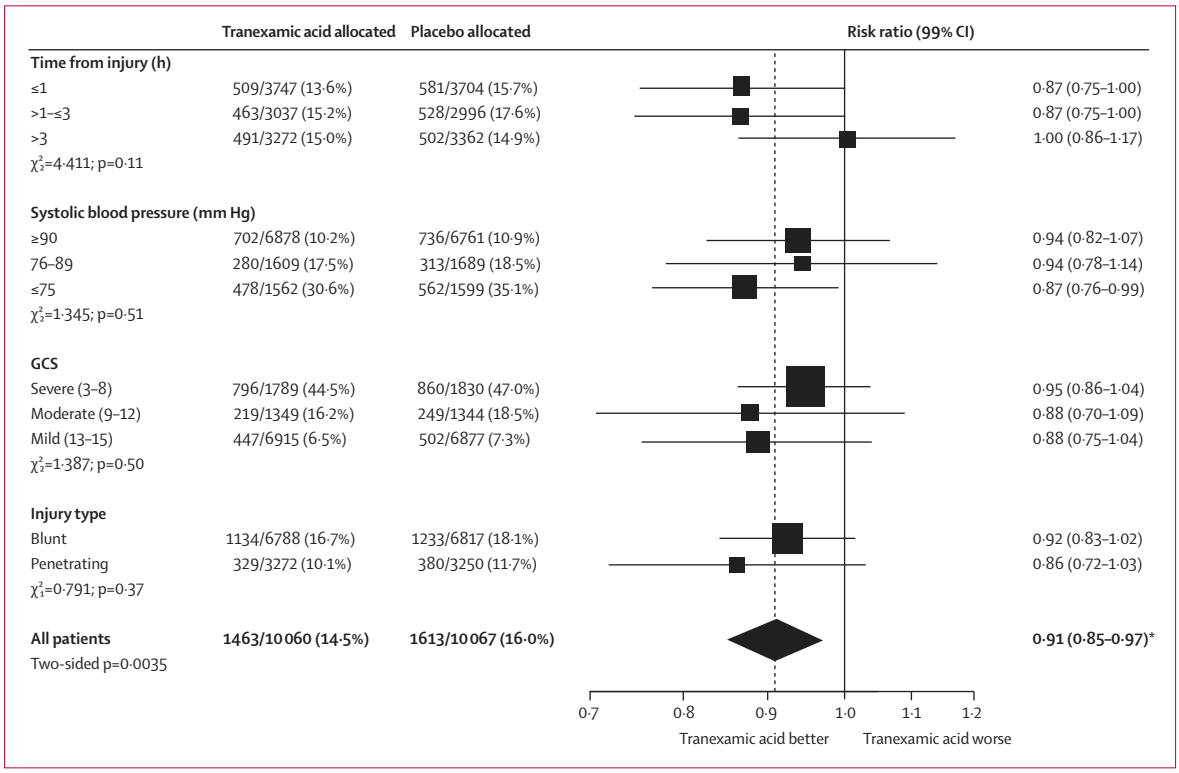
Data are number (%), unless otherwise indicated. Counts are for numbers of patients with at least one such event. RR=relative risk. *Includes both fatal and non-fatal events. †Transfused patients only. ‡Analysis used logarithmic transformation of mean units of blood products transfused.

Table 3: **Vascular occlusive events, need for transfusion and surgery, and level of dependency**

Therefore, we sought high specificity in the diagnosis of non-fatal vascular occlusive events and stipulated that occlusive events should be recorded only when there was clear clinical evidence. As a result, we might have under-reported the frequency of these events. However, our estimates of the RR of non-fatal occlusive events should be unbiased.[12]

One weakness of this trial is that it provides limited insight into how tranexamic acid reduces the risk of death in bleeding trauma patients. Early coagulation abnormalities are frequent in severely injured trauma patients and are associated with substantially increased mortality.[13] Recent research showing that hyperfibrinolysis is a common feature of these abnormalities raises the possibility that antifibrinolytic agents such as tranexamic acid might operate via this mechanism.[13] Furthermore, intravenous tranexamic acid administration has an early (within 4 h) antifibrinolytic effect.[14] However, although this mechanism is plausible, because we did not measure fibrinolytic activity in this trial we cannot conclude that this agent acts by reducing fibrinolysis, rather than another mechanism. Further studies are needed into the mechanism of action of tranexamic acid in bleeding trauma patients. Measurement of blood loss is difficult in trauma patients. Much of the bleeding occurs at the scene of the injury and the bleeding that occurs in hospital is often concealed and difficult to quantify, such as, for example, bleeding into the chest, abdomen, pelvis, and soft tissues. However, we did not find any substantial reduction in the receipt of a blood transfusion or the amount of blood transfused in trauma patients. This finding could be an indication of the difficulty of accurate estimation of blood loss in trauma patients when assessing the need for transfusion. Another possible explanation is that after the loading dose, tranexamic acid was infused over 8 h, whereas decisions about transfusion are made soon after admission. Finally, fewer deaths occurred in patients allocated to tranexamic acid than to placebo, and the patients who survived as a result of tranexamic acid administration would have had a greater opportunity to receive a blood transfusion (competing risks).

The tranexamic acid loading dose was given within 8 h of injury, followed by a maintenance infusion over 8 h. We chose the early administration of a short course of tranexamic acid because most deaths from bleeding occur on the day of the injury and we postulated that the drug would act by reducing bleeding. Generally, after the first day, the risk of death from haemorrhage is


Tranexamic acid allocated
Placebo allocated
Risk ratio (99% CI)
Time from injury (h)
≤1 509/3747 (13·6%) 581/3704 (15·7%) 0·87 (0·75–1·00)
>1–≤3 463/3037 (15·2%) 528/2996 (17·6%) 0·87 (0·75–1·00)
>3 491/3272 (15·0%) 502/3362 (14·9%) 1·00 (0·86–1·17)
χ^2_2=4·411; p=0·11
Systolic blood pressure (mm Hg)
≥90 702/6878 (10·2%) 736/6761 (10·9%) 0·94 (0·82–1·07)
76–89 280/1609 (17·5%) 313/1689 (18·5%) 0·94 (0·78–1·14)
≤75 478/1562 (30·6%) 562/1599 (35·1%) 0·87 (0·76–0·99)
χ^2_2=1·345; p=0·51
GCS
Severe (3–8) 796/1789 (44·5%) 860/1830 (47·0%) 0·95 (0·86–1·04)
Moderate (9–12) 219/1349 (16·2%) 249/1344 (18·5%) 0·88 (0·70–1·09)
Mild (13–15) 447/6915 (6·5%) 502/6877 (7·3%) 0·88 (0·75–1·04)
χ^2_2=1·387; p=0·50
Injury type
Blunt 1134/6788 (16·7%) 1233/6817 (18·1%) 0·92 (0·83–1·02)
Penetrating 329/3272 (10·1%) 380/3250 (11·7%) 0·86 (0·72–1·03)
χ^2_1=0·791; p=0·37
All patients 1463/10 060 (14·5%) 1613/10 067 (16·0%) 0·91 (0·85–0·97)*
Two-sided p=0·0035
0·7
0·8
0·9
1·0
1·1
1·2
Tranexamic acid better
Tranexamic acid worse

Although evidence suggests that this drug reduces post-partum bleeding, the quality of the existing trials is poor and none has been large enough to assess the effect of tranexamic acid on endpoints that are important to women.[24] A large trial is being undertaken to assess the effect of tranexamic acid on the risk of death and hysterectomy in women with post-partum haemorrhage.[25]

In conclusion, tranexamic acid could be given in a wide range of health-care settings, and safely reduced the risk of death in bleeding trauma patients in our study. The option to use tranexamic acid should be available to doctors treating trauma patients in all countries, and this drug should be considered for inclusion on the WHO List of Essential Medicines. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.

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