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Tranexamic Acid Timing and Mortality Impact After Trauma

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PMID: 40751727 DOI: 10.1016/j.annemergmed.2025.06.609

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The paper discussed here is the continuation of an **exploratory analysis** of the randomized clinical trial (RCT) **PATCH-Trauma** (1).

What is an **exploratory analysis of data?** This is an analytical approach using summary statistics to examine sets of data, in order to identify patterns, anomalies, and atypical values, and it can even help determine if appropriate statistical techniques are used. Therefore, the goal is not to confirm a hypothesis, but to focus on generating questions that may be used to guide future research.

As for the use of tranexamic acid (TXA) in polytraumatized patients, it all started with the publication of the **CRASH-2** (2) RCT in 2010, which proved that the use of TXA reduced overall mortality after 28 days in these patients, with a relative risk (RR) of 0.91 (95% CI: 0.85-0.97) and a very significant p (0.0035). This is why the main European guideline on trauma management (3) recommends using it with a 1A evidence level. However, the significance decreased when analyzing the best time for its administration. According to the CRASH-2 RCT, using it 3 hours after the trauma did not reduce overall mortality, and if administered before 3 hours, there was a clear tendency to improve, without reaching statistical significance [RR: 0.87 (0.75-**1**)], since the CI included 1 (Figure 1).

Nevertheless, a **further exploratory analysis of CRASH-2** (4) showed that the decrease in mortality due to bleeding was indeed significant when TXA was administered within 3 hours (RR: 0.87; CI 95%: 0.77-0.97).

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CRASH-2 (2010)

RCT: TXA vs PLACEBO **within 8 h** of trauma
Impact on **mortality** at **28 days**

274 hospitals, from 40 countries

	TXA (N=10 060)	PLACEBO (N=10 067)	p
Time (≤1h)	37,2%	36,8%	pns
Contusion	67,5%	67,7%	pns
TAs<90 mmHg	31,5%	32,7%	pns
GCS <13	31,2%	31,6%	pns
Thrombosis	0,3%	0,5%	pns
Exitus 28 days	0,91 (0,85-0,97)		0,0035
Exitus bleeding	0,85 (0,76-0,96)		0,0077
Exitus if adm ≤3h	0,87 (0,75-1)		pns
Exitus if adm > 3h	1 (0,86-1,17)		pns

PATCH-Trauma (2023)

RCT: TXA vs PLACEBO **within 3 h** of trauma and **prehospital**
Impact on **GOSE** at **6 months**. Favorable GOSE ≥5

21 hospitals, from 3 countries (Australia, New Zealand, Germany)

	TXA (N=652)	PLACEBO (N=635)	p
Time (≤1h)	32,6%	27,5%	pns
Contusion	92,8%	91,4%	pns
TAs<90 mmHg	72,6%	71,1%	pns
GCS <13	42,8%	44,3%	pns
Thrombosis	23,6%	19,7%	pns
Exitus 28 days	17,3%	21,8%	<0,05
GOSE ≥ 5	53,7%	53,5%	pns
Exitus if adm 1-<2h	RR: 1,09 (0,93-1,26)		pns
Exitus if adm ≥2h	RR: 0,83 (0,66-1,03)		pns
ISS (average)	29 (18-41)	29 (17-38)	pns
COAST Score ≥ 3	94%	94%	pns

Figure 1. ECA CRASH-2 versus ECA PATCH-Trauma

Since CRASH-2 was not designed to determine the best time for the administration of TXA, patients were recruited in 2014 for a new RCT aimed at assessing whether the administration of TXA **within 3 hours** of the trauma improved the functional outcome of these patients (the **PATCH-Trauma** RCT). The results were published in 2023 (1). In the summary in Figure 1, we can see how the main goal of the PATCH-Trauma trial was not mortality after 28 days, but a favorable functional outcome measured by the GOS-E scale (GOSE≥5) at 6 months. This new RCT could not prove an improvement in GOSE after 6 months with the administration of TXA within 3 hours.

In summary, CRASH-2 concluded that TXA improved mortality for any cause after 28 days if administered within **8 hours** of the accident (suggesting that the appropriate timing was probably within **3 hours**, according to a subsequent exploratory analysis showing a decrease in mortality due to bleeding), and the **PATCH-Trauma** trial concluded that TXA administered within **3 hours** did not improve GOSE at 6 months. **Why such differences?**

- Inclusion of different patients. As can be seen in Figure 1, patients included in PATCH-Trauma seemingly presented a higher risk of coagulopathy than patients in CRASH-2 (twice as many patients in shock, higher ratio of moderate-severe TBI, and with a very high score in a risk scale for coagulopathy -COAST score-).
- Considering as favorable evolution patients with GOSE 5 (unable to go back to work or take part in social activities) is very controversial. Therefore, we must wonder, would the results of the PATCH-Trauma trial be different if GOSE 5 had been assessed as an unfavorable evolution? (Figure 2)
- PATCH-Trauma uses COAST (5) as a predictive scale for coagulopathy, seldom used in Europe, where the IS score (Figure 3) is preferred. The sensitivity of the COAST scale to predict coagulopathy is 60%, and specificity is 96.4%. So, if the scale score is <3, we will probably be right if we consider a very low coagulopathy risk; however, if the score is 3 or more, we will only get the coagulopathy prediction right in 60% of the cases.

GOS-E (Glasgow Outcome Scale – Extended)

Unfavorable	1	Death	Death
	2	Vegetative state	Vegetative State
	3	Full dependence on others	Lower Severe Disability
	4	Dependence on others for some activities	Upper Severe Disability
Favorable	5	Unable to go back to work or take part in social activities	Lower Moderate Disability
	6	Back to work or able to take part in social activities with limitations	Upper Moderate Disability
	7	Good recovery with mild mental and social deficiency	Lower Good Recovery
	8	Good recovery with no deficiency	Upper Good Recovery

Figure 2. GOS-E scale

COAST Score (Coagulopathy of Severe Trauma)

Item	Value	Score
Trapping in vehicle	Yes	1
TAs	<100 mmHg <90 mmHg	1 2
Temperature	<35ºC <32ºC	1 2
Major thorax trauma	Yes	1
Abdominal or pelvic trauma	Yes	1

COAST ≥ 3 predicts coagulopathy with Se 60% and Sp 96.4%

Figure 3. COAST scale

However, although the **PATCH-Trauma** trial concluded that TXA does not help improve the evolution within 6 months, **it did observe a significant reduction in mortality within 28 days** (Figure 1): 21.8% to 17.3%. **The exploratory analysis in the paper discussed emerges as a consequence of this secondary conclusion from PATCH-Trauma.** Thus, Ali et al., by applying the most appropriate statistical analysis to predict the best time for TXA administration (multivariable fractional polynomial regression, ideal for continuous covariates, such as time), found that mortality within 28 days was significantly reduced if TXA was administered **within 90 minutes of the trauma.**

The authors of this analysis remind that, since most patients in the PATCH-Trauma trial suffered a contusion, that time should not be extrapolated to patients with other trauma mechanisms with penetrating wounds, such as those caused by cold weapons or firearms. Furthermore, since data from another study (PATCH-Trauma) are also explored, this might not have the appropriate statistical power. Still, when calculated, it is very close to 80%, and therefore, probably appropriate.

The other question considered in this exploratory analysis is **why TXA might not have any effect or even be harmful when administered after 90 minutes.** The authors put forward a biological explanation based on preclinical studies suggesting that this deleterious effect could be due to a delayed surge in urokinase expression and changes in its conformation that promote plasmin activity, leading to fibrinolysis and effects on the immune function.

In conclusion, as a consequence of this **exploratory analysis of the PATCH-Trauma trial**, I reckon it is very likely for future trauma management guidelines to include those 90 minutes as appropriate for the administration of the first dose of TXA.

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