

Targeted Update

In trauma patients with bleeding requiring (or likely to require) red-blood-cell transfusion, what is the effect of transamic 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.

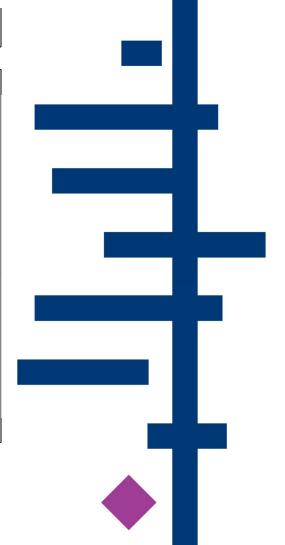
The search methods; changes to methods; screening results; characteristics of studies, risk of bias, and data and analyses tables; Cochrane authors' conclusions; and references can be found in <u>Supplementary material</u>. This Targeted Update was prepared by the Cochrane Editorial Unit

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 bleedingrelated 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



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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.

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% Cl 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% Cl 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
		Without TXA (placebo group)	With TXA	— N° of participants & stodies	(GRADE)
All-cause mortality	TXA reduces all-cause mortality in trauma patients	160 per 1000 Difference 14 fewer (95% CI: 24 to 5 few	146 per 1000 per 1000 patients per 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 Difference 9 fewer p (95% CI: 14 to 2 few	48 per 1000 per 1000 per 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 difference 0.1 (95% CI: 0.39 fewer	•	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	reases the 5 per 1000 3 per 1000 Difference 2 fewer per 1000 patient (95% CI: 3 to 0 fewer per 1000 patie		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% Cl: 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 o 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 Difference o 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

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

¹Downgraded 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.

²Downgraded 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	come Plain language summary			Relative effect (95% CI) No of participants & studies	Certainty of the evidence	
		Without TXA	With TXA	14 of participants a scoules	(GRADE)	
		(placebo group)				
Mortality due to bleeding -	TXA given ≤3 hours may reduce mortality due	70 per 1000	51 per 1000	RR 0.72 (0.63 to 0.83)	N/A ¹	
TXA given ≤3 hours	to bleeding in trauma patients	Difference 19 fewer p	er 1000 patients	Based on data from 13484		
		(95% CI: 26 to 12 few	er per 1000 patients)	patients in 1 RCT		
Mortality due to bleeding -	TXA >3 hours may increase mortality due to	31 per 1000	44 per 1000	RR 1.44 (1.12 to 1.84)	N/A 1	
TXA >3 hours	bleeding in trauma patients	Difference 13 more p	er 1000 patients	Based on data from 6634		
		(95% CI: 4 to 26 more per 1000 patients)		patients in 1 RCT		
,		Difference 13 more p	er 1000 patients	Based on data from 6634	N/A ¹	

Cl=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 Mortality due to bleeding – in patients with blunt 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

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	Tranexamic acid Placebo Risk Ratio Risk Ratio	$\oplus \oplus \oplus \oplus$
TXA reduces all-cause mortality in	Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI	HIGH
trauma patients	CRASH-2 2010 1463 10060 1613 10067 100.0% 0.91 [0.85, 0.97]	
	Total (95% CI) 10060 10067 100.0% 0.91 [0.85, 0.97]	
	Total events 1463 1613	
	Heterogeneity: Not applicable 0.1 0.2 0.5 1 2 5 10	
	Test for overall effect: Z = 2.92 (P = 0.004) TXA better TXA worse	
Mortality due to bleeding	Tranexamic acid Placebo Risk Ratio Risk Ratio	$\oplus \oplus \oplus \oplus$
TXA reduces mortality due to	Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI	HIGH
bleeding in trauma patients	CRASH-2 2010 489 10060 574 10067 100.0% 0.85 [0.76, 0.96]	
	Total (95% CI) 10060 10067 100.0% 0.85 [0.76, 0.96]	
	Total events 489 574	
	Heterogeneity: Not applicable 0.1 0.2 0.5 1 2 5 10	
	Test for overall effect: Z = 2.66 (P = 0.008) TXA better TXA worse	
Volume of blood transfused (units)	Tranexamic acid Placebo Mean Difference Mean Difference	⊕OOO
The effect of TXA on the volume of	Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI	VERY LOW
blood transfused in trauma patients is	CRASH-2 2010 3.05 7.7 10060 3.22 8.02 10067 100.0% -0.17 [-0.39, 0.05]	
uncertain	Total (95% CI) 10060 10067 100.0% -0.17 [-0.39, 0.05]	
	Heterogeneity: Not applicable	
	Test for overall effect: Z = 1.53 (P = 0.13) TXA better TXA worse	
Thromboembolic/vascular occlusive	Tranexamic acid Placebo Risk Ratio Risk Ratio	$\oplus \oplus \oplus O$
event: myocardial infarction	Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl	MODERATE
There is no evidence that TXA	CRASH-2 2010 35 10060 55 10067 100.0% 0.64 [0.42, 0.97]	
increases the risk of myocardial	Total (95% CI) 10060 10067 100.0% 0.64 [0.42, 0.97]	
infarction	Total events 35 55	
	Haterogeneity Not applicable	
	Test for overall effect: Z = 2.09 (P = 0.04) Test for overall effect: Z = 2.09 (P = 0.04) TXA better TXA worse	
	TAA pellet TAA Worse	

Thromboembolic/vascular occlusive	_	Tranexami	ic acid	Place	bo		Risk Ratio			Risk Ratio		$\oplus \oplus \oplus O$
event: stroke	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixed, 95% CI		MODERATE
There is no evidence that TXA	CRASH-2 2010	57	10060	66	10067	100.0%	0.86 [0.61, 1.23]					
increases the risk of stroke												
increases the risk of stroke	Total (95% CI)		10060		10067	100.0%	0.86 [0.61, 1.23]			•		
	Total events	57		66				20	241		27 10	
	Heterogeneity: Not ap							0.1	0.2	0.5 1 2	5 10	
	Test for overall effect:	Z= 0.81 (P=	= 0.42)					0.1		XA better TXA worse	0 10	
Thromboembolic/vascular occlusive	=	Tranexami	ic acid	Place	bo		Risk Ratio			Risk Ratio		$\oplus \oplus \oplus O$
event: pulmonary embolism	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixed, 95% CI		MODERATE
There is no evidence that TXA	CRASH-2 2010	72	10060	71	10067	100.0%	1.01 [0.73, 1.41]			100 Tel		
increases the risk of pulmonary	Total (95% CI)		10060		10067	100.0%	1.01 [0.73, 1.41]			•		
embolism	Total events	72		71						08		
	Heterogeneity: Not ap	plicable						0.1	0.2	0.5 1 2	5 10	
	Test for overall effect:	Z= 0.09 (P=	= 0.93)					0.1		XA better TXA worse	3 10	
Thromboembolic/vascular occlusive	_	Tranexami	ic acid	Place	bo		Risk Ratio			Risk Ratio		$\oplus \oplus \oplus O$
event: deep vein thrombosis	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixed, 95% CI		MODERATE
There is no evidence that TXA	CRASH-2 2010	40	10060	41	10067	100.0%	0.98 [0.63, 1.51]					
increases the risk of deep vein	T-4-1/05% OB		40000		40007	400.00/	0.0010.00.4.541					
thrombosis	Total (95% CI)		10060		10067	100.0%	0.98 [0.63, 1.51]					
Uniomosis	Total events	40		41				20	20		0 9	
	Heterogeneity: Not ap		202001					0.1	0.2	0.5 1 2	5 10	
	Test for overall effect:	Z = 0.11 (P =	= 0.91)							XA better TXA worse	-	

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		Tranexami		Place	T. 1757		Risk Ratio			Ratio	_	N/A
given ≤3 hours	Study or Subgroup	Events				Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI		
TXA given ≤3 hours may reduce	3.1.1 Tranexamic acid	less than							_			
	CRASH-2 2010	345	6784	470		100.0%						
mortality due to bleeding in trauma	Subtotal (95% CI)	5 <u>2.592</u> 5	6784	19/200	6700	100.0%	0.72 [0.63, 0.83]		•			
patients	Total events	345		470								
Mortality due to bleeding - TXA >3	Heterogeneity. Not app		- 0 000	01)								N/A
hours	Test for overall effect:	Z = 4.68 (P	< 0.000	01)								,, .
	3.1.2 Tranexamic acid	more than	3 hours									
TXA >3 hours may increase mortality	CRASH-2 2010	144	3272		3362	100.0%	1.44 [1.12, 1.84]			_		
due to bleeding in trauma patients	Subtotal (95% CI)	144	3272	103		100.0%				-		
	Total events	144	T	103								
	Heterogeneity. Not app											
	Test for overall effect:		= 0.004	i.								
								0.1 0.2		 	+ 10	
								0.1 0.2	U.5	TXA worse	5 10	
	Test for subgroup diffe	erences: Chi ^z	= 22.51	df = 1	(P < 0)	.00001),	$I^2 = 95.6\%$		TAA DELLET	I AA WUISE		

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		Tranexami		Place		222000000	Risk Ratio		Risk Rat		·	N/A
patients with penetrating trauma	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 9	95% CI		
TXA has similar effects on bleeding-	2.1.1 Penetrating trau	ma										
1 33	CRASH-2 2010	181	3272	227	3250	100.0%	0.79 [0.66, 0.96]					
related mortality for the subgroups	Subtotal (95% CI)		3272		3250	100.0%	0.79 [0.66, 0.96]		•			
of penetrating and blunt trauma	Total events	181		227								
Mortality due to bleeding – in patients with blunt trauma	Heterogeneity: Not app Test for overall effect: 2		0.02)									
TXA has similar effects on bleeding-	2.1.2 Blunt trauma											
related mortality for the subgroups	CRASH-2 2010 Subtotal (95% CI)	308	6788 6788	347	6817 6817	100.0% 100.0 %	0.89 [0.77, 1.04] 0.89 [0.77, 1.04]					
of penetrating and blunt trauma	Total events Heterogeneity: Not app Test for overall effect: 2		0.13)	347								
	Test for subgroup diffe	erences: Chi	²= 0.92,	df=1 (P	= 0.34)	, I² = 0%		0.1 0.2	0.5 1 TXA better TX	2 (A worse	5 10	