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The Role of Tranexamic Acid (TXA) in Military Trauma:

Current Practices and Implications for the Future

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Abstract

Objectives: To review current literature on the use of Tranexamic acid in battlefield trauma to assess its effects on mortality and determine whether or not it should become more widely used in both civilian and military trauma.

A subsection was to look at the feasibility of administering Tranexamic acid in a pre-hospital setting to minimise the time between injury and drug administration.

Methods: A search of the literature was performed on a variety of databases using the terms described in table 1. The papers were then reviewed and analysed regarding the effects of the drug in trauma.

Patients: The papers selected reviewed 21,160 patients as detailed in Table 2. These patients were across both military and civilian trauma units.

Outcomes: The main outcomes being examined were the effects on short term mortality at 24 and 48 hours and whether there was any increase in the thromboembolic risk associated with the administration of Tranexamic acid.

Results: The review of the literature showed that Tranexamic acid had a significant effect on improving mortality across the board (17.4% vs 23.9% mortality ($p = 0.03$)). This was most marked in the more severely injured who had received over 10 units of transfused blood (14.4% vs 28.4% mortality ($p = 0.004$)).

In terms of side effects Tranexamic acid was shown to be safe in large doses, which is key for battlefield administration where there is a tendency to err on the side of overtreating. Interestingly, the risk of thromboembolic events was similar to those not receiving Tranexamic acid.

Conclusions: Tranexamic acid is a very safe and effective means of improving survival when used in combination with current practices involving the use of blood products and surgical interventions. Tranexamic acid can safely be administered in the pre-hospital setting to minimise the delay between injury and treatment. The use of Tranexamic acid should be incorporated into trauma management across the board in the both military and civilian cases particularly in the most severe cases.

Background

Haemorrhage is a major cause of death in trauma, particularly on the battlefield. Effective control of haemorrhage is a critical measure required to increase survival and ensure the stability of casualties until they arrive at a trauma centre. In the last decade a major overhaul of the techniques used on the battlefield has led to an increase in the survival rates due to

better management of haemorrhage[13,14]. Improvement in the control of haemorrhage is imperative in the current operative climate as the method of injury has been become largely penetrative, from gunshots or explosive fragmentation, in almost 75% of cases[14].

The care of trauma on the battlefield in the early 2000s was very different to it is now. The protocols were based on experience from non-combat situations and included many aspects that have since been overhauled[13]. These include advising against the use of tourniquets to control haemorrhages in the extremities and external haemorrhages managed by direct pressure which impaired the ability of medics to treat multiple casualties[13]. In addition there was no pre-hospital monitoring or administration of antibiotics. There was also no specific management for traumatic brain injuries and the possible effects they may have on inducing hypotension or hypoxia in the patient[13]. The management of hypotension was with large volumes of crystalloid solution through 2 large bore venous cannulas that were inserted in all patients regardless of condition[13].

With the recent combat experiences in Iraq and Afghanistan the management of battlefield trauma has been revised and updated to reflect the knowledge gained from these campaigns. There is now better integration of medics within frontline units as well as a better protocol of care for different tactical situations[13]. Pre-hospital management is now much more aggressive with extensive use of tourniquets, haemostatic bandages and an improved triaging system to ensure targeted care to the casualties who require it the most[13]. In addition to this there are now protocols for the use of intra-osseous lines if intravenous access is difficult. Cannulas are only placed in those casualties who require fluid resuscitation or intravenous medications[13]. When put together, the revised guidelines have resulted in a significantly improved casualty survival rate over the last decade although haemorrhage is still the largest cause of fatalities. Therefore there is still room for improvement[13,14].

In Iraq and Afghanistan the deaths from injuries classified as potentially survivable, were as result of haemorrhage in over 90% of cases, with the truncal region being the most common site of fatal haemorrhage (67.3%)[14]. Further analysis of the data showed that the truncal region haemorrhage was thoracic in 36% of cases and abdominopelvic in 64% of cases[14]. These are sites of non-compressible haemorrhage and surgical intervention is the most effective form of management, which can only be performed at a trauma centre[10]. Getting the casualties to the hospital as quickly and as stably as possible is critical and has been achieved through improved evacuation and medical techniques. In recent years Tranexamic acid has been shown to be effective in controlling haemorrhage[4] and has been implemented across civilian and military medical units.

Tranexamic acid competitively inhibits lysine binding sites on plasminogen which prevents the breakdown of plasminogen to plasmin[4,12,18]. This stabilises the clot and allows for maintenance of bleeding control through its antifibrinolytic function[11]. There is no effect on the platelet count or functionality at therapeutic doses[18]. Tranexamic acid has a half-life of around two hours and is mainly excreted unchanged through the kidneys and the dose should be adjusted accordingly in patients with renal impairment[18]. There is a therapeutic effect of the drug for at least 17 hours in tissues and 7–8 hours in serum[18].

Tranexamic acid is very safe in therapeutic doses with few major side effects. The most common of these are nausea, vomiting and diarrhoea but can also include myalgia and arthragia[7,18]. There is a risk of thromboembolic events occurring but this is minimal. The drug is contraindicated in cases of haematuria because of the risk of causing blood clots in the ureters and subsequently obstructing the outflow of the kidneys[18]. It is also not advised if there is a history of thromboembolic disease, convulsions or in situations where disseminated intravascular coagulation is occuring[7,18].

Currently Tranexamic acid is used in the treatment of menorrhagia, epistaxis, hereditary angioedema and trauma[7]. The aim of this literature review is to highlight the role of Tranexamic acid in the management of battlefield trauma and the improvements in survival that it brings, as well as to examine its role on the battlefields of the future and in future civilian trauma management.

Methods & Search Strategy

A search was performed on the databases listed. Papers were excluded on the basis of their content after reading the abstract and if they were in a language other than English. Duplicate papers were picked up on a number of searches across the different databases. A citation search, performed on the papers selected, to check for additional papers, picked up an additional 2 papers. Upon reading the papers an additional two studies that are currently ongoing were discovered and included.

As the studies are all related, despite being different publication types, they were reviewed as a whole using the Critical Appraisal Skills Programme (CASP) tools.

Results

Of the studies found by my search, one was a randomised control trial, one a retrospective cohort study and two were observational studies done on the basis of data in the field. The other papers found were describing areas of use of Tranexamic acid, its use alongside other anti-fibrinolytics, details of the future uses of the drug and the areas where further research is needed. Two of the studies are large randomised placebo controlled trials only recently started and will hopefully answer some of the outstanding questions with regards to the use of Tranexamic acid in trauma.

The CRASH-2 trial analysed Tranexamic acid use in trauma across 274 hospitals in 40 countries; although not a military trial this research is the basis for the battlefield trials. Most of the research was done in low and middle income countries where 90% of the world's trauma deaths occur[4]. The findings indicated that Tranexamic acid had a significant impact on decreasing mortality from all causes, from 16% in the non-treatment group to 14.5% in the treatment group[4]. In addition the risk of fatal haemorrhage was reduced from 5.7% to 4.9%[4]. The trial calculated that the number needed to treat to save a life with Tranexamic acid in trauma was 1 in 67[4]. This was the first indication of the effectiveness of the drug in a trauma environment.

In the study 1g Tranexamic acid was given as a loading dose as a slow infusion over 10 minutes followed by an 8 hour infusion of a further 1 gram. The trial was not a completely randomised placebo controlled trial as if there were clinical indications for Tranexamic acid to be used then it was[4]. Only in instances where there was uncertainty over whether it should be used was the randomisation implemented[4]. The limitations of the study, as discussed in further trials, were that if patients were not severely injured the benefit from the drug was minimal, as evidenced in later trials where the benefit of the drug was shown to increase proportionally with injury severity[1].

The side effect profile of Tranexamic acid and the amount of blood products provided to the patients in both arms of the trial were also analysed. These results showed that despite the antifibrinolytic properties of Tranexamic acid there was no increase in the number of fatal or non-fatal incidents of vaso-occlusive events[4]. This is important for the implications of the use of Tranexamic acid in trauma as if there was a marked increase in the risk of vaso-occlusive events then despite the effective anti-haemorrhagic properties it would not be suitable for widespread use. In terms of the amount of blood products given there was found to be no significant difference between the two groups with around 6 units of blood given to both[4].

The key finding of the study was that to be most effective Tranexamic acid was needed to be provided to the patients within three hours of injury and ideally within the first hour. However it was also found that Tranexamic acid increased mortality rates if given after the three hour period although the reasons for this are unknown[4].

The use of Tranexamic acid in military trauma started in 2009 in the British military and 2010 in the US military and led to a retrospective observational study on causalities in Afghanistan from the British and American military trauma registries; the MATTERs study[1]. The results confirmed those observed in the CRASH-2 trial. A subset of the MATTERs study was to examine the role of Tranexamic acid in 231 patients who had received more than 10 units of transfused blood to treat their injuries. In this subsection it was found to be even more effective than in the rest of the cohort with the mortality rate dropping to 14.4% in the treatment group versus 28.1% in the non-treatment group[1]. Overall the decrease in absolute mortality was 6.5% in the non-major transfusion group and 13.7% in the major transfusion group[1]. The study further confirmed the need to use Tranexamic acid within the first hour as well as the observation that the drug does not increase the need for more blood products. The study concluded that the number needed to treat in order to save one life was between 1 in 7 and 1 in 15 depending on patients: a marked reduction in that observed in the CRASH-2 trial[1,3].

However there were increased levels of vaso-occlusive events in the Tranexamic acid cohort, without any fatalities[1]. These were 9 times the average for deep vein thrombosis and 12 times the average for pulmonary emboli[11]. It is theorised that because the patients in the Tranexamic acid group were more severely injured this contributed to the raised levels of vaso-occlusive events, partly due to the acute coagulopathy of trauma[1]. Further investigations are needed in this area as the other trials did not see raised levels of events and analysis of the data revealed no confirmed link between Tranexamic acid and the events.

The decrease in mortality was only observed after 48 hours. Similar levels of mortality were observed in both groups prior to this. This confirms that the most effective time period for administering the drug is in the first hour although further trials needed to be done on the pre-hospital applications of the drug. These have since been done in both civilian and military populations.

The studies of the pre-hospital applications of Tranexamic acid examined the role of the drug at the scene of injury and the impact on extraction. The studies are from the Israeli Defence Force and from British Columbia, in the use of the drug in air evacuation, which is an integral part of trauma pathways around the world.

These studies found that it is possible to administer Tranexamic acid at the scene of injury without adverse effects to the patient or the extraction process[5]. The Israeli study highlighted the tendency of medics to overtreat with Tranexamic acid in the pre-hospital period but due to the safety of the drug this had no adverse effects on the patient. The protocol used by the Israeli Defence Force takes account of this by being very sensitive but not very specific to ensure Tranexamic acid is given to those that need it[2]. This also means that there were patients who, whilst not clinically indicated for the drug, were still given it, particularly those who had decreased conscious levels due to blunt force head trauma, misdiagnosed as haemodynamic instability[2].

The role of Tranexamic acid in head trauma and intracranial haemorrhage is not well understood and is currently being investigating in the CRASH-3 trail[6,8]. The Israelis also showed that drug administration would not impact the extraction process; however the outcomes post-hospital were not described and are one of the limitations of the study. The Canadian study in civilian trauma patients, as part of air evacuation protocol, also showed that Tranexamic acid could be administered easily in the field although the end results of the cases were not followed up due to limitations in the study[5].

Discussion

Overall the studies show that Tranexamic acid has a significant role in the effective management of trauma particularly if administered within the first hour. The greatest beneficial effects are in those most severely injured and who have required at least ten units of transfused blood products. For the military this is important as these are the cases that generally have the worst prognosis for survival.

The ability for Tranexamic acid to be effectively administered in the field, without it delaying evacuation to advanced trauma centres, is an area requiring further research assessing the role that pre-hospital administration can have on improving survival. For best prognosis it is recommended to be used in conjunction with other local haemostatic agents and bandage techniques to provide a useful adjunct until surgery can be performed[10].

The studies all used the same dosing regimen of Tranexamic acid and defined haemodynamic instability with the same guidelines. This means the patients are comparatively similar despite the different causation of injuries: being mainly penetrative in military and blunt in civilian trauma.

Positive effects on mortality were observed in all the papers but further studies are required to ensure the drug can be safely and effectively administered to those most in need. Tranexamic acid was implemented into battlefield trauma management in the British military in 2009, the United States military in 2010, as well as some civilian trauma systems following on from the CRASH-2 trial.

However despite the further studies done there are still a number of unanswered questions with regards to the mechanisms of Tranexamic acid. The mechanisms of action of the drug are incompletely understood: whilst the clot stabilising effects are clear, it is postulated that there are also anti-inflammatory effects that provide the answers to the longer term improvements in survival associated with use of the drug. Clinical trials are being carried out, looking into the biological effects and who will benefit most from treatment. The CRASH-3 trial is looking at the effects of Tranexamic acid on survival in cranial haemorrhage and the PATCH trauma trial in Australia at the role the drug plays in a well-developed trauma system and its biological effects[6,11,16,17]. A particular area of interest requiring further study, is the haemorrhagic complications associated with hyperfibrinolysis in the acute coagulopathy of trauma and the possible role that Tranexamic acid can have in the progression of the condition. The resultant increase in the knowledge and understanding of the mechanisms of action of the drug and the patients most likely to benefit from its use are important to the future management of trauma both in the military and civilian life.

A significant limitation of all the studies was they focused on the short term effects at the detriment of the longer term effects. This is an area which needs to be further studied too.

There are a number of areas lacking research in Tranexamic acid. The beneficial role it plays in the management of trauma is undisputed: the mechanisms of beneficial action, which are most pronounced 48 hours post injury when the risk of haemorrhage is markedly reduced, needs further research. As part of the PATCH trauma study in Australia the beneficial role Tranexamic acid could have in a modern advanced civilian trauma system is being evaluated[11,15]. This study will have wide reaching effects on the management of trauma in all settings and could see Tranexamic acid becoming an integral part of pre-hospital and hospital management of trauma. On the basis of the CRASH-2 trial the authors have already recommended the drug be added to the WHO’s list of essential medicines and be made available worldwide in trauma[5]. This is still not fully implemented although the military are ahead in its implication. The studies they have conducted show an even greater beneficial effect than the original CRASH-2 results with similarly low levels of side effects[1,2,3].

In the future it seems likely Tranexamic acid will become available on the battlefield in a similar way to morphine is today. A study looking at the feasibility of introducing self-injectable kits for Tranexamic acid has shown that once a suitable dose has been agreed it would be relatively easy to implement. However the current concentrations are not strong enough to enable a suitable dose to be available for intramuscular injection. Intramuscular administration would be the best compromise between quickness of action, ease of administration, storage and transportability when compared to oral or intravenous forms[3]. The same dose would be used as that in the studies done with intravenous Tranexamic acid.

It has been calculated that even with the tendency of battlefield medics to overtreat it would require 70 doses to cause any problems[3].

With the possibility of future conflicts being similar in nature to the current conflicts and with the probability of increased extraction times, effective management of haemorrhage on the battlefield is paramount to maintaining increased survival. Currently over 87% of fatal injuries never make it to the hospital from the battlefield, the majority of these succumbing to haemorrhage[3]. The continual development of the management of trauma through the experiences on the battlefield and in civilian life has led to a revolution in trauma management. With current techniques of local and systemic measures of haemorrhage control applied before the hospital, casualty survival will continue to improve.

Conclusions

Tranexamic acid is known to be safe even in large doses and remains effective over a wide range of temperatures, making transport and storage much easier, particularly in remote areas. The cost, combined with the positive effects of the drug, should not be ignored in the management of trauma and its use should be implemented across the board with treatment supplied as soon as possible.

The requirement for the drug to be administered optimally within the first hour, means that pre-hospital applications are key, particularly in situations where access to frontline healthcare may be delayed, such as on the battlefield or in remote rural areas.

Prompt effective management of the casualty at the scene and en route to the hospital are the critical stages for haemorrhage management. Incorporating Tranexamic acid into the trauma protocols, particularly in these regions, will result in reduced morbidity and improved mortality.

Tranexamic acid has been shown to be beneficial in the management of trauma as shown in completed trials. The data from the two trials currently in progress should provide further information on its effectiveness and how best to utilise it but will not affect its use. On the basis of the data studied it should be implemented across the board in the management of traumatic haemorrhage.

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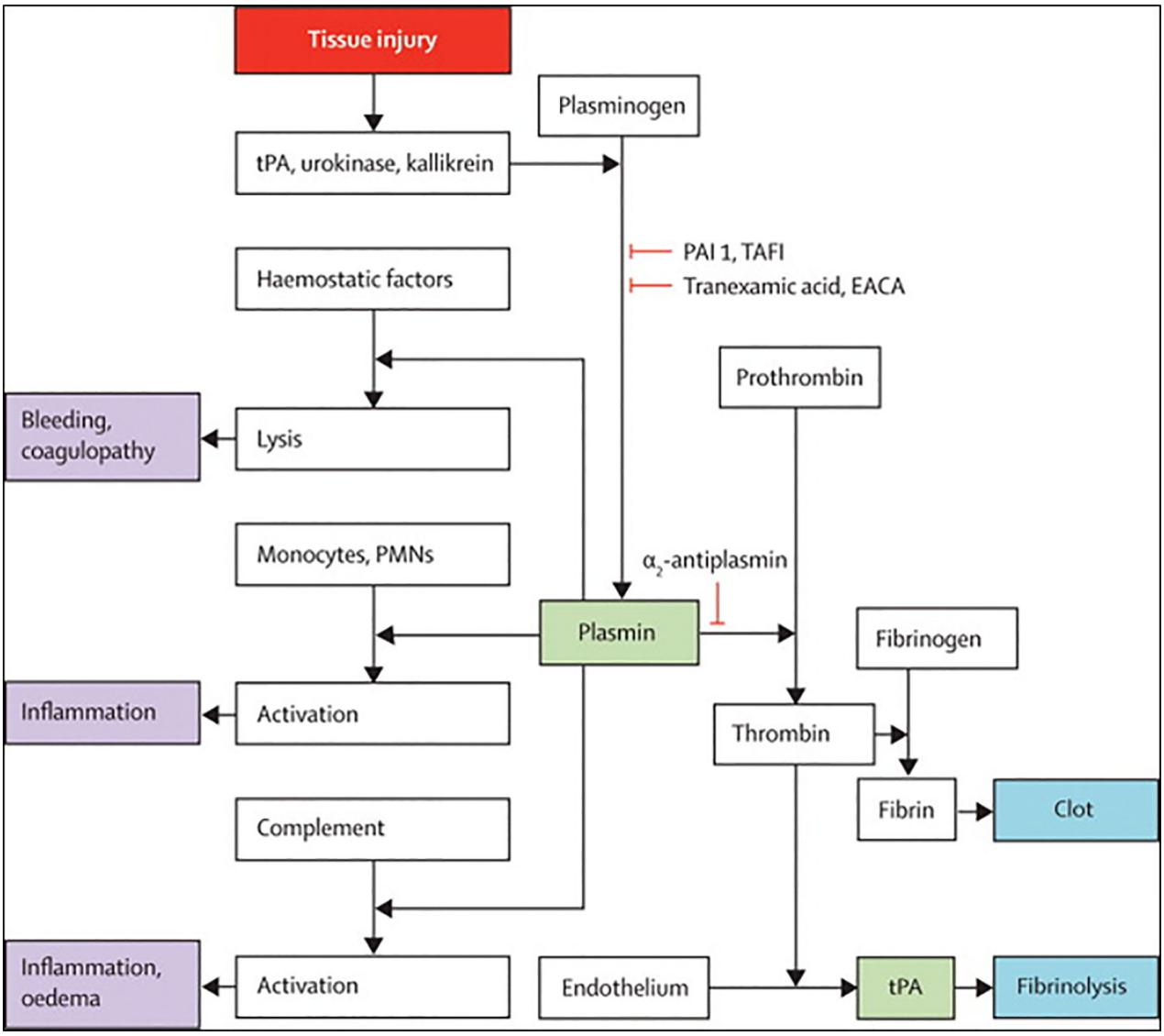

Figure 1:
The Pathway following tissue injury showing the location of action of Tranexamic Acid[15]

Table 1:

Comparison of battlefield trauma care in 2001 and 2011, adapted from Butler & Blackbourne[13]

Battlefield Trauma Care (2001)	Battlefield Trauma Care (2011)
• No consideration of tactical situation	• Tactical situation considered in phased casualty management
• Tourniquets not advised	• Aggressive use of tourniquets
• Prolonged direct pressure to manage external haemorrhage	• Combat Gauze where tourniquets are not able to be used
• Haemostatic dressings not used	• Nasopharyngeal airways used to protect airway if no facial/ neck trauma
• 2 large bore cannulas in every causality	• If facial trauma sit the patient up and forwards to allow blood to drain out
• Crystalloid fluid for hypovolaemia	• If not possible surgical airway established
• No considerations of the effects of traumatic brain injury	• Tension pneumothorax managed with needle thoracostomy
• Endotrachael intubation if airway compromised via facial trauma / unconscious	• Spinal precautions applied as tactically feasible
• No guidelines to manage hypothermia or secondary coagulopathy	• IV access only if required
• No Intraosseous access techniques	• Intraosseous access if no IV
• No electronic monitoring before the hospital	• Hypotension managed with colloid solutions
• IM morphine for analgesia	• More aggressive fluid resuscitation in those with traumatic brain injury + oxygen
• No non-parenteral analgesic medications	• IV morphine + oral fentanyl for analgesia
• Antibiotics not given pre-hospital	• Improved preventative management of hypothermia and secondary coagulopathy
• No triaging of which casualities would benefit most from supplemental oxygen	• Antibiotics given on the battlefield
• Spinal precautions applied without regard to tactical situation or injury mechanism	• 1:1 volume of plasma and Red blood cells if casualties in shock and being evacuated
	• Improved triaging to determine whether supplemental oxygen is required
	• Tranexamic acid to assist in prevention of death from non-compressible haemorrhage

Table 2:

Details of the studies examined and the number of patients involved[1,2,4,5]

Study	Number of Participants	Number given TXA	Number not given TXA
CRASH-2	20211	10096	10115
MATTERs (incl. MT)	896	293	603
MATTERs - Massive Transfusion Subgroup	231	125	196
IDF	40	40	0
Pre-hospital in BC	13	13	0
Totals	**21160**	**10442**	**10914**

Table 3:

Mortality rates in the group given Tranexamic acid and the group not given Tranexamic acid[1,4]

Study	Mortality (Treatment Group)	Mortality (Placebo / No TXA)	P Value
CRASH-2	14.5%	16%	0.0035
MATTERs (incl. MT)	< 24 Hours – 9.6%	< 24 Hours – 12.4%	0.2
	< 48 Hours – 11.3%	< 48 Hours – 18.9%	0.004
	In Hospital – 17.3%	In Hospital – 23.9%	0.03
MATTERs – Massive Transfusion Subgroup	< 24 Hours – 9.6%	< 24 Hours – 14.8%	0.17
	< 48 Hours – 10.4%	< 48 Hours – 23.5%	0.003
	In Hospital – 14.4%	In Hospital – 28.1%	0.004

Table 4:

Details of time between administration and peak plasma times in the different forms of TXA[3]

Method of Administration	Time to maximum plasma concentration
Intravenous	10 minutes
Intramuscular	30 minutes
Oral	120 minutes