

# Tranexamic acid for traumatic hemorrhage

## *Ácido tranexâmico no tratamento da hemorragia no trauma*

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### INTRODUCTION

Besides being directly responsible for most of the early in-hospital deaths, bleeding can also contribute to late mortality related to multiorgan failure in trauma<sup>1</sup>. Bleeding trauma patients may develop a complex and unique coagulopathy; where multiple mechanistic factors such as dilution, consumption, acidosis, hypothermia, poor fibrinogen utilization, and excessive clot breakdown (hyperfibrinolysis) are responsible for its development<sup>2</sup>.

Clot breakdown (fibrinolysis) is a normal response to surgery and trauma in order to maintain vascular patency and can become exaggerated (hyperfibrinolysis) in some cases. The antifibrinolytic drug tranexamic acid (TXA), a lysine analogue, interferes with the binding of plasminogen to fibrin, which is necessary for plasmin activation. Fibrinolysis consists of activated plasmin cleaving fibrin. Antifibrinolytic drugs can prevent clot breakdown and thus reduce blood loss in surgery<sup>3</sup>. In elective surgery, TXA reduces blood transfusion by a third, without significant reduction in mortality or increased postoperative complications<sup>3</sup>. TXA has recently been shown to reduce deaths in a large population of trauma patients<sup>4</sup>.

The TBE-CiTE Journal Club performed a critical appraisal of the most important evidence recently published on the topic and provides evidence-based recommendations on the use of TXA in trauma.

### STUDY 1<sup>4</sup>

CRASH-2 Trial Collaborators: ***Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) a randomized, placebo-controlled trial.*** Lancet 2010 Jul 3; 376(9734):23-32.

#### Rationale

Excessive hyperfibrinolysis is present in some trauma patients with bleeding and is associated with increased

risk of death. Antifibrinolytic drugs, particularly TXA, can prevent excessive clot breakdown and reduces blood transfusion in surgery. It is hypothesized that the use of TXA might reduce mortality due to bleeding in trauma patients.

#### Question

Does Tranexamic acid (1g load, then 1g over 8h) reduce mortality and blood transfusion without increasing vascular occlusive complications in trauma patients with or at risk of significant bleeding?

#### Main Findings of this Study

All-cause in-hospital mortality (within 4 weeks of injury) was reduced (14.5% in the tranexamic acid group vs 16% in the placebo group; relative risk 0.91, 95% CI 0.85 – 0.97; p=0.0035). Based on subgroup analysis, the sooner the drug is given, greater the benefit. Bleeding-related death was also reduced (4.9% vs. 5.7%, respectively). However, no statistically significant differences in transfusion requirements were observed between groups. Fatal or non-fatal vascular occlusive events were similar in both groups.

#### Strengths

- Largest placebo-controlled randomized clinical trial in transfusion in trauma to date, including 20.211 patients from 40 countries;
- Positive trial: 95% power to detect a 2 % (relative risk of 0.9) difference in mortality between groups at a p value < 0.05;
- Reduction in all-cause mortality and bleeding-related death were observed, supporting the hypothesis of tranexamic acid preventing bleeding and improving survival in trauma;
- The large sample size resulted in a well-balanced study with respect to baseline prognostic factors between groups;
- Easy inclusion criteria (based on systolic blood pressure <90mmHg or heart rate >110 beats per min and bleeding or at risk of significant hemorrhage) and the

TBE-CiTE Journal Club: January 17, 2012, with the participation of the following institutions: Trauma Research Program of the Department of Surgery of the Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada; Division of Trauma Surgery, University of Campinas, Campinas, Brazil.

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number of different health-care settings helps the generalizability of the results;

- Relatively inexpensive drug, safe and of easy administration;
- The study demonstrated no increase in vascular occlusive events (safety);
- CRASH-2 used a small dose of TXA (2 to 10 times lower than those used in cardiac surgery where TXA has been implicated with postoperative seizures<sup>5</sup>).

### Limitations

- The study cohort is heavily made by a few countries; 75% originated in 6 nations (India 4768, Colombia 2940, Egypt 2234, Nigeria 2053, Georgia 1783, Ecuador 1198). Only 2 patients from Canada; and none from Brazil or the USA were enrolled. The results may have been driven by a few or even a single center. The study did not report on outcome and patient characteristic data according to each major participating country.
- The study did not demonstrate that TXA reduces mortality by preventing bleeding (blood transfusion was not statistically different in the two groups) or reducing hyper fibrinolysis (no laboratory tests on fibrinolysis were done). Thus, it is conceivable that the drop in mortality may have been caused by other effects of this drug, including its known anti-inflammatory properties due to plasmin inhibition<sup>6</sup>
- Despite similar vascular occlusive events in both groups, the possibility of increased risks associated with the use of TXA cannot be totally excluded due to the large confidence intervals (low precision of estimates). Under-reporting might also account for the low frequency of events;
- A wide spectrum of severity of injury might be present due to the very pragmatic inclusion criteria, which makes difficult to determine the group of patients that would benefit the most from using TXA; only 50% of the entire cohort received a transfusion.

## STUDY 2<sup>7</sup>

CRASH-2 Trial Collaborators: ***The Importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomized controlled trial.*** Lancet 2011 Mar 26; 377 (9771): 1096-101, 1101.e1-2.

### Rationale

TXA is expected to reduce bleeding by preventing clot breakdown. However, despite reducing all-cause mortality, the CRASH-2 trial showed no difference in transfusion requirements between the TXA and placebo groups. Furthermore, the CRASH-2 study did not include any laboratorial evidence of decreased fibrinolytic activity to support its biological rationale. Therefore, CRASH-2 collaborators performed an

exploratory post-hoc analysis of the effect of TXA on mortality due to bleeding.

### Question

How Does Tranexamic acid (1g load, then 1g over 8h) affect mortality due to bleeding according to time to treatment from injury (in the prespecified subgroups where the study intervention was administered d" 1, > 1-3, and > 3 hr)?

### Main Findings of this Study

The risk of death due to bleeding was significantly reduced with TXA; 4.9% in the TXA group versus 5.7% in the placebo group (relative risk 0.85, 95% CI 0.76 – 0.96; p=0.0077). The effect of TXA on death due to bleeding varied according to time to treatment (p<0.0001); <1h from injury: 5.3% in TXA group vs. 7.7% in placebo group (p<0.0001); between 1 and 3 hours from injury: 4.8% in TXA vs. 6.1% in placebo (p=0.03); >3h from injury: 4.4% in TXA vs. 3.1% in placebo (p=0.004).

### Strengths

- Subgroup variables were specified *a priori* in the original research protocol and measured at baseline;
- The hypothesis of TXA reducing early deaths due to bleeding was specified *a priori*
- The effect of TXA was demonstrated in one of the largest placebo-controlled randomized clinical trial (20.211 trauma patients from 40 countries) to date, which allowed well-balanced, and large subgroups;
- Test of interaction between subgroups demonstrated that it is very unlikely that the study findings occurred by chance (p<0.0001);
- Adjusted analysis showed that the subgroup effect is independent of pre-specified baseline prognostic factors and other non-significant interactions;
- Subgroup effect was large; <1h from injury: relative risk 0.68, 95% CI 0.57 – 0.82; between 1 and 3 hours from injury: relative risk 0.79, 95% CI 0.64 – 0.97;
- The TXA reduction in bleeding-related mortality was consistent with the reduction observed in all-cause deaths, which supports the hypothesis of tranexamic acid preventing bleeding and improving survival in trauma.

### Limitations

- Similar to all subgroup *post hoc* analyses, the original study was not designed/powerd for secondary outcomes;
- Interaction was not consistent across subgroups (TXA might increase risk of death due to bleeding if given >3h of injury); this was an unexpected finding not hypothesised *a priori* and without a clear rationale;
- Exact data on timing from injury to treatment and certainty that bleeding was the cause of death may not be accurate. However, in the setting of a large placebo-controlled randomized clinical trial it is expected that

baseline differences (measured and unmeasured) confounders are well-balanced between study groups.

## STUDY 3<sup>8</sup>

***Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study.*** Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Archives of Surgery 2011 Oct 17. [Epub ahead of print]

### Rationale

The CRASH-2 trial demonstrated that the use of TXA reduced mortality in civilian trauma patients. Due to differences in the CRASH-2 study patient population (mostly blunt trauma; unknown severity of injury, but likely comprised by a significant proportion of patients with low injury severity scores; only half of the patients received a transfusion or required an operation), its findings are not fully applicable to military trauma (lower proportion of blunt trauma; higher injury severity scores and proportion of patients requiring transfusion and/or operations). Therefore, the MATTERs study evaluated the effect of TXA on blood product usage, thromboembolic complications, and mortality in combat trauma patients receiving any blood transfusion.

### Question

What is the effect of TXA on measures of coagulopathy and survival following wartime injury?

### Main Findings of this Study

TXA use was independently associated with survival in the multivariate logistic regression analysis in the massive transfusion group (odds ratio 7.228; 3.016 – 17.322;  $p < 0.01$ ). In the overall cohort (patients receiving any blood transfusion within 24 hours of hospitalization), a 6.5% absolute reduction in in-hospital mortality was observed in the TXA group. However, the use of TXA was not associated with improved survival when adjusted for other prognostic factors in the logistic regression analysis. The unadjusted analysis for the massive transfusion group showed an absolute reduction of 13.7% (relative reduction of 49%) with the use of TXA.

### Strengths

- Large retrospective cohort (896 consecutive admissions) involving combat patients that received any blood transfusion; it is assumed that bleeding patients are most likely to benefit from the intervention;
- Study assessed the effect of TXA not only on death but also on important secondary outcomes (coagulopathy and transfusion);
- Authors tried to address confounders and baseline differences between groups performing an adjusted analysis (multivariate logistic regression); included parameters that had  $p < 0.15$  in their univariate analysis

of mortality in both overall and massively transfused cohorts;

- Study addressed the biological rationale. The results demonstrated lower proportions of hypocoagulable patients receiving TXA in either the overall cohort or the massive transfusion subgroups on admission to the Intensive Care Unit;

- Effect size might be even higher due to selection bias against showing favorable outcome for the TXA group. The TXA group had higher injury severity score (25.2 vs. 22.5,  $p < 0.001$ ); higher proportion of GCS d"8 on admission (63.3% vs. 35.6%,  $p < 0.001$ ); and SBP d"90mmHg (22.8% vs. 13.8%,  $p = 0.003$  in the overall cohort). However, the TXA group received more red blood cells, plasma, platelet, and cryoprecipitate transfusion than the no TXA group.

### Limitations

- Retrospective study design performed in a single center;

- Variation in practice during the study period (January 2009 to December 2010) may have occurred. The hemostatic protocol was implemented late throughout the study period and the CRASH-2 Trial was published in June 2010 (which might have influenced the study). Only at the end of the study period TXA was given as part of a bleeding protocol. During the pre-protocol phase indications and doses of TXA were determined by the attending physicians, which make it a challenge to interpret the results. Furthermore, the bleeding protocol introduced co-interventions and the time to treatment, which might have affected the results, was not analyzed.

- The TXA group received more red blood cell, plasma, platelet and cryoprecipitate transfusions than the placebo group;

- Approximately half of the patients included in the study did not have coagulation data available for analysis;

- In TXA group, 9.9% of the patients were lost by the end of the follow-up period, whereas no patients were lost to follow-up in the no TXA group;

- Thromboembolic complications were identified by billing codes, which might not be accurate.

## TBE-CITE CONCLUSION

The conclusions reached by at the telemedicine meeting are based on 3 recent publication and a systematic review:

- The CRASH-2 study, a large placebo-controlled randomized clinical trial that included over 20.000 trauma patients;

- Its subgroup analysis; and

- The MATTERs trial, a fairly large retrospective study in combat injury including 896 patients;

· A Cochrane systematic review of the literature published in 2011, on the use of anti fibrinolytic for the treatment of traumatized patients that are bleeding<sup>9</sup>.

These 4 publications together studied over 30.000 patients and they suggest that TXA reduces mortality in civilian and military trauma patients without increasing the risk of complications. The two studies of the CRAS-2 suggest the drug should be administered in low-doses and routinely in the management of bleeding trauma patients, but only in the first 3 hours after the trauma.

#### TBE-CiTE Recommendation on the use of tranexamic acid for the management of traumatic bleeding

1. Tranexamic acid should be routinely used in trauma patients with evidence of bleeding;
2. Tranexamic acid should be included in transfusion protocols for trauma;
3. Tranexamic acid should be given within 3 hours of injury;
4. Administer 1g of TXA intravenously (bolus over 10 minutes) followed by the infusion of 1g over 8 hours.

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