CJEM Journal Club

The use of tranexamic acid for trauma patients?

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Clinical question
Does giving tranexamic acid to trauma patients who are actively bleeding or at risk for significant hemorrhage have an impact on mortality?
Article chosen
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 randomised, placebo-controlled trial. *Lancet* 2010;376:23-32.
Objective
The study collaborators sought to evaluate the effect of tranexamic acid on mortality in trauma patients who were actively bleeding or at risk for significant hemorrhage. Secondary outcomes included the incidence of vascular occlusive events and the number of blood transfusions required.

Keywords: CRASH-2, tranexamic acid, trauma

BACKGROUND

Trauma remains a leading cause of mortality and morbidity in both the developed and developing world despite advances in the medical and surgical care of these patients.[1] Hemorrhage in both blunt and penetrating trauma accounts for a significant proportion of deaths due to shock and complications such as multiorgan failure.[2,3] Any adjunct to standard trauma care that may mitigate hemorrhage would be of great interest.

Tranexamic acid is a derivative of the amino acid lysine. It is thought to inhibit fibrinolysis in a competitive manner by occupying lysine binding sites on plasminogen and limiting the interaction with fibrin.[4] Tranexamic acid has previously been shown to decrease bleeding in surgical patients, although without a demonstrated mortality benefit.[5] Specifically, for cardiac,[6,7] liver transplant,[8] and orthopedic[9–12] surgical patients, tranexamic acid has been shown to decrease perioperative bleeding. There is no reason to believe that the body's hemostatic response to a surgical insult would be any different than it is to trauma.[13] This was the premise of the present study.

POPULATION STUDIED

This study enrolled adult ($\geq$ 16 years) trauma patients presenting to the study centres. Patients had to present within 8 hours of penetrating or blunt injury with significant hemorrhage (defined as systolic blood pressure < 90 mm Hg, or heart rate > 110 bpm, or both) or be considered at risk for significant hemorrhage. Entry into the study was based on the uncertainty principle and required the responsible physician to be "reasonably uncertain" about whether or not to treat with tranexamic acid. If, in the treating physician's opinion, there was a clear indication for tranexamic acid or a contraindication to antifibrinolytics, the patient was not randomized.

STUDY DESIGN

This study was a large, prospective, randomized, placebo-controlled trial with 274 participating hospitals in 40 different countries. Randomization was stratified by centre, with an allocation sequence based on a block size of eight, and occurred via telephone or by a local pack system if telephone randomization was not practical. Patients were randomized to receive either a 1 g tranexamic acid intravenous bolus over 10 minutes followed by 1 g over 8 hours, or placebo,

which was indistinguishable from the treatment drug. Patients were followed for 28 days. Outcome data were collected and analyzed on an intention-to-treat basis.

OUTCOMES

The primary outcome in this study was in-hospital mortality within 4 weeks of injury. The cause of death was categorized as due to bleeding, vascular occlusion (myocardial infarction, stroke, or pulmonary embolism), multiorgan failure, head injury, or other causes.

Secondary outcomes included nonfatal vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, or deep vein thrombosis), surgical intervention (neurosurgery; thoracic, abdominal, or pelvic surgery), receipt of blood transfusion, and units of blood products transfused. Outcomes were recorded for up to 28 days after randomization in those remaining in hospital or up to discharge from hospital.

RESULTS

This study randomized 20,211 patients, with 20,116 of those patients using the local pack randomization method and 95 using the telephone randomization process. There were no statistically significant differences in baseline characteristics. All randomized patients were appropriately accounted for, and data on the primary outcome were available for 20,127 patients (99.6%). Four patients were excluded because of withdrawal of consent, and an additional 80 patients had no follow-up.

All-cause mortality was 1,463 (14.5%) in the tranexamic acid group and 1,613 (16%) in the placebo group, giving a relative risk (RR) of 0.91 (95% CI 0.85–0.97, $p = 0.0035$). Mortality due to bleeding was 489 (4.9%) in the tranexamic acid group and 574 (5.7%) in the control group, with an RR of 0.85 (95% CI 0.76–0.96, $p = 0.0077$). There were no significant differences in mortality due to any other cause.

The study showed no statistical difference between groups for nonfatal vascular occlusive events, surgical intervention, blood transfusion, or the amount of blood product received by those transfused.

STUDY CONCLUSION

The authors concluded that tranexamic acid significantly reduced the risk of death from bleeding in

trauma patients without increasing the rate of adverse events and recommended the use of tranexamic acid for trauma patients who demonstrate or are at risk for significant hemorrhage.

COMMENTARY

There is demonstrated evidence for the use of tranexamic acid in surgical patients, as outlined in the study background, although there has been little previous evidence for its use in trauma patients.[14] Consensus guidelines in Europe have advocated the use of tranexamic acid for trauma patients based on an extrapolation of the data in surgical patients.[15] The CRASH-2 study suggests that tranexamic acid can reduce the risk of death in bleeding trauma patients. This was demonstrated using clinical inclusion criteria and an early simplified dosing regimen thought to maximize benefit in bleeding patients and minimize potential side effects. This study adhered to the principles of appropriate randomization, blinding, and concealment and followed the principles of an intention-to-treat analysis with appropriate follow-up. The all-cause mortality reduction was 1.5%, giving a number needed to treat of 67 to save one life over 28 days. Considering the mortality benefit and the absence of evidence in the study to suggest a risk of harm, this is a clinically significant result. The use of tranexamic acid should be considered for use in major trauma patients.

This study does help characterize the overall safety of tranexamic acid, showing that there was an equal amount of vaso-occlusive events in both groups. The authors required high specificity in the reporting of adverse events, and as such, only those based on clear evidence were recorded. This specificity may have underestimated any increased risk. In addition, it is possible that adverse events occurring later than 28 days may have occurred and would not have been captured in this study, although this seems unlikely given the single-dose administration.

There have been reports of an increased incidence of seizures with the use of higher doses of tranexamic acid as used in cardiac surgery.[16,17] The average total dose in those circumstances approaches 100 mg/kg, or 7 g for a 70 kg patient, about 2 to 10 times higher than the dose in the present study.[18] This complication is suggested to be partly due to inhibition of γ-aminobutyric acid (GABA)-A receptors.[18,19] It is unclear if this adverse event

was observed but not reported in the current study and is a potential risk that will need to be followed.

There was no explanation in the current study indicating the mechanism by which tranexamic acid improved mortality. The measure of fibrinolysis was not part of the study design, and there was no significant difference in the rate and amount of blood transfusions between the two groups. Additionally, there were no pre-established criteria for transfusing a patient, leaving it to the discretion of the physician, introducing another possible source of bias.

One of the initial concerns regarding the ability to generalize the results of this study was the lack of clearly defined indications or contraindications to the use of tranexamic acid in trauma. Randomization required the treating physician to be "substantially uncertain" about whether or not to treat with tranexamic acid. There were no published data to suggest the number or injury severity of patients who were treated with tranexamic acid or from whom it was withheld. However, the authors have since disclosed that 20,225 patients were screened and 20,211 patients were randomized, leaving only 14 patients who were excluded (CRASH-2 Trial Collaborators, personal communication, March 15, 2011).

This study was conducted in a large number of hospitals across many countries, which ensured heterogeneity in the participating emergency medical services and trauma systems. This heterogeneity makes it difficult to ascertain what impact regional variations in trauma care may have had on the observed mortality benefit. In countries such as Canada with well-developed trauma programs and access to advanced trauma care in urban settings, it is possible that the mortality benefit of tranexamic acid may be less pronounced. On the other hand, the vastness of Canada's geography and spectrum of access to advanced trauma care across rural and tertiary care centres may render tranexamic acid as an adjunct to trauma management even more important. For instance, in severely injured patients with a delay for transport to a tertiary care centre with surgical capabilities, early administration of tranexamic acid may be prudent.

All-cause mortality across both the treatment and control groups was 15.3%. Approximately 30% of all patients randomized presented with significant hypotension (blood pressure < 90 mm Hg), and about 18% had a Glascow Coma Scale (GCS) score < 8, with another 13% having a GCS score between 9 and 12. These numbers suggest that the study population was a cohort of trauma patients with a high severity of injuries. Based on this information and the broad inclusion criteria, it is not possible to conclude that tranexamic acid should be a standard of care for all trauma patients.

CONCLUSION

This study provides valuable information on the safety and mortality benefit of tranexamic acid for trauma patients with active bleeding or at risk for hemorrhage. Tranexamic acid should be an early consideration for those patients with significant traumatic injury who are at risk for hemorrhage. Further study may be needed to validate these findings in patient populations and the practice environment found in rural and tertiary care centres throughout Canada and to further monitor the safety profile of tranexamic acid.

Competing interests: None declared.

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