The Importance of Early Treatment with Tranexamic Acid in Bleeding Trauma Patients: An Exploratory Analysis of the CRASH-2 Randomised Controlled Trial

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Study Objectives:
To assess the effect of tranexamic acid on mortality in bleeding trauma patients based upon time to administration of tranexamic acid in order to find potential subgroups who benefit greater from administration of tranexamic acid

Background:
The CRASH-2 trial showed a statistically significant treatment effect in regards to all-cause mortality in trauma patients (blunt and penetrating) presenting to participating trauma centres as part of a RCT (RR 0.91, CI 0.87-0.95, p-value 0.0035). However, no difference was noted in requirements for transfusion between the 2 study groups. Therefore, the biological basis of the treatment (tranexamic acid) appears to still be unknown. This sub-group analysis was performed in order to assess if bleeding related deaths were a function of timing of administration of tranexamic acid. The CRASH-2 trial, despite methodological problems, has become standard of care in many modern massive transfusion protocols.

Methods
Study Design:
Post-hoc subgroup analysis from the CRASH-2 trial. The CRASH-2 trial was a double blinded RCT performed in 275 hospitals in 40 countries with randomization started in May 2005
Patients were eligible for randomization if they were an adult (>18y) presenting post trauma with SBP<90mmHg or HR>110 or who were considered to be high risk for hemorrhage and were presenting within at least 8 hours of injury. Patients were randomized if the responsible physician felt there was clinical equipoise on the use of TXA. Randomization was only stratified according to centre via block allocation either by telephone or a pre-specified pack system. Intention to treat analysis was performed.
20211 patients were enrolled with 10096 in TXA arm and 10115 in placebo arm.

Intervention:
Treatment with 1gram of TXA as an infusion over 10 minutes followed by 1gram of TXA as infusion over 8 hours. Placebo was 0.9%NS (~100-200ml)
Outcome Measures/Endpoints:
Effect of treatment on death due to bleeding in 4 subgroups 1) Time from injury
2) Severity of injury based on SBP 3) GCS and 4) Type of injury

Statistical Analysis:
Heterogeneity in treatment effect via Chi2 analysis and logistic regression

Results:

![Diagram](image)

No major differences between groups in baseline characteristics. Predominantly male/blunt trauma. Time of treatment not known in 9 patients.

1063 of 3076 deaths were due to bleeding. Significant reduction in risk of death from bleeding in TXA group (RR 0.85 p=0.0077). No change in death due to other causes. If TXA given either <1h or 1-3h after injury there was a decrease in the death from bleeding (RR 0.68 p<0.0001 and RR 0.79 p = 0.03). TXA given >3hrs post injury increased the risk of death(RR 1.44 p= 0.004)

There were no differences in the other subgroups on mortality from bleeding or non-bleeding mortality.

![Graph](image)

Conclusions:
Early treatment with TXA(<3h from injury) appears to confer benefit whereas if TXA given greater than 3h there may be harm. They give no good plausible clinical reason for why there may be an increased risk of death in the late group. Some issues raised 1) Competing risks 2) A Change to a prothrombotic state.
Discussion:
Strengths:
Large RCT performed in multiple institutions with clinically relevant hypothesis.

Weakness/Potential Bias:
Randomization not stratified in many institutions. Overall benefit was not initially seen secondary to change in bleeding deaths. No real explanation for time related effect in outcomes. The reason for delayed administration of TXA was related to presentation time of the patient. Therefore these patients clearly may have had more bleeding prior to arrival and had the “triad of death’ leading to futility of treatment due to these factors. (i.e. bleeding death unrelated to TXA administration)
Is the subgroup large enough and adequately powered? Is a qualitative difference in subgroups valid? Is a post-hoc defined subgroup a valid subgroup or simply due to chance?

Applicability:
Common problem with cheap drug that is easy to administer. Likely patient population to benefit may be trauma patients in remote/austere conditions with poor access to surgical control of traumatic hemorrhage

Conclusion:
If decision is made to give TXA it likely needs to be given early after injury (<3hr post injury) in order to have effect on mortality. There is a perceived, but not proven, potential for harm if given late. Further clinical trials are required in order to assess the effect of timing of TXA on bleeding related mortality.

Appropriate paper for assessment of Subgroup analysis
Analysis and Interpretation of Treatment Effects in Subgroups of Patients in Randomized Clinical Trials
S Yusuf, J Witted, J Probstfield, H Tyroler
JAMA 1991 266(1): 93-98