National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Emergencies and injuries

Date: 15 October 2015

Medication: Tranexamic acid (TXA)

Indication: Trauma-related haemorrhage

Background
Tranexamic acid (TXA) is an antifibrinolytic medicine, which is Medicines Control Council (MCC) approved for the following indications:

- Short-term use in the treatment of hyphaema and in patients with established coagulopathies who are undergoing minor surgery.
- Dental extraction in haemophiliacs
- Hereditary angioneurotic oedema
- Menorrhagia

TXA is also used off-label for the treatment of significant haemorrhage in adult trauma patients. TXA is included on the World Health Organisation (WHO) Essential Medicines List

Objective
The aim of this review is to evaluate the effectiveness of TXA in trauma patients who present with significant haemorrhage. This review will inform decision-making regarding the inclusion of TXA on the Adult Hospital Level Essential Medicines List.

Search
Electronic databases (PubMed, Google Scholar, Cochrane Library) were searched using key words, “Tranexamic acid” AND “Trauma” AND “Bleeding” OR “Haemorrhage”.

Study selection
Randomised Clinical Trials (RCTs) and Systematic Reviews of RCTs.
Population: patients with haemorrhage due to trauma
Intervention: tranexamic acid
Comparison: placebo / alternative treatment / standard of care
Outcomes: morbidity and mortality

Results of search
The search yielded:

1. 1 RCT
2. 1 exploratory analysis of the included RCT
3. 1 Cochrane Systematic Review

1. Shakur H et al. 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.

Background and Methods: This was a multicentre pragmatic randomised placebo-controlled trial conducted in a hospital setting throughout 40 countries. The trial evaluated the effectiveness and safety of the TXA in adult trauma patients with haemorrhage. TXA was administered within 8hrs of trauma as an initial 1 g intravenous loading dose over 10 minutes, followed by 1 g infusion over 8 hours. The primary outcome was death within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. Secondary outcomes were vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis), surgical intervention (neurosurgery, thoracic, abdominal, and pelvic surgery), receipt of blood transfusion, and units of blood products transfused. The trial analyses were based on the intention to treat principle. Patients were eligible if they had significant haemorrhage (systolic blood pressure <90 mm Hg or heart rate >110 beats per min, or both), or who were considered to be at risk of significant haemorrhage, and presented within 8 h of injury. Moreover the study implemented an "uncertainty principle" which governed inclusion i.e. patients were only included if the treating physician was uncertain about whether to treat with TXA or not.

Results: A total of 20,211 patients were randomly assigned to TXA (n= 10 096) or placebo (n= 10 115). Follow-up was complete for > 99% of participants in both groups. Baseline characteristics were similar between the two groups. All-cause mortality at 4-weeks was lower with TXA (n= 1463, 14.5%) compared with placebo (n= 1613, 16.0%); relative risk [RR], 0.91; 95% confidence interval [CI], 0.85-0.97; p = 0.0035). Absolute reduction in all-cause mortality at 4-weeks was 1.5%, which translates into a number needed to treat (NNT) of 67 to prevent one death. TXA was associated with a statistically significant reduction in mortality due to bleeding: TXA (n= 489, 4.9%) vs. placebo (n= 574, 5.7%); RR 0·85, 95% CI 0.76–0.96, p=0.0077). There was no difference in the occurrence of vascular occlusive events: TXA (n= 201, 2.0%) vs. placebo (n= 168, 1.7%). There was no difference in the number of participants requiring blood transfusions: TXA (n= 5067, 50.4%) versus placebo (n= 5160, 51.3%). Furthermore, there was no difference in the mean number of units required among patients requiring transfusion: TXA (6.06, SD= 9.98) versus placebo (6.29, SD= 10.31)

Conclusions: TXA reduced the risk of death in bleeding trauma patients and should therefore be available to doctors treating trauma patients in all countries.

2. Roberts I et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011; 377:1096-1101.

Background: This was an exploratory analysis of the abovementioned CRASH-2 trial, which assessed the effect of early treatment on mortality due to bleeding.

Results: The effect of TXA on mortality due to bleeding varied according to the time from injury to treatment (test for interaction p<0.0001) as follows:

- Early treatment (≤1 h from injury) significantly reduced the risk of death due to bleeding (198/3747 [5.3%] events in tranexamic acid group vs. 286/3704 [7.7%] in placebo group; relative risk [RR] 0.68, 95% CI 0.57-0.82; p<0.0001).
- Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4.8%] vs. 184/2996 [6.1%]; RR 0.79, 0.64-0.97; p=0.03).
- Treatment given after 3 h seemed to increase the risk of death due to bleeding (144/3272 [4.4%] vs. 103/3362 [3.1%]; RR 1.44, 1.12-1.84; p=0.004).
- No evidence that the effect of TXA on mortality due to bleeding varied by systolic blood pressure, Glasgow coma score, or type of injury.

Conclusion: TXA should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, tranexamic acid is less effective and could be harmful.

3. Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD004896.

Background and Methods: This was a Cochrane Systematic Review of RCTs of antifibrinolytic drugs (TXA, aprotinin, epsilon-aminocaproic acid and aminomethyl -benzoic acid) in patients with acute trauma. The search was conducted in January 2015. Outcome measures included: all-cause mortality; adverse events (vascular occlusive and renal failure); number of patients undergoing surgical intervention or receiving blood transfusion; volume of blood transfused; volume of intracranial bleeding; brain ischaemic lesions; death or disability.

Results: Three RCTs were included. TXA was evaluated in 2 trials (n = 20,451). While the larger CRASH-2 trial (n= 20 211) included patients with a variety of types of trauma; the smaller trial (n = 240) was limited to patients with traumatic brain injury (TBI) only. One trial (n = 77) assessed aprotinin in participants with major bony trauma and shock.
The pooled data (CRASH-2 contributed 99% of pooled data) indicated that antifibrinolytic drugs:

- reduce all-cause mortality (RR 0.90, 95% CI 0.85 to 0.96; P =0.002) - The quality of the evidence for this outcome was graded as “high”.

There was no evidence that antifibrinolytics have an effect on:

- the risk of vascular occlusive events (quality of evidence: moderate),
- the need for surgical intervention or receipt of blood transfusion (quality of evidence: high).

Conclusions: TXA safely reduces mortality in trauma patients with bleeding without increasing the risk of adverse events. TXA should be given as early as possible and within three hours of injury, as further analysis of the CRASH-2 trial showed that treatment later than this is unlikely to be effective and may be harmful.

Relevant studies – non-RCT

4. Thurston B et al. Time since injury is the major factor in preventing tranexamic acid use in the trauma setting: An observational cohort study from a major trauma centre in a middle-income country. S Afr J Surg. 2015; 53:13-18.

Background and Methods: The exploratory analysis of the CRASH-2 trial suggested that the greatest benefit on mortality due to bleeding is achieved is when TXA is administered within

3 hours. In view of the findings of this analysis, this prospective observational study was conducted at the trauma unit at Groote Schuur Hospital, Cape Town, to determine if patients arrived at hospital soon enough after injury for TXA administration to be effective and safe. Fifty consecutive patients admitted to the trauma unit with similar inclusion criteria as for the CRASH-2 trial were included.

Results: Thirteen (26%) patients presented early enough for TXA administration – 3 patients presented within 1 hour after injury, with a further 11 patients presenting >3 hours after injury. There was uncertainty regarding time of injury in 26 patients, although it was suspected to be >3 hours.

Conclusions: In view of the majority (74%) of patients not presenting within the timeframe allowed for safe administration of TXA, the authors suggest that TXA may be more effective if incorporated into prehospital rather than in-hospital protocols. Furthermore, they suggest that future studies should evaluate this approach.

Other sources

5. National Institute for Health and Clinical Excellence (NICE). Evidence summary: unlicensed or off-label medicine. Significant haemorrhage following trauma: tranexamic acid.

This is an "evidence summary" generated by NICE for off-label medicines, and is therefore not intended as a NICE "guidance" document.

Evidence on the efficacy, safety and cost implications of TXA was reviewed and summarised. The sources of evidence included:

- CRASH-2 trial[1]
- CRASH-2 exploratory anlaysis[2]
- Cost effectiveness and cost[6]

The key points of this NICE evidence summary are as follows:

- *"A large high-quality international RCT found that administration of tranexamic acid reduces mortality in patients with or at risk of significant haemorrhage following trauma."*
- *"An exploratory analysis of the trial data indicates that overall benefit may apply only to people treated within 3 hours of injury."*
- *"A health economic analysis has found that tranexamic acid for the prevention and treatment of significant haemorrhage in trauma patients has an incremental cost of $64 international dollars (£43) per life saved."*

Summary

Evidence from a single RCT indicates that TXA reduces the risk of death compared with placebo. This benefit is greatest if TXA is administered within 3 hours of injury. A small prospective observational study conducted in South Africa, found that most patients did not present within the timeframe considered safe for TXA administration.

References

1. Shakur H et al. 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.
2. Roberts I et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011; 377:1096-1101.
3. Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD004896.
4. Thurston B et al. Time since injury is the major factor in preventing tranexamic acid use in the trauma setting: An observational cohort study from a major trauma centre in a middle-income country. S Afr J Surg. 2015; 53:13-18.
5. National Institute for Health and Clinical Excellence (NICE). Evidence summary: unlicensed or off-label medicine. ESUOM1: Significant haemorrhage following trauma: tranexamic acid. Published: 16 October 2012. URL: https://www.nice.org.uk/advice/esuom1/resources/significant-haemorrhage-following-trauma-tranexamic-acid-1503234970355653
6. Guerriero C, Cairns J, Perel P et al. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. PLoS one. 2011; 6(5).