REVIEW ARTICLE

Early tranexamic acid in traumatic brain injury: Evidence for an effective therapy

Syed Sarmad Bukhari, Rashid Jooma

Abstract

The guidelines for management of traumatic brain injury (TBI) are based largely on measures to maintain an optimum internal milieu for prevention of secondary brain injury and enhancing recovery. One of the most common reasons for worsening outcomes following TBI is expanding intracranial haematoma which is compounded by the fibrinolytic physiology that follows TBI. Tranexamic acid (TXA) has a time tested role in preventing poor outcomes linked to excessive haemorrhage in trauma patients. Historically, patients with isolated head trauma were excluded from TXA use due to a theoretical increased risk of thrombosis. Recent evidence that redefines the beneficial role of early TXA administration in preventing mortality amongst patients with TBI is now at hand and offers a real prospect of a pharmacological intervention that would be adopted as a recommendation based on Class I evidence.

Keywords: Tranexamic Acid, Brain Injuries, Traumatic, Randomized Controlled Trial.

Introduction

It is estimated that 69 million people suffer from traumatic brain injury (TBI) each year all over the world with more than 10 million deaths or hospital admissions. This number is on the rise with increasing motorization in the developing countries.[1] Estimates from Canada put the economic cost of TBI at a staggering $945 million.[2] A disproportionate number of individuals who suffer from such injuries are in the productive age group (young to middle aged healthy males) of these populations. This results in a significant burden of disease in Low Middle Income Countries (LMICs) due to the overwhelming dependence on this age group as the main breadwinners. Models of disease burden of TBI suggest a 17% to 50% difference in mortality between high income countries (HICs) and LMICs.[3] Two thirds of patients with TBI have intracranial haemorrhage and neurosurgical management may be safely carried out by trained neurosurgeons for as little as $300 in a LMIC, however, 90% of the population at risk of TBI in LMICs does not have access to such services. This is the reason for which we need a low cost solution to prevent intracranial haematoma expansion that can be easily, safely and economically administered to patients in hospital and pre-hospital settings.[4]

Outcomes following TBI, in some grades, are to a large extent dependent on secondary injury. A major cause of this secondary brain injury is blossoming or expanding haematomas which cause significant morbidity and mortality. Simply stated, the larger the haematoma, the greater the morbidity and mortality.[5] Tranexamic acid (TXA) is an antifibrinolytic haemostatic drug that acts on plasmin. Plasmin binds to fibrin via lysine binding sites and then splits fibrin into fibrin degradation products. Being a molecular analogue of lysine TXA inhibits fibrinolysis by reducing the binding of plasmin to fibrin. [6] It has a well-established role in preventing excessive bleeding in a wide variety of scenarios. It enjoys an impressive safety profile following decades of use and is also considered safe for administration in pregnant females.

The role of TXA in preventing contusion blossoming has been cemented by several high quality studies but its effect on morbidity and mortality has been widely debated, especially in the light of theoretical thrombotic risks to patients. We performed a review of latest available evidence that examines TXA's role in preventing adverse outcomes in TBI

Literature Review: Classically TBI has been described clinically as mild, moderate and severe but there are certain radiological features that are significant predictors of poor outcome. One of them is the presence or absence of intraparenchymal haematoma/contusion. Haematoma expansion/blossoming contusion is thought to occur in half of all cases. This results in significant secondary brain injury. Most TBI research is aimed at preventing this secondary brain injury.[7]

Corticosteroid use in TBI patients was aimed at reducing oedema associated with contusions. Evidence gathered from several trials demonstrated that their effect in improving outcomes was not significant. The CRASH trial (corticosteroid randomisation after significant head injury) concluded that there is no improvement in early

Department of Surgery, Aga Khan University, Karachi.
Correspondence: Rashid Jooma. Email: rashidjooma@gmail.com

mortality following steroid use but there is increase in mortality within 2 weeks following corticosteroid administration.[8]

Strategies aimed at preventing clot expansion include the use of TXA which is an antifibrinolytic agent administered intravenously as soon as possible following head trauma. There was good evidence to support that TXA reduces blood loss in surgical patients and mortality in patients with traumatic haemorrhage. The Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial randomized an impressive 20,211 patients to two arms, 10,096 received TXA as infusion within 8 hours of injury.[9] A subset analysis from this trial is referred to as CRASH-2 IBS (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage intracranial bleeding study). Published in 2011, it included CRASH-2 patients who also had TBI [Glasgow Coma Score (GCS) score of $\leq$14 and a brain computerised tomography (CT) scan compatible with TBI]. These patients were from India and Colombia, both of which are considered LMICs. It examined the effect of TXA administration on total haemorrhage growth and several secondary outcomes that impact survival and outcomes in TBI. Historically this was the first randomized controlled trial to evaluate the effect of TXA in TBI patients. Although the trial failed to establish benefits or risks of TXA administration, it laid the ground work for what is the largest randomized double blind study to evaluate the role of TXA administration in isolated TBI, the CRASH-3 trial.[10]

The second randomized, double blinded, placebo controlled trial which aimed at determining the effect of early TXA administration in patients with TBI was published by Yutthakasemsunt et al in November 2013. This Thai study enrolled 238 subjects who were randomized and one arm was administered TXA with the primary observed endpoint being progressive intracerebral haemorrhage (PIH). This study had low power, like the CRASH-2 IBS, and failed to demonstrate a significant difference in PIH between the two arms but a decreasing trend of PIH in the short term TXA arm was evident with no increase in thrombotic adverse events. The study concluded that larger studies with sufficient power were needed to settle this debate.[11]

TXA is a widely available, affordable medication with evidence of safety from decades of use for a wide variety of haemorrhagic indications. The risk of severe side effects of TXA is decidedly low with the most feared complications being thrombotic. Based on latest available data by Chornenki et al of pooled data from 22 studies with a cumulative number of 49,538 patients showed no increased risk of arterial or venous thrombosis associated with the use of TXA.[12] This data shows that TXA can be safely and easily administered in LMICs where 90% of the population does not have access to specialist neurosurgical care. Early administration is now considered important and this makes it imperative that TXA administration MUST begin at the point of first contact with health care providers. CRASH-2 showed that administration within 1 hour of injury had significantly better survival than between 1-3 hours amongst all patients. This could mean ambulance personnel, paramedics, lady health workers and others. Lipsky et al (2014) published the first report of prehospital administration of TXA in trauma patients and showed that it could be reliably and safely administered in zones of conflict. There were no reported adverse effects.[13] A multi-center double-blind randomized controlled trial with 3 treatment arms has been completed with results yet to be published that compares the effect of TXA on survival in TBI when administration performed in the prehospital setting vs emergency room.[14]

Jokar et al (February 2017) reported a randomized, single blinded, placebo controlled trial from Iran which confirms the efficacy of TXA in reducing PIH in patients with TBI. This study however has several design limitations.[15] Chang et al recently (May 2019) reported data that suggests that the use of TXA in TBI results in decreased mortality. This study is a prospective non-randomised observational trial in which the decision to use TXA was left to the on call neurosurgeon.[16]

The CRASH-3 trial is a prospective, international, multi-centre, parallel group, placebo-controlled randomized trial of patients with isolated TBI.[17] It sought to examine the effect of TXA administration on patients with TBI who satisfied the following criteria;

i. Adults with TBI presenting within 3 hours of injury Intracranial bleeding on computed tomography (CT)

ii. Glasgow coma score of 12 or less

iii. No significant extracranial bleeding

Eligible patients with a count of 12,737 were randomly allocated (1:1) to receive tranexamic acid or matching placebo (0.9% sodium chloride) in 175 hospitals in 29 countries. The 1gram loading dose of the trial treatment was administered by intravenous injection within minutes of randomisation in the hospital. The 1 gram maintenance dose was administered by intravenous infusion as soon as the loading dose was completed. Tranexamic acid or placebo were given as an additional treatment to the routine management of TBI.[18] Results of

the CRASH-III were published in The Lancet in October 2019 and established two important facts; early TXA administration in patients with isolated TBI reduces mortality and that the risk of adverse thrombotic complications from TXA was not significantly different from placebo. And even more importantly, CRASH III identifies WHICH patients benefit from TXA.

Patients with severe TBI (GCS <8, non-reactive pupils at presentation) did not receive any significant benefit in terms of prevention of early or late death (RR 0·99 [0·91-1·07]). This was expected as these patients have primary TBI that is severe and TXA would not benefit in these circumstances. TXA was expected to prevent worsening of intracranial haemorrhage with resultant poor outcomes in patients with mild to moderate TBI. This was reflected in the risk reduction for death in these patients (RR 0·78 [95% CI 0·64-0·95]). The benefit to these patients was tied to the time of administration of TXA. Administration within the first 3 hours following injury was correlated with better outcomes in patients with mild to moderate TBI (p=0·005) while it did not affect outcomes in instances of severe TBI (p=0·73). When benefit from TXA was examined for reducing death within 24 hours following injury, the effect was found to be the greatest with an approximate risk reduction of 25% when compared to placebo [RR 0·72 (0·56-0·92)].[19]

With close to 13,000 patients randomised, this trial is one of the largest interventional studies of TBI. It provides for the first time Level l evidence of benefit of a pharmacological intervention in the head injured. Though the authors state "Our results show that tranexamic acid is safe in patients with TBI and that treatment within 3 hours of injury reduces head injury-related death. Patients should be treated as soon as possible after injury",[19] the effect is most marked in those with mild to moderate injury. Besides offering a therapeutic guideline, this study highlights the effect of progressive bleeding in the traumatized brain and points to the most fruitful avenue of future research to uncover therapies that would mitigate the burden of death and disability in this public health scourge of our time.

Conclusions

Intracranial bleeding and expansion of haemorrhagic contusions are amongst the significant adverse secondary pathophysiologies in TBI. Fibrinolysis has been established as a major factor in the coagulopathy progression of injury related haemorrhage following head injury and can be the target for therapeutic interventions to mitigate its mortality and morbidity. With 12,737 study subjects, CRASH-3 is the largest ever interventional TBI trial and the first acute stage pharmacological intervention in head injury to show improved outcomes. When tranexamic acid is given within 3 hours, there was a significant reduction of risk of death in patients with mild to moderate TBI (RR 0.78 [95% CI 0.64-0.95]). This beneficial effect was not seen in patients with severe head injury. The adverse effects of the drug particularly thrombotic or seizure complications were not in excess of the placebo group of the trial. The evidence at hand favours early administration of TXA to those with traumatic brain injury and will likely be incorporated in future TBI management guidelines as a recommendation with Level 1 evidence.

Disclaimer: None.

Conflict of Interest: Prof Rashid Jooma was a CRASH-3 Trial collaborator.

Source of Funding: None.

References

1. Bruns J Jr, Hauser WA. The epidemiology of traumatic brain injury: a review. Epilepsia 2003;44(Suppl 10):2-10.
2. Fu TS, Jing R, McFaull SR, Cusimano MD. Health & economic burden of traumatic brain injury in the emergency department. Can J Neurol Sci 2016;43:238-47. doi: 10.1017/cjn.2015.320.
3. Bhalla K, Ezzati M, Mahal A, Salomon J, Reich M. A risk based method for modeling traffic fatalities. Risk Anal 2007;27:125-36.
4. Rudolfson N, Dewan MC, Park KB, Shrime MG, Meara JG, Alkire BC. The economic consequences of neurosurgical disease in low- and middle-income countries. J Neurosurg 2018:1-8. doi: 10.3171/2017.12.JNS17281.
5. Perel P, Roberts I, Bouamra O, Woodford M, Mooney J, Lecky F. Intracranial bleeding in patients with traumatic brain injury: a prognostic study. BMC Emerg Med 2009;9:15. doi: 10.1186/1471-227X-9-15.
6. Mahmood A, Roberts I, Shakur H, Harris T, Belli A. Does tranexamic acid improve outcomes in traumatic brain injury? BMJ 2016;354:i4814. doi: 10.1136/bmj.i4814.
7. Chang EF, Meeker M, Holland MC. Acute traumatic intraparenchymal haemorrhage: risk factors for progression in the early post-injury period. Neurosurgery 2006;58:647-56.
8. Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 2004;364:1321-8.
9. Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess 2013;17:1-79. doi: 10.3310/hta17100.
10. CRASH-2 Collaborators, Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). BMJ 2011;343:d3795. doi: 10.1136/bmj.d3795.
11. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-

blinded, placebo-controlled trial. BMC Emerg Med 2013 22;13:20. doi: 10.1186/1471-227X-13-20.

12. Chornenki NLJ, Um KJ, Mendoza PA, Samienezhad A, Swarup V, Chai-Adisaksopha C, et al. Risk of venous and arterial thrombosis in non-surgical patients receiving systemic tranexamic acid: A systematic review and meta-analysis. Thromb Res 2019;179:81-86. doi: 10.1016/j.thromres.2019.05.003.
13. Lipsky AM, Abramovich A, Nadler R, Feinstein U, Shaked G, Kreiss Y, et al. Tranexamic acid in the prehospital setting: Israel Defense Forces' initial experience. Injury 2014;45:66-70. doi: 10.1016/j.injury.2013.08.025.
14. May S, Schreiber M, Rowell S, Powell J. Prehospital Tranexamic Acid Use for Traumatic Brain Injury. [Online] 2015 [Cited 2019 November 28]. Available from URL: https://apps.dtic.mil/dtic/tr/fulltext/u2/1002681.pdf
15. Jokar A, Ahmadi K, Salehi T, Sharif-Alhoseini M, Rahimi-Movaghar V. The effect of tranexamic acid in traumatic brain injury: a randomized controlled trial. Chin J Traumatol 2017;20:49-51. doi: 10.1016/j.cjtee.2016.02.005.
16. Chan DYC, Tsang ACO, Li LF, Cheng KKF, Tsang FCP, Taw BBT, et al. Improving survival with tranexamic acid in cerebral contusions or traumatic subarachnoid hemorrhage: univariate and multivariate analysis of independent factors associated with lower mortality. World Neurosurg 2019; 125: e665-70. doi: 10.1016/j.wneu.2019.01.145.
17. Mahmood A, Roberts I, Shakur-Still H. A nested randomised trial of the effect of tranexamic acid on intracranial haemorrhage and infarction in traumatic brain injury (CRASH-3 trial intracranial bleeding mechanistic study): Statistical analysis plan. Wellcome Open Res 2019;3:99. doi: 10.12688/wellcomeopenres.14731.2.
18. Dewan Y, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. Trials 2012;13:87. doi: 10.1186/1745-6215-13-87.
19. CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet 2019;394:1713-23. doi: 10.1016/S0140-6736(19)32233-0.