The Use of Tranexamic Acid in Trauma Patients- a Retrospective Review

Katie Yelle[1], BHSc.

Dr. Michael Y. Woo, MD[1,3]

Dr. Elianna Saidenberg, MD, FRCPC[1,4]

Dr. Jacinthe Lampron, MD, MPH, FRCSC[1,2]

[1] University of Ottawa, [2] Department of surgery, The Ottawa Hospital, [3] Department of Emergency, The Ottawa Hospital, [4]Department of Pathology and Laboratory Medicine

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Corresponding Author:

Jacinthe Lampron
1053 Carling Ave
Ottawa, ON
K1Y4E9
613-798-5555
jlampron@toh.on.ca

Abstract:

Background: Hemorrhagic shock is a leading cause of death in traumatically injured patients. Tranexamic acid (TXA) is an inexpensive antifibrinolytic agent that has been shown to decrease mortality in trauma patients. This study evaluated adherence to TXA use recommendations at a level 1 Trauma Centre.

Methods: A retrospective cohort study of consecutive trauma patients who received a blood transfusion in the Emergency Department (ED) from Sept 2011 to February 2014 was undertaken. Data was collected from a prospectively collected trauma database, which included demographic information as well as injury characteristics, baseline physiology, coagulation profile, blood product and TXA use.

Results: There were 103 patients of whom 87 met a priori criteria for analysis. The mean age was 43.5 years (range 16-92 years). 71.2% were male. TXA was administered in 62.1% (n=54). 18.4% of patients received the full TXA dose (1g initially followed by 1g infusion over 8h) initiated within 3 hours of injury time. Wide variation in practices between speciality care providers was observed. Initiation of a trauma code was a protective factor.

Discussion: TXA administration is present at our centre, although overall compliance to the CRASH-2 protocol merits improvement. Reasons for lack of compliance are unclear and require more investigation.

Conclusion: Knowledge translation regarding TXA in trauma resuscitation takes time. This study highlights the need for educational interventions to trauma health care providers. Current models of knowledge dissemination may be ineffective and novel methods to do so should be investigated.

Background

Trauma is one of the leading causes of death worldwide and the most common cause of death of individuals less than 35 year old[i]. Central nervous system injury is the leading cause of death among trauma patients followed by hemorrhagic shock. Injury-induced hemorrhage is exacerabated by trauma-induced coagulopathy (TIC) which is present in approximately 25% of trauma patients at presentation[ii,iii]. Tranexamic acid (TXA) is a lysine analogue antifibrinolytic[iv] agent that can mitigate TIC, decrease hemorrhage and need for consequent transfusions by preventing degradation of clot[v].

TXA therapy is an inexpensive therapy, with the cost per dose being approximately $11.40 USD[vi], that has also been shown to have mortality benefit in traumatically injured patients. Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) is large multicentre randomized controlled trial including over 20, 000 patients recruited in 40 countries. Published in 2010, it is considered a landmark trial in trauma resuscitation. Trial

participants were adult trauma patients who had evidence of or were at risk for significant hemorrhage[vii]. The results of the trial confirmed a decrease in mortality for trauma patients by 1.5% (RR=0.91) with administration of TXA within 3 hours (1g intravenous (IV) loading dose and 1g IV infusion over 8h)[vii]. Adverse outcomes related to TXA administration were rare. Given the evidence for benefit, the minimal cost and low risk for harm, many trauma centres (including deployed multinational military medical centres) have incorporated the use of TXA into resuscitation efforts for hemorrhaging trauma patients[viii].

A 2011 study showed that complete compliance to CRASH-2 protocol was non-existent and TXA at any dose was administered to only 13% of eligible patients at one Canadian trauma centre[ix]. The goal of this study was to determine the level of adherence to CRASH-2 protocol at a single Canadian Level 1 trauma centre as more time has elapsed since the publication of the CRASH-2 findings. Secondary outcomes were to determine whether there were differences in TXA use between clinicians, and if there has been any changes to TXA infusion rates over time at our centre.

Methods

This study is a retrospective cohort study of adult trauma patients admitted to a Canadian Level 1 trauma centre using a prospectively collected trauma database. The Ottawa Hospital, Civic Campus is the regional trauma referral centre for North-eastern Ontario and Nunavut. The Ottawa Hospital (TOH) is an academic health sciences centre and all members of the trauma unit are actively involved in trauma research as well as post-graduate medical education. Medical trainees are present and active care providers in all trauma cases treated at TOH and the team also includes nurses trained in Advanced Trauma Care for Nurses (ATCN) as well as other qualified health care professionals. The hospital currently has a laboratory-driven massive transfusion protocol (MTP) that recommends for early administration of TXA, which is supported by pharmacy services that stock the therapy in the trauma bay of the Emergency Department (ED). Additionally, a transfusion specialist is on call at all times for consultations and assistance at TOH.

1680 trauma patients were admitted to TOH from September 2011 to February 2014. 103 patients met the inclusion criteria: age greater than 16 and transfusion of at least one unit of packed red blood cells (pRBCs) in the ED. Included patients also showed evidence of at least one of the following additional signs of hemorrhage: multiple blood product transfusion (more than 2 units of pRBCs, or transfusion of any other blood product), systolic blood pressure (SBP) less than 90 mmHg, heart rate (HR) greater than 110 beats per minute (bpm), hypothermia (temperature less than 35°Celcius (°C)), a penetrating abdominal or chest wound, hemorrhage with a Glasgow Coma Scale (GCS) score of less than 13, amputation or severe extremity trauma[x,xi,xii,xiii]. These vital signs abnormalities had to be present on initial presentation, taken within 15 minutes of admission. Patients were excluded if known to be pregnant, allergic to TXA, had received TXA prior to admission to our hospital, arrival at the ED more than 8 hours after injury time, or if vital signs were absent (VSA) on arrival. The inclusion and exclusion criteria

were selected in order to ensure that study subjects matched as closely as possible the CRASH-2 patient population. The data collected from electronic patient records included patients' demographics, vital signs, mechanism of injury, Injury Severity Score (ISS), trauma code initiation, frequency of use of TXA, dosing and timing of TXA, blood products and crystalloid transfused, mortality, interventions in the ED, and outcome measures. The data was recorded in Microsoft Excel version 14.4.4 by one researcher (KY). Any missing data points were omitted from the subsequent calculations.

Descriptive statistics were calculated and reported as means with ranges and percentages. The data was analyzed in Excel and two web-based data analysis program, Social Science Statistics and MedCalc (Version 14.12). Chi-square tests and t-tests were used and displayed as risk ratios where appropriate.

Results

During the study period 1680 trauma patients were admitted to the centre, 87 patients met the inclusion criteria (Figure 1). 71.2% of the patients were male with mean ISS of 29 (range 1-66). Patients who received TXA and those who did not receive any of this therapy were comparable in regards of ISS, GCS, type of injury, and blood transfusion (Table 1). The majority of the patients suffered blunt trauma, mainly motor vehicle collision (35.6%) and fall (21.8%) (figure 2). 62.1% (n=54) of patients received the 1 gram initial dose of TXA. Of those, 50.0% (n=27) received the recommended second dose (1 gram infusion over 8 hours) within 8 hours of injury time and 18.4% (n=16) received it within 3 hours. Of the remaining 50% of patients, 33.3% (n=18) of patients only received the initial dose, 9.2% (n=5) received TXA more than 8 hours after the injury time, and 7.4% (n=4) received less than 1 gram of the drug. 84.9% (n=45) received their first dose of TXA in the ED, 9.4% in the Intensive Care Unit (ICU) 9.4% (n=5) and 5.7% (n=3) in the Operating Room (OR) 5.7%.

The overall mean time to TXA administration was 3 hours and 42 minutes after injury (range: 33 minutes to 20 hours and 43 minutes) with a median time of 2 hours and 12 minutes. Five patients had TXA administered more than 8 hours after injury, outside of the ED (range of 8 hours and 55 minutes to 20 hours and 43 minutes). The mean time to administration of the initial TXA dose in the ED was 2 hours and 35 minutes. One third (33.3%, n=23/66) of patients who arrived at the ED within 3 hours of injury and received the complete recommended dose of TXA administration.

Associations between administration of TXA and various factors were analyzed using chi-squared tests. As highlighted in table 2, the factor most positively associated with TXA use was the activation of a trauma code (RR 1.62). However, none of the factors analyzed reached statistical significance. Use of TXA by specialty of treating physician was also examined (see table 4). There were 11 individual Trauma Team Leaders (TTL) that practiced during the study period, representing four different specialties (General Surgery, Anaesthesiology, Vascular Surgery, and Emergency Medicine). Use of TXA as well as numbers of patients treated (range 3-11) varied

substantially between specialty TTLs. General surgeon TTLs were more likely to administer the initial dose of TXA at 75.0% (39/52) compared to Emergency Medicine TTLs at 40.0% (6/15). General Surgeons also had higher rates of infusion dose administration (24/52), compared to Emergency Medicine physicians (1/15).

Discussion:

Until a time is reached when there is a greater emphasis is placed on injury prevention by health care professionals and government organizations, optimization of treatment of the injured patient is the key focus of trauma care research. It is not frequent that randomized controlled trials evidence shows mortality benefit for use of an inexpensive, readily available and largely safe therapy. TXA, in the context of the CRASH-2 trial, is one of these rare instances. Consequently, it behooves all trauma care providers to utilize this therapy appropriately in every possible instance.

In the current study we found that 62.1% of trauma patients received TXA in the first 8 hours of the trauma. This is a significant improvement compared to a previous study that evaluated TXA administration from September 2010 to June 2011[11], where no hemorrhaging trauma patients received the correct dosing and with the correct timing. In fact, only 13% (n=9) of patients received *any* dose of TXA in that study. Given that the CRASH-2 trial was published only in 2010, it is expected that the integration of the use of TXA into routine clinical practice would increase over time. Considering the challenges of knowledge translation in a clinical setting**Error! Bookmark not defined.**, the observed improvements are suitable for a three year time period. Local educations sessions in the form of lectures, morbidity and mortality rounds, trauma research presentations, trauma journal club as well as individual CME activities are thought to have contributed to the improvement. However, there is room for further improvement in adherence to recommendations about use of TXA. Given the number of educational interventions on this matter in recent years, it is not certain that similar interventions in the future are what are needed to close the gap on TXA use. Alternatives include protocols that mandate the correct doses and timing as well as ongoing audit programs that include individual physician feedback.

There were large variations of TXA administration practices between TTLs from different specialities with General Surgeon TTLs having the highest rates of correct TXA use. The most frequent deviation from the CRASH-2 protocol was failure to administer a second dose of TXA. This fault may be owed to difficulties in communication when patients are handed over to the OR or ICU and the lack of continuity of care. The overall number of patients treated was small and it makes it difficult to draw conclusions on the significance of these observations. However, it suggests a possible need for future knowledge dissemination activities as well as policy modifications that include both surgery and emergency medicine, as well as other specialties routinely involved in trauma care, both in the ED and beyond.

There were no obvious clinical differences between the group that received TXA and the group that did not. They both met criteria for CRASH-2 protocol and would have both likely benefited from it. The factors that predicted for TXA use were activation of a trauma code (RR 1.62), followed by transfusions of 3 of more units of red cells in the ED (RR1.42). Limited inferences can be made based on this data due to the wide confidence intervals. However, it can be speculated the need for trauma code activation and for transfusion identifies patients as having serious ongoing hemorrhage, which leads to increased use of all possible therapies to minimize adverse outcomes of hemorrhage. However, it is important to consider TXA administration in all hemorrhaging trauma patients regardless of trauma code or other objective signs of severity, as TXA administration in less acutely injured patients has proven to be beneficial[xiv]. Conversely, hemorrhaging trauma patients with traumatic brain injury (TBI) received TXA 0.83 times less often than those without TBIs. Although it is uncertain if TXA can directly reduce the size of intracranial hemorrhages, its use with brain injury patients has not been shown to cause any damaging effects[xv]. TBI was not an exclusion criterion and should not be considered a contra-indication to use of TXA. The current study Clinical Randomisation of an Antifibrinolytic in Significant Head Injury (CRASH-3)[xvi] will apprise more on this sub-group of patients.

Limitations:

There were some limitations noted in this study. Since data was analyzed retrospectively, bias due to incomplete or missing chart information is possible. For example, no electronic orders are placed for TXA, so the drug administration is recorded by hand by a nurse or clerk. Error could have arisen if such data recording was omitted from the record or illegible. Items on the CRASH-2 study inclusion criteria are subjective; particularly the determination of the patients risk for a massive hemorrhage as there was no validated, objective method for determining this. In order to best mimic CRASH-2 inclusion criteria, broad but objective criteria were used in the present study. Consequently, this study may have included patients who would have been excluded from the original study, or vice versa.

Ott's 2011 study had less specific inclusion criteria compared to this study, which may have made our comparisons of changes over time somewhat less valid. As well, the relatively small population size of the current study makes it difficult to draw statistically significant conclusions.

Another relevant limitation of retrospective review is that we were not able to address the facilitators or barriers to administration of TXA overall or based on specialty.

Conclusion:

The administration of TXA to hemorrhaging trauma patients in our centre has greatly improved over time. There is a wide range of administration between different speciality providers. The initiation of a trauma code is a protective factor for administration of TXA. Further improvements in the administration of both the bolus and infusion doses of the drug are

required. This study recommends increasing educational interventions to trauma health care providers, possible protocol creation and audits to ascertain specific recommendations for administration of TXA in haemorrhaging trauma patients.

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Appendix:

Characteristic	Overall	TXA	no TXA	p-value
n (%)	87	54 (62.1%)	33 (37.9%)	-
Male (%)	71.2	77.8	60.6	0.09
Mean age [range] (years)	43.5 [16-92]	41.6	46.5	0.28
Mean HR [range] (bpm)	107 [20-183]	109	100	0.18
Mean SBP [range] (mmHg)	110 [40-180]	110	111	0.79
Mean GCS [range]	11 [3-15]	10	11	0.91
Mean ISS [median]	30.0 [29.0]	31.2	25.4	0.06
Pelvic fracture (%)	43.2	50.0	33.3	0.13
Extremity fracture (%)	52.3	54.7	50.0	0.64
Vertebral fracture (%)	23.0	22.2	25.0	0.83
C-spine fracture (%)	10.2	9.3	12.1	0.67
Rib fracture (%)	39.3	36.5	45.2	0.50
TBI (%)	33.7	29.6	40.6	0.30
Blunt injury (%)	78.2	79.6	75.8	0.67
Trauma Code Called (%)	86.4	92.6	78.8	0.13
Intubated (%)	54.0	59.3	45.5	0.21
Chest tube (%)	27.6	25.9	30.3	0.66
Mean RBCs first 24 hours of hospital arrival (units)	6.3	7.6	4.2	*0.01*

Table 1: Patient characteristics

Factor	Relative Risk associated with administration of TXA	95% Confidence Interval	P value
Trauma Code	1.62	0.747 - 3.530	0.13
Transfusion of 3 or more units of RBCs in the ED	1.43	0.935 - 2.175	0.08
Pelvic fracture	1.29	0.933 - 1.783	0.13
Initially Hypotensive (SPB<90 mmHg)	1.29	0.893 - 1.872	0.24
Intubation	1.23	0.879 - 1.743	0.21
Major Trauma (ISS >15)	1.10	0.678 - 1.794	0.68
Blunt trauma	1.09	0.715 - 1.669	0.67
Extremity Fracture	1.08	0.778 - 1.507	0.64
Vertebral (not c-spine) fracture	0.96	0.640 - 1.432	0.83
Chest tube	0.92	0.624 - 1.352	0.66
Penetrating trauma	0.92	0.599 - 1.399	0.67
Rib fracture	0.89	0.624 - 1.264	0.50
C-spine	0.88	0.481 - 1.626	0.67
TBI	0.83	0.568 - 1.205	0.30

Table 2: Relative risk factors for the administration of TXA

	Current Study (2014)	Ott (2011)	p-value
Total patients (n)	87	70	-
TXA administered % (n)	62.1 (54)	12.9 (9)	<0.001
Infusion dose administered % (n)	31.0 (27)	1.4 (1)	<0.001

Table 3: Comparison of study from Sept 2010 to June 2011 at TOH

Specialty	Total patients treated (n)	Administration of initial dose of TXA (% (n))	Administration of infusion dose of TXA (% (n))	Average Time before administration (h:mm)	Average patient/physician (n)
General Surgery	52	75.0 (n=39)	61.5 (n=24)	2:24	7.4
Emergency Medicine	15	40.0 (n=6)	16.7 (n=1)	1:48	7.5
Other	10	50.0 (n=5)	20.0 (n=1)	2:47	5.0

Table 4: Speciality profile of TXA administration and timing

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