Use of tranexamic acid in trauma patients requiring massive transfusion protocol activation: an audit in a major trauma centre in New Zealand

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ABSTRACT

AIM: To investigate prescribing behaviours around tranexamic acid (TXA) use in the early management of severe trauma, and compare against standards considered to be best practice internationally, as established by the current body of research.

METHODS: We undertook a retrospective analysis of all trauma patients requiring massive transfusion protocol (MTP) activation across a 20-month period. A combination of physical and electronic inpatient records and ambulance documentation were reviewed to determine dose and timing of TXA administration.

RESULTS: During the period studied, 27 adult trauma patients who required activation of the MTP were identified. Of the patients where TXA was indicated, 76.2% received at least an initial dose of TXA, with 19.0% receiving both doses. 21.1% of patients who received TXA were administered an initial dose within one hour of injury, 52.6% between one and three hours, 26.3% outside three hours.

CONCLUSIONS: TXA was found to be under-utilised and significant departures from best practice were found, likely due to persisting uncertainty and unfamiliarity. In particular, delayed administration beyond the three-hour therapeutic window occurred in a quarter of patients, increasing the risk of mortality secondary to haemorrhage. This pattern of use may apply to the wider population of trauma patients in this centre, and requires remedy and reassessment.

Trauma remains the leading cause of death and disability among young adults worldwide, many of whom die as a direct result of haemorrhagic shock. Hyperfibrinolysis is integral to the pathophysiology of factor depletion and acute traumatic coagulopathy in polytrauma. Tranexamic acid (TXA) is a synthetic lysine analogue discovered in the 1960s that at therapeutic doses acts as a competitive inhibitor of plasminogen activation, preventing the dissolution of established thrombi. The role of TXA in the management of traumatic haemorrhage has at times been contentious, but recent additions to the literature suggest it provides the largest mortality benefit when used as an adjunct in patients requiring balanced component massive transfusion protocol (MTP) activation.

CRASH-2 trial

The CRASH-2 trial was a pragmatic double-blinded randomised controlled trial of TXA in 20,211 trauma patients across 274 centres. TXA, or matching placebo, was given as a 1g intravenous (IV) initial dose over 10 minutes, followed by a further 1g infusion over eight hours. The absolute risk reduction (ARR) in all-cause 28-day mortality was 1.5% in the TXA arm, giving a relative...
risk (RR) of 0.91 (95% CI 0.85–0.97, p=0.0035) and a number needed to treat (NNT) of 67. Secondary outcomes such as rate of vascular occlusive events yielded no statistically significant differences.

A subsequent post hoc analysis found that effect size of TXA on mortality secondary to haemorrhage differed by time-to-treatment subgroup. TXA administered less than one hour following injury was associated with the greatest reduction in mortality, RR 0.68 (95% CI 0.57–0.82, p<0.0001), followed by administration 1–3 hours following injury, RR 0.79 (95% CI 0.64–0.97, p=0.03). However, when administered at intervals greater than three hours, TXA was associated with greater mortality, RR 1.44 (95% CI 1.12–1.84, p=0.004).

Among others, limitations included the small sample size of hypotensive patients (31.5% with systolic pressure <90mmHg) and the limited number of transfusions received within the study cohort (50.4% in the TXA arm).

MATTERs trial
The MATTERs trial was a retrospective study of 1,189 patients treated with TXA at a single trauma centre in Afghanistan, who had each received a minimum 1 unit of packed red blood cells (PRBC) within 24 hours of admission. While CRASH-2 had found a 1.5% ARR in all-cause mortality, the MATTERs trial found a 6.5% ARR, the largest benefit being observed in patients requiring massive transfusion (defined as receiving ≥10 PRBC units) with a 13.7% ARR, equating to a NNT of 7. The study authors concluded that the modest injury profile and low transfusion requirements of the CRASH-2 cohort likely introduced a conservative bias.

Christchurch Hospital
In light of this evidence, the purpose of conducting this audit was to investigate prescribing behaviours in the early management of severe trauma, specifically in those patients requiring massive transfusion. In the context of trauma, no specific unified guideline currently exists for the use of TXA within the Canterbury District Health Board (CDHB). The Christchurch trauma registry recorded 373 major trauma presentations in the 2017 year, defined by this centre as patients with an Injury Severity Score (ISS) >12. This was equivalent to 31.1 patients per month, with a mean ISS of 20. Following their initial presentation to Christchurch Hospital Emergency Department (ED), these patients often require shared care and surgical intervention by a number of different inheriting sub-specialties. Such an investigation was designed to provide feedback that better informed any future revision of major trauma protocols and streamline management between these services.

Methods
We conducted an audit of all trauma patients who required MTP activation in Christchurch Hospital ED from November 2015 to June 2017. National Health Index (NHI) numbers were accessed through CDHB blood bank records, with paediatric patients (defined as age <16) and patients transfused for indications other than recent trauma being excluded.

Of those patients identified for further analysis, physical copies of clinical notes were accessed via the CDHB clinical records audit office. Data such as age, sex, mechanism of injury, quantity of transfused blood products and mortality during admission were collated. The ISS of each patient was then calculated by the Christchurch trauma registry in accordance with the Abbreviated Injury Scale (AIS) coding system. TXA dose and administration time was determined by a comprehensive search of individual Christchurch Hospital ED trauma sheets, standard CDHB medication prescription charts and online records retained by MedChart® (DXC technology, NSW, Australia). Transfer time data was obtained by searching printed copies of the ambulance electronic Patient Report Forms (ePRF), with time of call to the emergency medical dispatcher treated as time of injury for the purposes of analysis. If a printed ePRF was unable to be located in the physical notes, the ambulance service was then contacted directly to obtain a digital copy. Despite these measures, two of the 27 patients' ePRF summaries were still unable to be located.

Results
During the time period studied, 27 adult patients required MTP activation following traumatic injury, or 1.35 per month. The sample had a median age of 45 (IQR 28–57), and 18 of the 27 patients were male (66.7%). Median ISS of the sample was 21 (IQR...
with the most frequent mechanism of injury being road traffic crash (RTC), which were responsible for 16 (59.3%) of the presentations. Patients received a median 6 units of PRBC (IQR 4–10), 2 units of Fresh Frozen Plasma (FFP) (IQR 2–6), 0 units of cryoprecipitate (IQR 0–3) and 0 units of platelets (IQR 0). In total, seven of the 27 patients (25.9%) died during the course of their admission, with four of these deaths occurring prior to leaving ED.

Of the 25 patients with a known time of injury, the median delay for ambulance services to reach patients was 28 minutes (IQR 9–40.5) and the median delay until patient arrival to ED was 65 minutes (IQR 43.5–119.5).

21 (77.8%) of all 27 patients in the sample received an initial dose of TXA. 19 (76.0%) of the 25 patients with a known time of injury received an initial dose, and of these; four (21.1%) received it within one hour of injury, 10 (52.6%) between one and three hours, and five (26.3%) outside three hours. Of the 21 patients with a known time of injury and who arrived in ED within three hours of injury, 16 (76.2%) received an initial dose. Of the 21 patients who received TXA, 19 (90.5%) received a 1g initial IV dose, the remaining two (9.5%) receiving 500mg IV. The median delay to initial dose was 109 minutes (IQR 61–182).

Six (28.6%) of the 21 patients who received the initial dose went on to receive the second, and of those, two (33.3%) were charted as an IV infusion over eight hours, the remaining four (66.7%) as a stat IV dose. The median delay to second dose was 393 minutes (IQR 220–515).

Six (22.2%) of all 27 patients in the sample received both doses regardless of dose size or administration, with four (19.0%) receiving both doses from the group of 21 patients who had a known time of injury and who arrived in ED within three hours.

**Discussion**

In light of the current best evidence, previous reviews have concluded that a rational approach for clinicians would be to administer TXA as a 1g IV initial dose administered over 10 minutes, followed by a 1g infusion over eight hours, in all trauma patients with a systolic blood pressure <75mmHg or where the use of blood products is anticipated, so long as the patient is less than three hours from time of injury.6,7 76.2% of patients who met these criteria received an initial dose of TXA, and only 19.0% of these patients received both doses. This proportion was lower than was expected, and is likely due to the persisting uncertainty and unfamiliarity with the existing evidence base, doubts surrounding efficacy and a high perceived risk of adverse effects.8,9

26.3% of our sample received TXA outside the three-hour window, and only 21.1% received it within one hour. This represents a departure from best practice and may apply to the larger population of trauma patients within the DHB, a situation requiring action and future reassessment. Though these thresholds are by nature arbitrary, they represent the real decay in the therapeutic effect of TXA with time, with administration outside the therapeutic window being shown to be actively harmful by increasing the relative risk of mortality.
secondary to haemorrhage. Again this is likely a result of widespread unfamiliarity, as it has been shown previously that only 10% of civilian doctors surveyed from clinically relevant specialties could correctly identify the optimal time of administration as less than three hours when asked.9

The median delay for ambulance services to reach a patient was 28 minutes, compared to a median delay of 65 minutes to reach ED. A much larger proportion of patients could receive TXA within one hour of injury if administration by appropriately trained pre-hospital personnel were possible, especially where a delay in transferring to a higher level of care is anticipated, such as in the event of prolonged vehicle extrication or long-distance transfer. The potential use in pre-hospital care may be further supported by research currently being conducted. The intent of the PATCH trauma and STAAMP trials, both multi-centre double-blinded randomised controlled trials, is to provide high-quality evidence on what effect pre-hospital use has on mortality, though these results are likely to be years in the making.

Only 28.5% of patients who received the first dose eventually received the second, and of these, few were charted as an eight-hour infusion. These omissions may be due to poor communication between specialties, and actively delegating this infusion to the inheriting surgical specialty as part of a formal protocol may minimise these oversights. Further research is required to determine the value of the second dose and what, if any, mortality benefit this infusion provides over and above the initial loading dose, and what temporal effects a delay to the second dose may have.

It is unclear what significance choosing to use a 500mg dose has on patient outcomes. It has been shown that bolus doses equivalent to 10mg/kg produce plasma concentrations sufficient to inhibit measures of fibrinolysis in vitro, with higher doses providing no additional haemostatic benefit,10 and it was on this basis the CRASH-2 trial dosage regimen was selected.

Limitations of these data include the small sample size of trauma patients requiring massive transfusion within the CDHB. It is also possible that a number of patients who received clinically significant volumes of blood products without activation of the MTP may have been omitted from these data. Furthermore, the use of the time of call to emergency medical dispatcher as a surrogate for time of injury introduces a bias underestimating the length of the delay to receiving TXA, and it is therefore possible that a larger proportion of patients receive TXA outside three hours from time of injury than was found in this study.

It should be noted that though TXA is specifically mentioned in the MTP for this centre, this is not specific to trauma and as such does not include specifications regarding timing of the first dose or use of a second dose. While this centre is yet to formalise guidelines surrounding the use of TXA in the context of trauma, it is not alone, as the wider adoption by many other trauma centres internationally has also been uncharacteristically slow, primarily due to the persisting uncertainty around the perceived risks and benefits.8 It should be emphatically stated that in medicine we regularly use more potentially harmful interventions for which we have far less robust evidence, and as an intervention TXA not only has high-quality evidence demonstrating its safety and efficacy, but in addition has been shown to be highly cost effective.11

**Conclusion**

Our best evidence would suggest that TXA is cheap, safe and effective, but that delayed administration may contribute to poorer outcomes. In this limited sample, only 76.2% of patients for whom TXA was indicated received an initial dose, and only 19.0% of patients received both doses. Delayed administration beyond the therapeutic window also occurred in 26.3% of all trauma patients requiring massive transfusion. This has been demonstrated to increase the risk of mortality secondary to haemorrhage when compared to placebo and this trend may extend to all other trauma patients, a situation requiring remedy and reassessment. The development of a protocol that prompts earlier and appropriate administration of the initial dose, potentially including its use by pre-hospital care providers, and the use of the maintenance infusion by surgical subspecialties who inherit these patients would bring the CDHB’s practices more in line with the evidence currently available.
Competing interests:
Nil.

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