Critical Review Form
Therapy

Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg. 2012 Feb;147(2):113-9.

Objectives: **"The objectives of this study are to report the experience of the use of [tranexamic acid] TXA in the combat setting and to characterize its effect on measures of coagulopathy and survival following wartime injury." (p. 114)**

Methods: **This was a retrospective cohort study performed at a single military surgical hospital at Camp Bastion in Southern Afghanistan involving consecutive trauma patients admitted between January 1, 2009 and December 31, 2010. Patients receiving transfusion of at least one unit of PRBCs within 24 hours of admission for combat-related injury were eligible for enrollment. Prior to 2010, the administration of TXA was at the discretion of the treating surgeon or anesthetist. Beginning in 2010, a major hemorrhage protocol was enacted requiring TXA administration to patients requiring emergency blood products or with demonstrated hyperfibrinolysis by rotational thromboelastography (ROTEM). The standard dose of TXA was 1 gram IV bolus, followed by repeat dosing as dictated by the treating physician. Patients who received TXA were included in the TXA group, while those who did not receive TXA were included in the no-TXA group. Patients who received ≥ 10 units of PRBCs within 24 hours were considered part of the massive transfusion (MT) cohort, analyzed in TXA^{MT} or no-TXA^{MT} groups.**

The primary endpoints were 24-hour, 48-hour, and in-hospital mortality (within 30 days of admission). Secondary endpoints included transfusion requirements and coagulation parameters, as measured by prothrombin time (PT) and activated partial thromboplastin time (aPTT). PT and aPTT were measure both at admission to the emergency department (ED) and at admission to the ICU following the initial operation. Hypocoagulopathy was defined as PT or PTT > 1.5 times the normal range (> 18 seconds or > 55 seconds respectively). An additional endpoint was the incidence of thrombotic events (PE or DVT). A Revised Trauma Score (RTS) (which is inversely related to trauma mortality), Abbreviated Injury Scale (AIS) (which reports anatomical injury patterns for 4 body regions: head, chest, abdomen, and

extremity), and Injury Severity Score (ISS) were calculated and recorded for all patients. Hypotension was defined as a systolic blood pressure (SBP) ≤ 90 mmHg; a significantly reducted level of consciousness was defined as a GCS ≤ 8; and a severe injury was defined as an AIS score of ≥ 3.

A total of 896 patients were enrolled, of whom 293 (32.7%) received TXA within 1 hour of injury (mean dose 2.3 g, with a SD of 1.3), while 603 (67.3%) did not receive TXA. The cohort was almost entirely male, and the mean age was low (24.9 and 23.1 in the TXA and no-TXA groups respectively. The predominant mechanism of injury was explosion, accounting for 612 (68%) cases. A total of 321 patients met MT criteria, of whom 125 (39%) received TXA.

<table>
<tr><th colspan="2">Guide</th><th>Comments</th></tr>
<tr><td>I.</td><td>Are the results valid?</td><td></td></tr>
<tr><td>A.</td><td>Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were patients randomized?</td><td>No. This was a retrospective cohort study. “Prior to 2010, TXA was administered at the discretion of the surgeon or anesthetist on the basis of clinical judgment and, in some instances, following demonstration of hyperfibrinolysis on rotational thromboelastography. Thereafter, as part of a major hemorrhage protocol or clinical practice guideline, TXA was administered to patients requiring emergency blood products or patients with evidence of hyperfibrinolysis.” (p. 114)</td></tr>
<tr><td>2.</td><td>Was randomization concealed (blinded)?</td><td>No. The study was not randomized.</td></tr>
<tr><td>3.</td><td>Were patients analyzed in the groups to which they were randomized?</td><td>No. The study was not randomized. Patients were analyzed according to whether or not they received TXA.</td></tr>
<tr><td>4.</td><td>Were patients in the treatment and control groups similar with respect to known prognostic factors?</td><td>No. Not surprisingly, patients who received TXA were on the whole sicker. They were more likely to have suffered trauma from an explosion, were more likely to have significant extremity injury based on AIS scores, had higher ISS scores, had lower RTS scores, and had lower GCS scores (Table 1). Additionally, patients receiving TXA spend less time in the ED and more time in the OR.

Table 1. Demographic and injury severity data for all patients
<table>
<tr><th></th><th>TXA (n = 293)</th><th>No-TXA (n = 603)</th><th>p-value</th></tr>
<tr><td>Mechanism of injury, %
• GSW
• Explosion</td><td>
25.3
74.7</td><td>
36.7
62.4</td><td>
< 0.001</td></tr>
</table>
</td></tr>
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		Mean ISS (SD) 25.2 (16.6) 22.5 (18.5) < 0.001 Extremity AIS ≥ 3, % 66.6 47.3 < 0.001 RTS, mean (SD) 5.53 (2.14) 6.04 (2.69) 0.01 GCS ≤ 8, % 63.3 35.6 < 0.001 SBP ≤ 90 mmHg, % 22.8 13.8 0.003 Table 2. Demographic and injury severity data MT patients TXA (n = 125) / No-TXA (n = 196) / p-value Mechanism of injury, % / / 0.14 • GSW 24.0 32.1 • Explosion 76.0 66.8 Mean ISS (SD) 26.1 (17.1) 25.2 (20.5) 0.11 Extremity AIS ≥ 3, % 68.0 51.0 0.003 RTS, mean (SD) 5.58 (2.21) 5.74 (2.88) 0.21 GCS ≤ 8, % 64.1 39.3 < 0.001 SBP ≤ 90 mmHg, % 20.4 18.2 0.67
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes. This was a retrospective cohort study, and all participants were aware of group allocation.
2.	Were clinicians aware of group allocation?	Yes. This was a retrospective cohort study, and all participants were aware of group allocation.
3.	Were outcome assessors aware of group allocation?	Yes. This was a retrospective cohort study, and all participants were aware of group allocation.
4.	Was follow-up complete?	No. The primary endpoints were 24 and 48 hour and in-hospital mortality. 24 hour mortality was easily assessed on all patients. 48-hour and in-hospital mortality were assessed on 264 patients in the TXA group (out of 293 subjects); 48-hour mortality was assessed on 507 of 603 subjects in the no-TXA group; interestingly, the authors report in-hospital mortality data on all 603 patients in the no-TXA group.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	Transfusion requirements were higher for the TXA group compared the non-TXA group for the overall cohort (Table 3), but were similar between the TXA^{MT} or no-TXA^{MT} groups,

with the exception of cryoprecipitate, which was higher in the TXA^{MT} group (Table 4).

Table 3. 24-hour transfusion requirements, mean (SD), units

	TXA (n = 293)	No-TXA (n = 603)	p-value
PRBCs	11.8 (12.1)	9.8 (13.1)	<0.001
FFP	10.3 (10.8)	8.6 (11.7)	<0.001
Platelets	1.6 (2.2)	1.4 (2.7)	0.001
Cryprecipitate	1.6 (2.7)	0.5 (1.3)	<0.001

Table 4. 24-hour transfusion requirements, mean (SD), units

	TXA^{MT} (n = 125)	no-TXA^{MT} (n = 196)	p-value
PRBCs	21.0 (12.8)	22.5 (15.9)	0.47
FFP	18.4 (11.5)	19.6 (14.3)	0.67
Platelets	3.2 (2.4)	3.6 (3.6)	0.84
Cryprecipitate	1.6 (2.6)	0.7 (1.6)	<0.001

All-cause mortality was lower in patients receiving TXA in both the overall cohort and massive transfusion cohort. This reduced mortality reached statistical significance at 48 hours and for in-hospital mortality (Table 5). The unadjusted relative risk (RR) for in-hospital mortality in the overall cohort was 0.73 (95% CI 0.54 to 0.98); the unadjusted RR for in-hospital mortality in the MT cohort was 0.51 (95% CI 0.32 to 0.83).

Table 5. All-cause mortality

	TXA	no-TXA	p-value
Overall			
• < 24 hours	9.6%	12.4%	0.20
• < 48 hours	11.3%	18.9%	0.004
• In-hospital	17.4%	23.9%	0.03
Massive transfusion			
• < 24 hours	9.6%	14.8%	0.17
• < 48 hours	10.4%	23.5%	0.003
• In-hospital	14.4%	28.1%	0.004

Multivariate logistic regression analysis revealed that the use of TXA was independently associated with reduced mortality in the massive transfusion subgroup of patients, with an odds ratio for survival of 7.23 (95% CI 3.02 to 17.32; $p < 0.001$).

Kaplan-Meier curves demonstrated better 30-day survival in the TXA group in both the overall cohort ($p = 0.006$) and the massive transfusion cohort ($p = 0.004$).

		No parameters, including administration of TXA, were associated with DVT or PTE.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	No. This was a study conducted on military patients suffering wartime injury, and is very different from patients seen in our practice. The cohort was almost entirely male, and the mean age was low (24.9 and 23.1 in the TXA and no-TXA groups respectively). The predominant mechanism of injury was explosion, accounting for 612 (68%) cases, and all of the remaining cases involved GSW. The majority of our trauma patients suffer motor vehicle collisions (primarily blunt trauma) with a much smaller percentage of GSWs. Given the increased apparent efficacy of TXA in the more severely injured patients in this study, it is likely that the treatment effect would be much lower in our patient population.
2.	Were all clinically important outcomes considered?	No. The authors considered mortality at various time-points, blood transfusion requirements, and coagulation parameters. The authors report that the rate of pulmonary thromboembolism and deep venous thrombosis was higher in the TXA group, but do not report actual numbers. The authors do not report hospital or ICU length of stay or healthcare cost. More importantly, long-term functional outcomes and dependency were not assessed.
3.	Are the likely treatment benefits worth the potential harm and costs?	Unclear. While TXA shows a clear benefit in young, healthy males suffering wartime injuries (in spite of the TXA group being significantly sicker than the control group), it is uncertain if this benefit will translate to an older, less healthy civilian population suffering primarily blunt non-explosive trauma. Further studies on a civilian population at large US trauma center will need to clarify the role of TXA in this patient population.

Limitations:

1. **This was an observational trial, and lacked randomization or blinding. The decision to give TXA was somewhat unclear: in the first half of the study, the decision was at the discretion of the surgeon or anesthetist, but after 2010 was part**

of a major hemorrhage protocol and was given to patients "requiring emergency blood products or patients with evidence of hyperfibrinolysis" (not well defined).

2. **The dosage of TXA was variable and not well defined: "an intravenous bolus of 1 g, repeated as felt indicated by the managing clinician." The mean dosage of TXA given during the study was not reported. Prior research suggests that the bolus should be followed by a continuous infusion in order to inhibit fibrinolysis (Fiechtner 2001).**

3. **This study was conducted at a military hospital and included patients suffering wartimes injuries: around 2/3 of all patients were involved in explosions, while the remainder suffered GSW, presumably with high power, high caliber weapons. The pattern of injury is different from that observed in US trauma centers, and may affect the efficacy of TXA (external validity).**

4. **The cohort was almost entirely male and primarily included younger patients (mean age of early 20s) with few if any chronic medical conditions. The demographics of patients seen in US trauma center is quite different, and this may affect the observed efficacy of TXA (external validity).**

5. **Important patient-centered outcomes such as disability and functional capacity were not assessed.**

Bottom Line:

In this retrospective observational study of military patients in Afghanistan suffering wartime injury, TXA was associated with statistically significant decrease in mortality in both the overall cohort (unbadjusted RR 0.73, 95% CI 0.54 to 0.98) and those requiring massive transfusion (unadjusted RR 0.51, 95% CI 0.32 to 0.83). This decrease in mortality was observed despite a large disparity in baseline characteristics between the two groups, with those receiving TXA have more severe injuries. The study is limited primarily by external validity: the patients in this study were largely young men with wartime injuries (a high number from explosions) and hence the results may not apply to our older population suffering primarily motor vehicle collisions. Further research in a civilian US trauma center will need to be undertaken to validate the results in our population.