Use of tranexamic acid in trauma patients requiring massive transfusion protocol activation: a reassessment of prescribing behaviours in a major trauma centre in New Zealand

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ABSTRACT

AIM: To re-investigate prescribing behaviours for tranexamic acid (TXA) use in the early management of severe trauma, and to compare against the standards considered to be best practice and the same study conducted at this centre two years prior.

METHODS: We undertook a retrospective analysis of trauma patients requiring massive transfusion protocol (MTP) activation across a 26-month period. Physical and electronic inpatient records and ambulance documentation were reviewed to determine dose and timing of TXA administration.

RESULTS: During the period studied, 53 trauma patients requiring activation of the MTP were identified. Of those for whom TXA was indicated, 90.9% received at least an initial dose of TXA and 50.0% received both doses. In total, 16.7% of patients received a dose within one hour of injury, 73.8% between one and three hours and 9.52% outside three hours.

CONCLUSIONS: Compared with the previous study, the utilisation of TXA is now more consistent with what is considered best practice. Delayed administration beyond the three-hour therapeutic window was less than the 26.3% figure previously reported, and comparable to that of major trauma centres internationally. Persistent issues include the under-utilisation of the second dose and the potential for much earlier use, as has been achieved at centres where pre-hospital administration is the norm.

Trauma remains one of the most prolific killers of young New Zealanders, largely due to our unenviable number of road deaths. We are not unique in this regard, as injury is a leading cause of death and disability for young adults worldwide.[1] Nationally the incidence of major trauma is 48 per 100,000. However, for the South Island, at 62 per 100,000, this figure is higher,[2] and the distances for patients to be transported to definitive surgical care are greater. Major trauma also represents a facet of New Zealand's health inequity, as it disproportionately affects Māori with rates 30% higher than that of non-Māori.[2] Nationwide data from the New Zealand Major Trauma Registry (MTR) shows that the case fatality rate for those involved in major trauma is 8.4%. Of these, haemorrhage remains the most common preventable cause to be identified and treated.[2–4]

It has been shown that tranexamic acid (TXA) may play a role in the management of these patients.[5–7] As a competitive inhibitor of plasminogen activation, TXA aids in haemostasis by preventing the dissolution of established thrombi. This is especially beneficial for those patients with

trauma-induced coagulopathy, the pathophysiology of which is largely driven by hyperfibrinolysis.

In 2010, the Clinical Randomisation of an Anti-fibrinolytic in Significant Trauma (CRASH-2) trial[5] was published. This randomised controlled trial of 20,211 patients demonstrated that TXA conferred a 1.5% absolute risk reduction (ARR) in all-cause 28-day mortality. Post-hoc analysis[6] of the trial data subsequently demonstrated that the effect size of TXA on mortality secondary to haemorrhage differed significantly by time-to-treatment sub-group, with the greatest reduction in mortality being found for those who had TXA administered less than one hour following injury (RR 0.68, 95% CI 0.57–0.82, p<0.01), followed by those who had TXA administered between one and three 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<0.01). Only 50.4% of the TXA arm required blood products, whereas in the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study,[7] a retrospective cohort study of 896 combat casualties, all patients received at least one unit of packed red blood cells (PRBC) within 24 hours of presentation. Although the CRASH-2 trial had found a 1.5% ARR in all-cause mortality, the MATTERs study found a 6.5% ARR and observed the largest benefit of 13.7% ARR in patients requiring massive transfusion (defined as ≥10 PRBC units). This equated to a number needed to treat (NNT) of seven. The study authors therefore concluded that a more modest injury profile and the low transfusion requirements of the patients within the CRASH-2 trial had introduced a conservative bias.

The existing body of evidence suggests that best practice is to administer TXA as early as possible as per the CRASH-2 trial protocol (a 1g dose given via an intravenous or interosseous (IV/IO) route over 10 minutes, followed by a 1g infusion over 8 hours) in all trauma patients with significant haemorrhage, especially where there is evidence of shock[8] or hyperfibrinolysis has been demonstrated on thromboelastography,[9] and as long as the patient is less than three hours from injury.

Christchurch Hospital is the largest tertiary centre in the South Island and each month records an average of 32.9 major trauma presentations, defined by the New Zealand MTR as patients with an Injury Severity Score (ISS) >12. There does not yet exist a dedicated trauma service for this centre, which instead relies on a shared model of care between surgical sub-specialties and admission under general surgery by default. A retrospective study of 27 adult trauma patients conducted in 2017[10] found that TXA was often omitted when the decision had been made to activate the centre's massive transfusion protocol (MTP). Only 76.2% of patients for whom TXA was indicated received it, and only 19.0% received both recommended doses. Of those who received at least one dose, 21.1% received it within one hour of injury, 52.6% at intervals between one and three hours and 26.3% at intervals greater than three hours. The under-utilisation and delayed administration were not in keeping with what was considered best practice, and it was thought to be due to unfamiliarity with the literature and uncertainty regarding the possibility of adverse effects.[11,12] More prompt and consistent use was recommended, followed by further re-assessment.

Methods

National Health Index (NHI) numbers were accessed for all trauma patients who required MTP activation in Christchurch Hospital between 1 January 2018 and 29 February 2020. Patients were excluded if their injuries consisted exclusively of burns, if MTP activation had been at intervals greater than 24 hours from time of injury, or if significant components of their clinical notes were not able to be located, such that no meaningful analysis could be undertaken.

Of those patients identified for further analysis, physical copies of clinical notes were accessed and 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 nurse co-ordinator in accordance with the Abbreviated Injury Scale (AIS) coding system.[13] TXA dose and

administration time was determined by a comprehensive search of Christchurch Hospital Emergency Department (ED) trauma sheet pro forma, paper medication charts, peri-operative anaesthetic charts and online records retained by MedChart® (DXC technology, NSW, Australia). TXA was considered to have been administered if documented as being given within 24 hours of injury. Transfer-time data were obtained by searching printed copies of the ambulance electronic Patient Report Forms (ePRFs). For those patients who were involved in the terrorist attack on 15 March 2019, time of injury was recorded as the time at which the attack first took place. For all other patients, time of call to the emergency medical dispatcher was 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 efforts, one patient transported by ambulance was unable to have their ePRF summary located, and one patient was transported by private vehicle. These two patients were considered to have an unknown time of injury.

Patient data were tabulated in a password protected electronic database. Non-parametric data had measures of central tendency and dispersion expressed as a median and interquartile range (IQR) respectively, which were then compared with the results of the study conducted in 2017.[10]

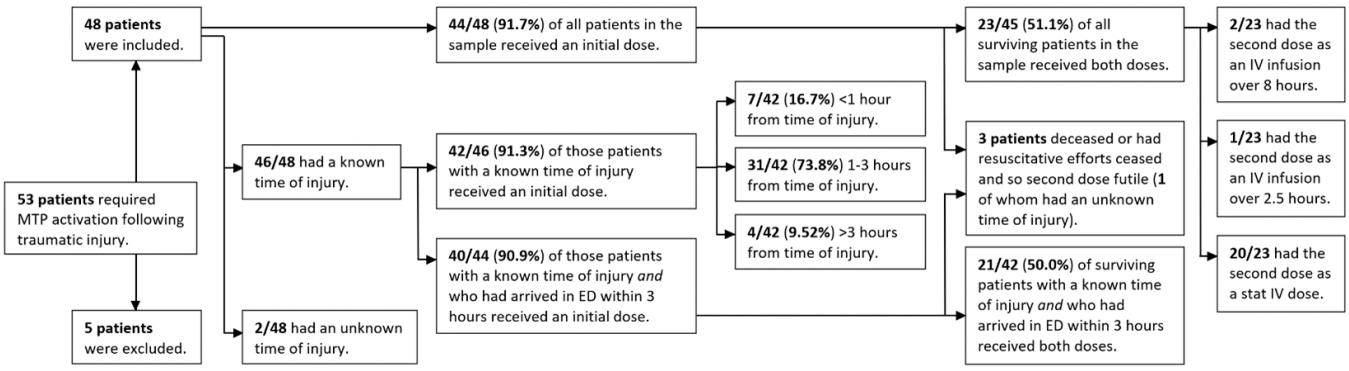
Results

During the data collection period, 53 patients required MTP activation following traumatic injury (eight of these were a result of the mass shooting on 15 March). This equates to 2.04 per month (or 1.73 per month if the 15 March mass casualty incident is excluded). Two patients were excluded as their injuries consisted exclusively of burns, two were excluded as they required MTP activation at intervals greater than 24 hours from injury, and one patient was excluded as their clinical notes, in their entirety, were not able to be located.

In total 48 patients met the inclusion criteria. Their median age was 36 (IQR 25.3–54.3) and 68.8% were male. The median ISS of the sample was 29 (IQR 17–40). The first and second most frequent mechanisms of injury were road traffic crashes and gunshot wounds, which were responsible for 28 (58.3%) and 9 (18.8%) presentations, respectively. Patients received a median six units of PRBC (IQR 3–8), three units of Fresh Frozen Plasma (FFP) (IQR 2–6), zero units of cryoprecipitate (IQR 0–3) and zero units of platelets (IQR 0–1). In total, eight of the 48 patients (16.7%) died during the course of their admission, with three of these deaths occurring prior to the patient leaving ED.

For those patients brought to hospital by ambulance, the median delay for pre-hospital services to reach a patient was 21 minutes (IQR 9.50–44.5). The median delay between injury and patient arrival in ED was 73 minutes (IQR 37.5–109).

Figure 1: Flow diagram demonstrating the proportions of patients who received tranexamic acid by time, dose and administration.



TXA, tranexamic acid; MTP, massive transfusion protocol; ED, emergency department.

Of all 48 patients in the sample, 44 (91.7%) received an initial dose of TXA. Of the 46 patients with a known time of injury, seven (16.7%) received TXA within one hour of injury, 31 (73.8%) between one and three hours and four (9.52%) outside three hours. Of the 44 patients with both a known time of injury and who had arrived in ED within three hours (and so for whom TXA was indicated), 40 (90.9%) received an initial dose. All adult patients who received TXA were given a 1g dose. No patients in the sample had TXA administered by pre-hospital personnel. The median delay to initial dose was 104 minutes (IQR 78.0–133).

Three patients had un-survivable injuries. Resuscitative efforts for these patients ceased following their initial dose of TXA, and so further intervention was intentionally withheld. Excluding these patients, 23 (51.1%) of all 45 actively managed patients received two doses of TXA. Of those 23, two had the second dose charted as an IV infusion over eight hours, one as an infusion over two and a half hours and the remaining 20 as a stat IV dose. Of the 42 patients with a known time of injury and who had arrived at ED within three hours with resuscitative efforts ongoing (and so for whom TXA was indicated), 21 (50.0%) received two doses of TXA. The median delay to second dose was 433 minutes (IQR 235–570).

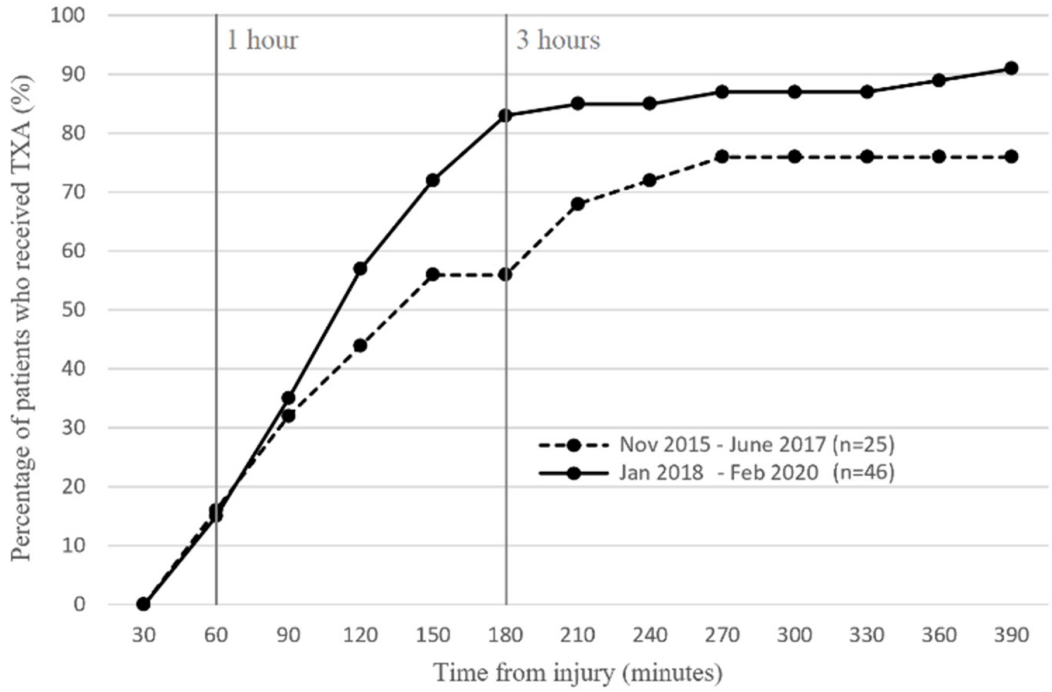
Six patients in the sample received three or more doses. The greatest amount administered within the initial 24-hour post-injury period was 4g.

Discussion

Interestingly, despite the median ISS being greater than that of the 2017 study (29 vs 21), the mortality rate was lower (16.7% vs 25.9%) and the use of blood products was unchanged.[10] Injuries due to firearms were disproportionately represented in this sample due to the events of the 15 March terror attack, which does not reflect the typical pattern of injury at this centre,[14] but median ISS was not significantly affected by the inclusion of these patients within the dataset. It is unclear why these differences have occurred.

Of patients for whom TXA was indicated, 90.9% received at least one dose, which is greater than the 76.2% figure reported by the 2017 study.[10] Though there is significant variation in utilisation rates between health systems,[15,16] this figure is similar to that of

Figure 2: Proportion of patients receiving at least one dose of tranexamic acid (TXA), plotted against time elapsed from point of injury, a comparison between study periods.



other comparable centres.[17] In addition, only 9.52% of our sample received TXA outside of the recommended three-hour window, compared to the 26.3% figure previously reported. This represents a significant improvement in practice. It is also comparable to the 8% figure found by a similarly designed study of 661 patients from five major trauma centres in the United Kingdom (UK) that was conducted in 2019.[18] This improvement is likely due to the promulgation of the relevant literature, advocacy for appropriate use during departmental teaching sessions for the Christchurch Hospital ED and discussion of the 2017 study[10] during a number of trauma grand rounds, which are open to nursing, paramedical and medical staff.

Unfortunately, still only 16.7% of patients received TXA within the first hour following injury, which is in large part due to the median delay of 73 minutes to reach ED. No patients in this sample received TXA prior to arriving in ED, and a much larger proportion of patients could have received it within one hour of injury if it were administered by pre-hospital personnel, who arrived on scene after a median delay of only 21 minutes. For major trauma centres in the UK, where pre-hospital administration is standard, 30–59% of patients have been shown to receive it within one hour.[17,18] Many guidelines, both civilian and military, now suggest the first dose of TXA should be administered en route to hospital, or preferably at the scene itself.[8,19] Recommendations exist for pre-hospital administration, especially in those instances where TXA would likely confer the most benefit, such as when attempting to manage non-compressible sources of bleeding[19] or when there is an anticipated delay in transferring to a higher level of care.[21] Some retrospective cohort studies have supported this practice,[22] though controversy around patient selection remains.[23] It is worth noting that these one- and three-hour thresholds are arbitrary and simply represent convenient targets with which to approximate the decay in therapeutic effect with time. Since our initial study was published, a meta-analysis of the CRASH-2[5] and WOMAN[24] trials combined the data of 40,000 patients and demonstrated this decay using logistic regression modelling, estimating that a 10% reduction in survival benefit exists for every 15 minutes that elapses from onset of haemorrhage.[25] It has previously been shown that, when transferring patients to urban major trauma centres, the interval between injury and administration of TXA can be halved by pre-hospital rather than in-hospital use.[17,18]

There is still insufficient evidence to demonstrate what, if any, benefit the second dose of TXA provides independent of the first, and what effects a delay to this second dose may have. In this study, 50% of surviving patients for whom TXA was indicated received both recommended doses of TXA. The improvement from the 19% figure found by the previous study[10] may in part be due to the fact that the 2017 study did not include medications given by the anaesthetic team intra-operatively (which are recorded on separate anaesthetic records and accounted for the second dose in three patients of this sample), nor did it exclude those patients where resuscitative efforts had ceased, for whom TXA may therefore have been intentionally withheld. As a result, it is difficult to conclude whether there has been any increased utilisation of the second dose of TXA across this time period. However, these data again support the conclusion that the second dose is under-utilised and is not being charted as an infusion. This has also been described in another major trauma centre.[26]

A number of patients received more than two doses, likely in error. It is common to have medications documented as being given on the trauma sheet pro-forma completed during the initial resuscitation, as well as on the separate paper medication charts completed by the intensive care unit upon admission. In theatre, medications are then recorded on a separate intra-operative anaesthetic record, and post-operatively an electronic prescribing system is used by the surgical high dependency unit. This significantly increases the risk of prescribing error, either by omission (under the incorrect assumption that a medication had been given) or by duplicating the charting of others. The variability of prescriber is also likely to contribute to the variation in administration time for the second dose. This may be somewhat ameliorated by the establishment of a unified trauma service to

better streamline the care of these patients or to actively delegate responsibility for the eight-hour infusion to the inheriting surgical speciality as part of a formalised protocol. Another recently proposed solution[27] is to combine the protocol into a single 2g IV/IO dose. Given that the second dose is often omitted and there is now good evidence that the window of benefit is short lived,[25] receiving it as a prolonged infusion may negate any survival benefit it would otherwise confer.

It is possible that other trauma patients presenting to this centre may have received significant volumes of blood products without activation of the MTP and may therefore have been omitted from these data. However, this is a study of patients who had an anticipated blood loss such that the MTP was activated, and whether, at this juncture, the treating clinician utilised TXA as an adjunct to the MTP, regardless of whether the patient ended up receiving volumes typically considered to constitute a massive transfusion. A small number of patients required MTP activation for thermal injuries without the presence of other concurrent injury causing haemorrhage. These patients were excluded on the basis that TXA's role in burns has not been established. Likewise, patients who had the MTP activated or re-activated at intervals greater than 24 hours from time of injury were excluded from this study. It is not uncommon for patients with complex injuries to have ongoing haemorrhage during the course of their admission. One of the patients in question only became haemodynamically unstable due to later disruption of a large retroperitoneal haematoma, and the other had post-operative intra-abdominal haemorrhage requiring a return to theatre. There is less certainty regarding the role of TXA in this context. The results of the HALT-IT trial,[28] which found no mortality benefit for TXA in the context of gastrointestinal bleeding, suggest that TXA has a more limited role when the time of haemorrhage onset cannot be determined. It is likely that patients who deteriorate on the ward and require further transfusion have had occult haemorrhage for a period of time prior to showing signs of shock, and therefore this window of benefit may have already elapsed.

Patients with inadequate documentation, or documentation that had subsequently been lost, represent a limitation of this study. Accurate contemporaneous record keeping is more difficult when patients are more severely injured, or when the resources available to treat them are stretched, and it is these same patients who are more likely to have TXA omitted due to the competing priorities of a complex resuscitation. The loss of these patients from the sample may therefore introduce a bias overestimating how many patients were in fact given TXA. Furthermore, the use of the time of call to the emergency medical dispatcher as a surrogate for time of injury also introduces a bias that underestimates the length of the delay to receiving TXA, and it is therefore possible that patients received TXA far later than has been found in this study.

Conclusion

By all estimates, TXA is a cheap, safe and effective medication that plays a small but important role in the early management of haemorrhagic shock in trauma. However, there is evidence that its therapeutic effect dramatically decreases with time, and it may even contribute to an increase in mortality due to haemorrhage when its use is delayed greater than three hours from time of injury. In this sample, 90.9% of patients for whom TXA was indicated received an initial dose, compared to 76.2% two years prior. Delayed administration beyond the three-hour therapeutic window occurred in just 9.52%—an improvement on the 26.3% figure previously reported and comparable to the findings of major trauma centres in the UK. The data demonstrate that prescribing behaviours are now more consistent with what is considered best practice. However, still only 50.0% received both recommended doses, and only 16.7% received TXA within an hour following injury, compared to 30–59% at other major trauma centres internationally. Persistent issues include the unrealised potential for earlier use of TXA by pre-hospital services, the under-utilisation of the second dose and its administration as an eight-hour infusion, and the discontinuity between departments with modes of prescribing. The establishment of a unified trauma service for this centre would likely aid in resolving these persistent issues.

Competing interests:
Nil.
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