Targeted Update

In trauma patients with bleeding requiring (or likely to require) red-blood-cell transfusion, what is the effect of tranexamic acid on survival?

This **Targeted update** is based on the Cochrane Review: Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD004896. DOI: 10.1002/14651858.CD004896.pub4.

The search methods; changes to methods; screening results; characteristics of studies, risk of bias, and data and analyses tables; Cochrane authors' conclusions; and references can be found in **Supplementary material**. This Targeted Update was prepared by the Cochrane Editorial Unit

What's new?

The updated Cochrane Review, published in May 2015, identified no additional studies. Full details for mortality due to bleeding, for the subgroups of blunt and penetrating trauma, and tranexamic acid given at ≤3 hours and >3hours, have been added to this Targeted Update (August 2015). Search up to date as of 6 January 2015.

Key statements

- TXA reduces all-cause mortality and bleeding-related mortality compared with placebo in trauma patients
- The effect of TXA on the volume of blood transfused in trauma patients is uncertain
- There is no evidence that TXA increases the risk of vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis)
- TXA given at ≤3 hours may reduce bleeding-related mortality, but TXA >3 hours may increase bleeding-related mortality, when compared with placebo
- TXA has similar effects on bleeding-related mortality for the subgroups of penetrating and blunt trauma

Sources of Support: Funded by Cochrane as part of a pilot project.

Abstract

Background

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

Objectives

To assess the effect of TXA in trauma patients with bleeding requiring (or likely to require) red-blood-cell (RBC) transfusion.

Search methods

We ran the most recent search in January 2015. We searched the Cochrane Injuries Group's Specialised Register, The Cochrane Library, Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R), Embase Classic+Embase (OvidSP), PubMed and clinical trials registries.

Selection criteria

Randomised controlled trials of TXA in trauma patients with bleeding requiring (or likely to require) RBC transfusion.

Data collection and analysis

From the results of the screened electronic searches, bibliographic searches, and contacts with experts, two authors independently selected trials meeting the inclusion criteria, and extracted data. One review author assessed the risk of bias for key domains.

Main Results

One trial (CRASH-2, n = 20,211) met the inclusion criteria. The trial was previously included in the Cochrane Review (full update published May 2015), and no new studies were added to this Targeted Update. The trial was conducted in 40 countries and included patients with a variety of types of trauma. The risk of bias for the study, for all domains, was low.

All trauma patients, TXA administered at any time

There was high quality evidence that TXA reduces all-cause mortality (1 RCT, 20,127 participants; RR 0.91, 95% CI 0.85 to 0.97; 14 fewer deaths per 1000 patients with TXA) and bleeding-related mortality (1 RCT, 20,127 participants; RR 0.85, 95% CI 0.76 to 0.96; 9 fewer deaths per 1000 with TXA), when compared with placebo. The effect of TXA on the volume of blood transfused in trauma patients was uncertain (1 RCT, 20,127 participants; MD -0.17 units, 95% CI -0.39 units to 0.05 units; very low quality evidence). There was no evidence that TXA increases the risk of vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis).

TXA delivered at or within 3 hours and after 3 hours

There was evidence from subgroup analyses that TXA ≤3 hours reduces bleeding-related mortality when compared with placebo (1 RCT, 13,484 participants; RR 0.72, 95% CI 0.63 to 0.83; 19 fewer deaths per 1000 with TXA), but evidence from subgroup analyses that TXA >3 hours increases bleeding-related mortality when compared with placebo (1 RCT, 6634 participants; RR 1.44, 95% CI 1.12 to 1.84; 13 more deaths per 1000 with TXA).

The difference between these subgroups was statistically significant by interaction testing (Chi^2 = 22.51, df = 1 [P < 0.00001], I^2 = 95.6%).

Patients with blunt and penetrating trauma

TXA had similar effects on bleeding-related mortality for the subgroups of penetrating and blunt trauma (test for subgroup differences: Chi^2 = 0.92, df = 1 [P = 0.34], I^2 = 0%).

Implications and conclusions

TXA reduces mortality in trauma patients with bleeding without increasing the risk of vascular occlusive events. TXA should be considered as early as possible and within three hours of injury, as further analysis of the CRASH-2 trial showed that treatment later than this is unlikely to be effective and may be harmful.

Summary of findings table 1: In trauma patients with bleeding requiring RBC transfusion, what is the effect of TXA?

***Patients and setting*: Bleeding trauma patients in hospital settings in 40 countries**
***Comparison:* TXA versus placebo**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	**Certainty of the evidence (GRADE)**
		Without TXA (placebo group)	With TXA		
All-cause mortality	TXA reduces all-cause mortality in trauma patients	160 per 1000	146 per 1000 Difference 14 fewer per 1000 patients (95% CI: 24 to 5 fewer per 1000 patients)	RR 0.91 (0.85 to 0.97) Based on data from 20127 patients in 1 RCT	⊕⊕⊕⊕ HIGH
Mortality due to bleeding	TXA reduces mortality due to bleeding in trauma patients	57 per 1000	48 per 1000 Difference 9 fewer per 1000 (95% CI: 14 to 2 fewer per 1000 patients)	RR 0.85 (0.76 to 0.96) Based on data from 20127 patients in 1 RCT	⊕⊕⊕⊕ HIGH
Volume of blood transfused (units)	The effect of TXA on the volume of blood transfused in trauma patients is uncertain	Mean: 3.22 units	Mean: 3.05 units Mean difference 0.17 units fewer (95% CI: 0.39 fewer to 0.05 more)	Mean difference 0.17 units fewer (95% CI: 0.39 fewer to 0.05 more) Based on data from 20127 patients in 1 RCT	⊕OOO VERY LOW[1,2]
Thromboembolic/vascular occlusive event: myocardial infarction	There is no evidence that TXA increases the risk of myocardial infarction	5 per 1000	3 per 1000 Difference 2 fewer per 1000 patients (95% CI: 3 to 0 fewer per 1000 patients)	RR 0.64 (0.42 to 0.97) Based on data from 20127 patients in 1 RCT	⊕⊕⊕O MODERATE[2]
Thromboembolic/vascular occlusive event: stroke	There is no evidence that TXA increases the risk of stroke	7 per 1000	6 per 1000 Difference 1 fewer per 1000 patients (95% CI: 3 fewer to 1 more per 1000 patients)	RR 0.86 (0.61 to 1.23) Based on data from 20127 patients in 1 RCT	⊕⊕⊕O MODERATE[2]
Thromboembolic/vascular occlusive event: pulmonary embolism	There is no evidence that TXA increases the risk of pulmonary embolism	7 per 1000	7 per 1000 Difference 0 fewer per 1000 patients (95% CI: 2 fewer to 3 more per 1000 patients)	RR 1.01 (0.73 to 1.41) Based on data from 20367 patients in 2 RCTs	⊕⊕⊕O MODERATE[2]
Thromboembolic/vascular occlusive event: deep vein thrombosis	There is no evidence that TXA increases the risk of deep vein thrombosis	4 per 1000	4 per 1000 Difference 0 fewer per 1000 patients (95% CI: 1 fewer to 2 more per 1000 patients)	RR 0.98 (0.63 to 1.51) Based on data from 20367 patients in 2 RCTs	⊕⊕⊕O MODERATE[2]

CI=confidence interval; MD=Mean difference; RR=Risk ratio; TXA=tranexamic acid

[1]Downgraded two levels for serious indirectness: in trauma patients many transfusions are given as soon as the patient arrives, at the same time as the treatment, and therefore any treatment effect is biased towards the null.

[2]Downgraded one level for imprecision: uncertainty around effect estimate

Summary of findings table 2: In trauma patients with bleeding requiring RBC transfusion, what is the effect of *timing* of TXA on mortality due to bleeding?

***Patients and setting*: Bleeding trauma patients in hospital settings in 40 countries**
***Comparison:* TXA versus placebo**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	**Certainty of the evidence (GRADE)**
		Without TXA (placebo group)	With TXA		
Mortality due to bleeding - TXA given ≤3 hours	TXA given ≤3 hours may reduce mortality due to bleeding in trauma patients	70 per 1000	51 per 1000 Difference 19 fewer per 1000 patients (95% CI: 26 to 12 fewer per 1000 patients)	RR 0.72 (0.63 to 0.83) Based on data from 13484 patients in 1 RCT	N/A [1]
Mortality due to bleeding - TXA >3 hours	TXA >3 hours may increase mortality due to bleeding in trauma patients	31 per 1000	44 per 1000 Difference 13 more per 1000 patients (95% CI: 4 to 26 more per 1000 patients)	RR 1.44 (1.12 to 1.84) Based on data from 6634 patients in 1 RCT	N/A [1]

CI=confidence interval; MD=Mean difference; RR=Risk ratio; TXA=tranexamic acid

[1] Findings from subgroup analyses have not been rated using GRADE considerations due to the high degree of uncertainty involved in this approach

Summary of findings table 3: In patients with *blunt or penetrating trauma* with bleeding requiring RBC transfusion, what is the effect of TXA on mortality due to bleeding?

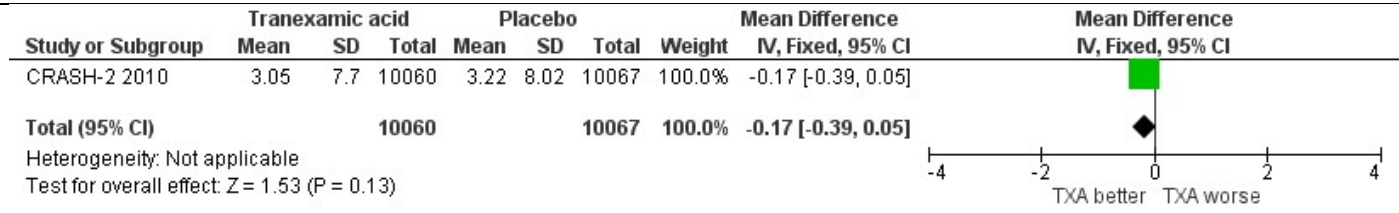
***Patients and setting*: Bleeding trauma patients in hospital settings in 40 countries**
***Comparison:* TXA versus placebo**

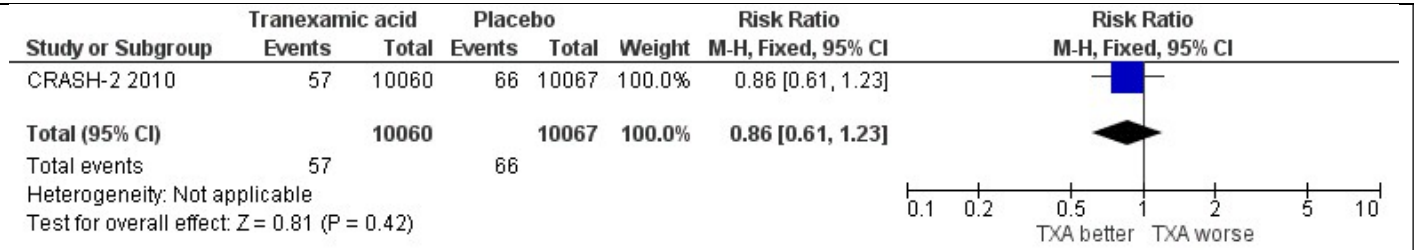
Outcome	Plain language summary	Relative effect (95% CI) Nº of participants & studies	**Certainty of the evidence (GRADE)**
Mortality due to bleeding – in patients with penetrating trauma	TXA had similar effects on bleeding-related mortality for the subgroups of penetrating and blunt trauma.	The best estimate of the effect in both subgroups is the overall risk ratio for bleeding-related mortality (see Summary of findings table 1)	N/A [1]
Mortality due to bleeding – in patients with blunt trauma			

TXA=tranexamic acid
[1] Findings from subgroup analyses have not been rated using GRADE considerations due to the high degree of uncertainty involved in this approach

Forest plots 1: In trauma patients with bleeding requiring RBC transfusion, what is the effect of TXA?

***Patients and setting*: Bleeding trauma patients in hospital settings in 40 countries**
***Comparison:* TXA versus placebo**

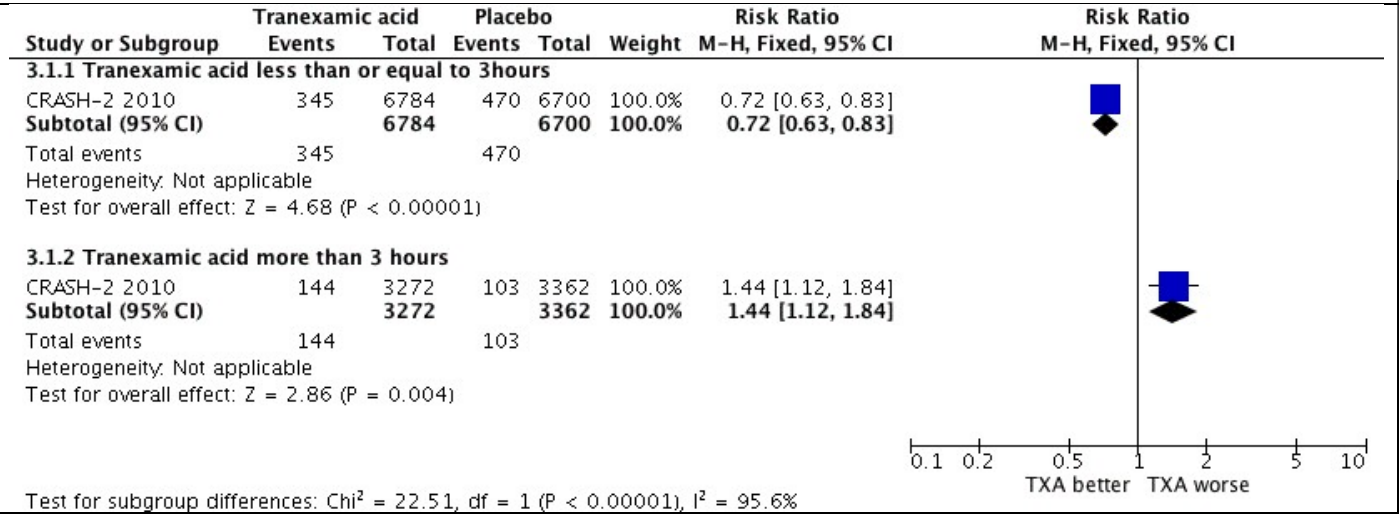
Outcome	Forest plots	Certainty of the evidence (GRADE)
All-cause mortality *TXA reduces all-cause mortality in trauma patients*		⊕⊕⊕⊕ HIGH
Mortality due to bleeding *TXA reduces mortality due to bleeding in trauma patients*		⊕⊕⊕⊕ HIGH
Volume of blood transfused (units) *The effect of TXA on the volume of blood transfused in trauma patients is uncertain*		⊕OOO VERY LOW
Thromboembolic/vascular occlusive event: myocardial infarction *There is no evidence that TXA increases the risk of myocardial infarction*		⊕⊕⊕O MODERATE

Thromboembolic/vascular occlusive event: stroke *There is no evidence that TXA increases the risk of stroke*		⊕⊕⊕O MODERATE
Thromboembolic/vascular occlusive event: pulmonary embolism *There is no evidence that TXA increases the risk of pulmonary embolism*		⊕⊕⊕O MODERATE
Thromboembolic/vascular occlusive event: deep vein thrombosis *There is no evidence that TXA increases the risk of deep vein thrombosis*		⊕⊕⊕O MODERATE

TXA=tranexamic acid

Forest plot 2: In trauma patients with bleeding requiring RBC transfusion, what is the effect of *timing* of TXA on mortality due to bleeding?

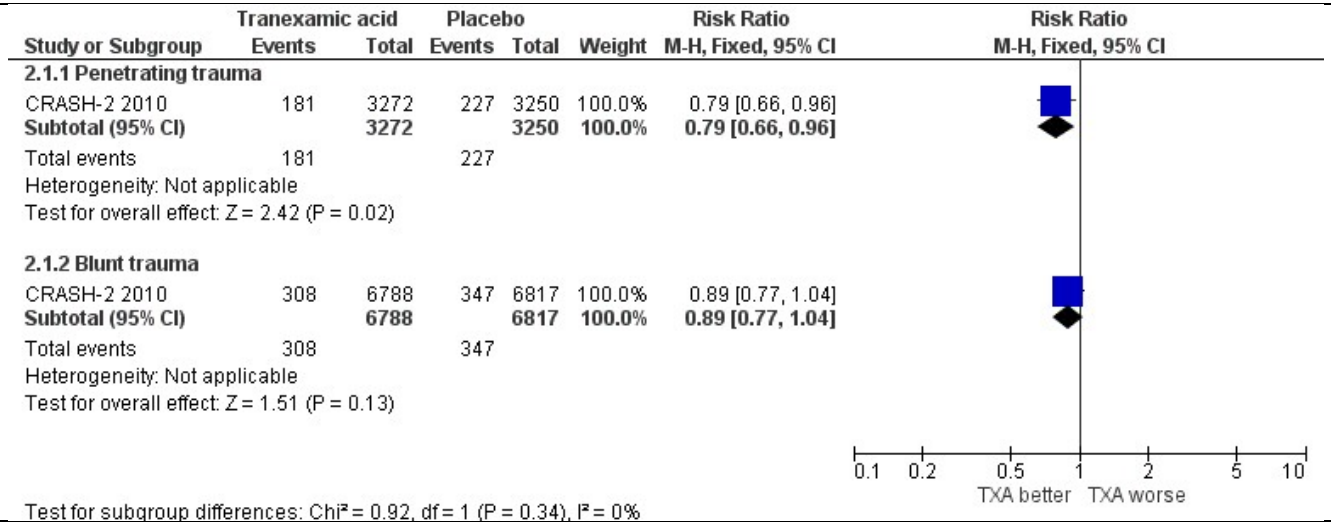
***Patients and setting*: Bleeding trauma patients in hospital settings in 40 countries**
***Comparison:* TXA versus placebo**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Mortality due to bleeding - TXA given ≤3 hours *TXA given ≤3 hours may reduce mortality due to bleeding in trauma patients*		N/A
Mortality due to bleeding - TXA >3 hours *TXA >3 hours may increase mortality due to bleeding in trauma patients*		N/A

TXA=tranexamic acid

Forest plot 3: In patients with *blunt or penetrating trauma* with bleeding requiring RBC transfusion, what is the effect of TXA on mortality due to bleeding?

***Patients and setting*: Bleeding trauma patients in hospital settings in 40 countries**
***Comparison:* TXA versus placebo**

Outcome	Forest plot	**Certainty of the evidence (GRADE)**
Mortality due to bleeding – in patients with penetrating trauma *TXA has similar effects on bleeding-related mortality for the subgroups of penetrating and blunt trauma*		N/A
Mortality due to bleeding – in patients with blunt trauma *TXA has similar effects on bleeding-related mortality for the subgroups of penetrating and blunt trauma*		

TXA=tranexamic acid