Compliance of tranexamic acid administration to trauma patients at a level-one trauma centre

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ABSTRACT

Introduction: Current practice for the treatment of traumatic hemorrhage includes fluid resuscitation and the administration of blood products. The administration of tranexamic acid (TXA) within 8 hours of injury has been shown to significantly reduce mortality in a large, prospective, randomized controlled trial. As a result, TXA is widely used in trauma centres to manage trauma patients with major bleeding. The primary aim of this study was to assess the compliance of TXA administration at a level-one trauma centre in Hamilton, Ontario, Canada.

Methods: We conducted a retrospective medical record review of consecutive adult trauma patients received at the Hamilton General Hospital between January 1, 2012 and December 31, 2014. Compliance with TXA administration was based on the inclusion criteria of the CRASH–2 trial.

Results: Five hundred and thirty-four of 2,475 trauma patients met the inclusion criteria for TXA administration. Twenty-one patients who received TXA at peripheral hospital prior to their arrival at the level-one trauma centre were excluded from the analysis, and 18 patients were excluded due to missing data. One hundred and thirty-four patients received TXA, representing a compliance rate of 27%. Mean time from arrival to TXA administration was 47 minutes. Compliance increased for those who required massive transfusion and as the number of criteria for TXA administration increased.

Conclusions: Compliance with TXA administration to trauma patients with suspected major bleeding was low. Quality improvement strategies aimed at increasing appropriate use of TXA are warranted.

RÉSUMÉ

Introduction: La pratique courante du traitement des hémorragies graves, causées par un trauma comprend le remplissage vasculaire et l'administration de produits sanguins. Il a été démontré dans un essai comparatif, prospectif, à répartition aléatoire, mené à grande échelle que l'administration d'acide tranexamique (ATX) au cours des 8 heures suivant l'accident permettait de réduire de manière significative la mortalité. Aussi observe-t-on dans les centres de traumatologie un recours fréquent à l'ATX chez les traumatisés en état d'hémorragie grave. L'étude avait pour objet principal d'évaluer le respect des critères d'administration de l'ATX dans un centre de traumatologie de niveau I, à Hamilton, en Ontario, au Canada.

Méthode: Nous avons procédé à un examen rétrospectif des dossiers médicaux d'adultes traumatisés consécutifs, qui ont été traités à l'Hamilton General Hospital, entre le 1er janvier 2012 et le 31 décembre 2014. La conformité aux règles d'administration de l'ATX reposait sur le respect des critères de sélection appliqués dans l'essai CRASH–2.

Résultats: Sur 2475 patients ayant subi un trauma, 534 respectaient les critères de sélection pour l'administration d'ATX. Vingt et un patients qui avaient déjà reçu de l'ATX dans un autre hôpital périphérique, avant leur arrivée au centre de traumatologie de niveau I ont été exclus de l'analyse, et dix-huit autres ont également été écartés en raison de données manquantes. Cent trente-quatre patients ont reçu de l'ATX, ce qui représente un taux de respect de 27 %. Le temps moyen écoulé entre l'arrivée au centre de traumatologie et l'administration d'ATX était de 47 minutes. Plus les traumatisés avaient besoin de transfusions massives de sang et plus le nombre de critères d'administration de l'ATX augmentait, plus les critères étaient respectés.

Conclusions: Les critères de sélection pour l'administration d'ATX chez les patients traumatisés chez qui l'on soupçonne la présence d'une hémorragie importante sont peu respectés. Les résultats de l'étude justifient l'élaboration de stratégies d'amélioration de la qualité visant à accroître l'utilisation appropriée de l'ATX.

Keywords: Trauma, TXA, tranexamic acid, resuscitation, massive hemorrhage, compliance, bleeding, emergency, transfusion

INTRODUCTION

Hemorrhage resulting from vascular disruption remains the leading cause of preventable death in civilian trauma.[1] Tranexamic acid (TXA) is an antifibrinolytic agent that inhibits fibrinolysis by binding to plasminogen and interfering with the conversion to plasmin, thereby reducing blood loss.[2] It also inhibits tissue factor–induced

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fibrinolysis.[3] It has been proven that TXA reduces blood loss and the need for blood transfusion in patients undergoing elective and emergency surgery.[3,4] The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH–2) trial, published in 2010, was a randomized controlled trial on the effect of tranexamic acid on death and vascular occlusive events in bleeding trauma patients. A total of 20,211 adult trauma patients with significant bleeding who were within 8 hours of injury were randomly allocated to receive TXA (1 g over 10 min followed by an infusion of 1 g over 8 hours) or matching placebo. The primary outcome was in-hospital death within 4 weeks. TXA significantly reduced death due to bleeding and all-cause mortality with no significant side effects. The reduction in death due to bleeding was greatest when TXA was given within 3 hours of injury.[5] The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study, published in 2012, was a retrospective, observational, cohort study of 896 trauma patients who received at least 1 unit of packed red blood cells (PRBCs) after admission to hospital in southern Afghanistan. This study showed a 6.5% absolute reduction in mortality in those receiving TXA following a wartime injury.[6]

The guidelines of the Eastern Association for the Surgery of Trauma, published in January of 2017, recommended the use of TXA in hospital as a hemostatic adjunct in the management of severely injured adult trauma patients.[7] NICE guidelines, published in February of 2017,[8] recommended the administration of TXA to major trauma patients with active or suspected active bleeding within 3 hours of injury. Based on the evidence of benefit, low cost, and minimal risk of harm, many trauma centres adapted the use of TXA in resuscitating trauma patients with suspected major bleeding.

To our knowledge, no previous studies have evaluated the compliance of TXA administration in a level-one trauma centre. We conducted a health records review to explore the compliance rate of TXA administration to trauma patients with suspected active bleeding at the Hamilton General Hospital, a level-one trauma centre.

METHODS

Study design

This was a retrospective health records review of consecutive adult trauma patients who presented to the Hamilton General Hospital, a level-one trauma centre, over a two-year period between 1 January 2012 and 31 December 2014.

The Trauma Association of Canada guidelines stratify individual hospitals according to standardized levels of the trauma care they provide.[9] The nomenclature includes levels 1 through 5, with level 1 being the highest grade of available care. Peripheral hospitals, designated levels 2–5, can provide definitive care to single-system trauma cases but also play an important role in the stabilization of complex or multi-system trauma patients prior to transfer to a level-one lead trauma centre for definitive care.

The Hamilton General Hospital is a regional level-one trauma centre that serves a population of 2.5 million in southern Ontario. It is staffed 24 hours a day with certified emergency physicians and is an academic teaching centre. The trauma team consists of a trauma team leader (TTL), who is a staff emergency physician, an anesthesiologist, or a general surgeon; a trauma fellow; and residents from emergency medicine, anesthesia, general surgery, and orthopedic surgery. The trauma team is activated for about 650 patients annually, with some 60% of patients having an injury severity score (ISS) ≥12.[10]

Selection of patients

We included patients 16 years of age or older who met one or more of the following criteria: (1) tachycardia (defined as a heart rate [HR] ≥110 beats per minute on arrival to the emergency department [ED]); (2) hypotension (defined as a systolic blood pressure [SBP] ≤90 on ED arrival); and/or (3) requiring at least 1 unit of PRBCs in the ED. Patients who received TXA at a peripheral hospital were excluded.

Data collection and analysis

Patients were identified through the Hamilton General Hospital Trauma Registry. The trauma registry contains data on all patients with an ISS ≥12 and those with an ISS <12 with trauma team activation. Eligible patients were divided into the following seven groups according to their eligibility criteria: (1) tachycardic on presentation to the ED (HR ≥ 110); (2) hypotensive on presentation to the ED (SBP ≤ 90); (3) transfused with at least 1 unit of PRBCs in the ED; (4) hypotensive and tachycardic; (5) transfused and tachycardic;

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(6) transfused and hypotensive; or (7) tachycardic, hypotensive, and transfused. Data elements and outcome measures were obtained from the trauma registry and through review of electronic medical records.

Data were analyzed using descriptive statistics. Categorical variables are expressed herein as frequencies and percentages, and continuous variables as means with standard deviations. To assess compliance of TXA administration, we calculated the number of patients who received TXA as a percentage of patients meeting at least one eligibility criterion for TXA administration. Additional analyses related to compliance included number of doses administered and time from arrival at the level-one trauma hospital to first dose. Eligible patients were subdivided into those who received TXA and those who did not. Differences between groups with regard to patient demographics, injury, and treatment measures were assessed using chi-square and Fisher's exact tests for categorical variables, and Student's t-test for continuous variables. All statistical analyses were carried out using SPSS (v. 22.0, IBM Corporation, Armonk, NY). P-values below 0.05 were considered statistically significant. The study received ethics approval from the Hamilton Integrated Research Ethics Board.

Outcome measures

Our primary outcome was the compliance rate of TXA administration.

RESULTS

A total of 2,475 patients presented to the Hamilton General Hospital trauma program between 1 January 2012 and 31 December 2014. Some 534 patients (21.6%) met our inclusion criteria; however, 18 patients had incomplete data and were excluded from the analysis. A total of 21 patients who received TXA at a peripheral hospital prior to their arrival at the level-one trauma centre were also excluded. According to individual eligibility criteria, 325 patients (65.7%) presented with tachycardia, 86 (17.4%) patients were hypotensive, and 200 (40.4%) received at least 1 unit of PRBCs in the ED. Most patients presented with one eligibility criterion only (389 patients or 78.6%), while 106 (21.4%) met two eligibility criteria, and 10 (2%) presented with all three criteria (Table 1).

The baseline characteristics for our study cohort are provided in Table 1. Nearly all cases in our study cohort (458, 92.5%) were trauma team activations, and most sustained blunt trauma (82.2%). Most cases came to our level-one trauma hospital direct from the scene (319, 64.4%).

Table 1. Baseline characteristics of the study cohort

Consecutive cases identified in the trauma registry	2475
Eligible cases*	534
Exclusions	
Incomplete data, excluded from the study cohort	18
TXA administered pre arrival at LTH	21
Study cohort	495
Eligibility criteria†	
Tachycardia	325/495 (65.7%)
Hypotensive	86/495 (17.4%)
Transfused	200/495 (40.4%)
Met one criteria only	389/495 (78.6%)
Tachycardic	248
Hypotensive	40
Transfused	101
Two or more criteria	106/495 (21.4%)
Tachycardic and transfused	60
Hypotensive and transfused	29
Tachycardic and hypotensive	7
Tachycardic, hypotensive, and transfused	10
Age (years), mean ± SD	46.1 ± 20.8
Males (%)	343 (69.3%)
Trauma team activation (%)	458 (92.5%)
Injury severity score, mean ± SD	18 ± 12
Mechanism of injury	
Blunt	407 (82.2%)
Penetrating	77 (15.6%)
Other (burn, drowning, asphyxia)	11 (2.2%)
Direct from scene	319 (64.4%)
Heart rate bpm, mean ± SD	108 ± 28
Systolic blood pressure, mmHg, mean ± SD	126 ± 38
Number of blood products transfused in the first 24 hours	
Packed red blood cell (units), mean ± SD	7.2 ± 8.3
Fresh frozen plasma (units), mean ± SD	4.1 ± 5.7
Platelets (adult buffy coat units), mean ± SD	1.1 ± 1.8
Received massive transfusion in the first 24 hours	48/200 (24%)
Compliance rate of TXA administration	134 (27.1%)
One dose	104 (77.6%)
Two or more doses	27 (20.1 %)
TXA given but doses not specified	3 (2.2%)
Time of first TXA dose administration from arrival to the hospital (mean, SD)	47 ± 62 min

*Patient met at least one of the following inclusion criteria of the CRASH–2 or MATTERs studies: tachycardia, defined as heart rate ≥110 beats per minutes on emergency department (ED) arrival; hypotension, defined as systolic blood pressure (SBP) ≤90 on ED arrival; and/or required at least 1 unit of PRBCs in the ED.
†Patients meeting more than one inclusion criterion are represented in each applicable category. Sums to more than 100% due to double counting.

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Table 2. TXA administration versus no TXA according to eligibility grouping

	TXA	No TXA	Total	p value
Number of cases (%)	134 (27.1%)	361 (72.9%)	495 (100%)	
Tachycardic only	23 (9.3%)	225 (90.7%)	248 (100%)	<0.001
Hypotensive only	8 (20.0%)	32 (80.0%)	40 (100%)	0.075
Transfused only	42 (41.6%)	59 (58.4%)	101 (100%)	<0.001
Tachycardic and hypotensive	3 (42.9%)	4 (57.1%)	7 (100%)	0.344
Tachycardic and transfused	33 (55.0%)	27 (45.0%)	60 (100%)	<0.001
Hypotensive and transfused	18 (62.1%)	11 (37.9%)	29 (100%)	<0.001
Tachycardic, hypotensive, and transfused	7 (70%)	3 (30%)	10 (100%)	<0.05

A total of 134 patients received TXA, for an overall compliance rate of 27.1% (134/495). Most patients received only one dose of TXA (104 patients, 77.6%), while 27 (20.1%) received two or more doses (Table 1). Compliance with TXA administration according to eligibility criteria is presented in Table 2. The compliance rate increased for patients who presented with more than one eligibility criterion. For example, when all three criteria were met, the compliance rate reached 70%. The mean time from arrival at the level-one trauma hospital to the first TXA dose administration was 47 min (±62 min). During the study period, a massive transfusion protocol was implemented. A total of 48 of the 200 patients who received a blood transfusion in the ED required the massive hemorrhage control protocol, with 35 patients (73%) receiving TXA.

When comparing the group who received TXA to the group who did not, the baseline characteristics differed, with a higher mean ISS (24 vs. 17, $p < 0.001$), a higher rate of emergency surgery (67 vs. 43%, $p < 0.001$), a lower SBP upon arrival (112 vs. 131, $p < 0.001$), and a higher trauma team activation rate (100 vs. 90%) in the TXA group (Table 3).

The mean numbers of blood products transfused in the first 24 hours—including PRBCs, fresh-frozen plasma (FFP), and platelets—were all higher in the TXA group versus the no-TXA group (PRBCs 9.3 vs. 5.1, $p < 0.001$; FFP 5.5 vs. 2.6, $p < 0.001$; platelets 1.5 vs. 0.7, $p < 0.05$; Table 3).

DISCUSSION

Summary

To our knowledge, this is the first study evaluating compliance of TXA administration at a level-one trauma facility. We found that the compliance rate was low and that most patients received only one dose of TXA. Patients receiving TXA had higher ISS scores, required emergency surgery more often, had lower SBP on arrival, higher trauma team activation rates, and more blood product usage in the first 24 hours than those not receiving TXA.

TXA was given to bleeding trauma patients at the discretion of the TTL. The low compliance rate of administrating TXA to eligible patients in our study could be explained by uncertainty about whom the therapy would benefit most. The CRASH–2 trial included trauma patients who were either tachycardic, hypotensive, or judged to be at risk of significant hemorrhage by the treating physician, which represents a wide spectrum of trauma patients. In the MATTERs study, the mortality reduction was greatest in those who required massive transfusions, suggesting that the benefit of TXA may be greater in subpopulations of patients. The CRASH–2 trial nevertheless identified an overall mortality benefit to those presenting with tachycardia, hypotension, or both, suggesting that routine administration of TXA to all trauma patients at risk for major bleeding is warranted. This strategy was recommended by Napolitano et al. (2013)[11] in their review of the literature. Another strategy may be to administer TXA to patients with the potential for greatest benefit, such as those with significant injury and more severe hemorrhagic shock, defined by an SBP of 75 mmHg or less within the first 3 hours from the time of injury.

Binz et al. (2015)[12] highlighted that one of the major recruitment problems in the CRASH–2 trial was that of the uncertainty principle of randomization, as it was based on the clinical sense of the treating physician whether or not to treat with TXA. They concluded that TXA may not be widely accepted due to perceived problems regarding data collection and methodology.

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Table 3. Patient characteristics according to TXA administration

	TXA	No TXA	Total	p value
Total (%)	134 (27.1%)	361 (72.9%)	495 (100%)	
Age, mean ± SD	47.2 ± 20.2	45.6 ± 21.0	46.1 ± 20.8	0.451
Injury severity score, mean ± SD	24 ± 13	16 ± 12	18 ± 12	<0.001
Trauma team activation	134 (100%)	324 (90.0%)	458 (92.5%)	<0.001
Direct from scene	92 (68.7%)	227 (62.9%)	319 (64.4%)	0.233
Heart rate bpm, mean ± SD	104 ± 28	109 ± 29	108 ± 28	0.093
Systolic blood pressure (mmHg), mean ± SD	112 ± 33	131 ± 38	126 ± 38	<0.001
Surgery	90 (67.2%)	156 (43.2%)	246 (49.7%)	<0.001
Number of blood products transfused in the first 24 hours				
Packed red blood cell (units), mean ± SD	5.5 ± 6.7	2.6 ± 3.9	4.1 ± 5.7	<0.001
Fresh frozen plasma (units), mean ± SD	1.5 ± 2.1	0.7 ± 1.4	1.1 ± 1.8	<0.05
Platelets (adult buffy coat units), mean ± SD	9.3 ± 9.8	5.1 ± 6.0	7.2 ± 8.3	<0.001
Received massive transfusions within 24 hours of arrival at level-one trauma hospital	35 (73%)	13 (27%)	48 (100%)	<0.001

Pusateri et al. (2013)[13] conducted a systematic review exploring knowledge gaps in the use of TXA in trauma. It is noteworthy that only half of the patients in the CRASH–2 trial were transfused, and less than half met either the blood pressure or heart rate inclusion criteria. TXA may play a more important role, particularly in developing countries, where definitive management of hemorrhage control may not be readily accessible.

Although the compliance rate in our study was poor, TXA was given within the first 3 hours of arrival, which was shown previously to afford the greatest benefit.[14,15]

STRENGTHS

TXA administration to eligible patients is an important quality-assurance metric in many trauma programs, yet no data have been published on TXA compliance at lead trauma centres. To date, ours is the first study to assess compliance with TXA administration in eligible patients. We included the CRASH–2 inclusion criteria, as this was the largest and most rigorous trial to date, which also established an overall mortality benefit for TXA. We also included the MATTERs trial inclusion criteria, as this was a large retrospective study demonstrating significant mortality reduction with the use of TXA. Both these studies define a clear role for TXA in trauma patients at risk of major hemorrhage. We separated eligible patients into seven groups wherein one can see the compliance rate for individual inclusion criteria and thus assess trends in TXA administration. Our data involve consecutive trauma patients to avoid selection bias, and we used 2012–2014 data to allow adequate time for knowledge translation regarding the use of TXA. Although retrospective medical record reviews may be subject to bias, we feel that this design is necessary when studying compliance to minimize a possible Hawthorne effect.

LIMITATIONS

All medical records were reviewed by one author (AG), so that errors in data extraction are possible. Ideally, two reviewers consecutively extracting the data with a kappa statistic allows for greater reproducibility of results; however, most data were obtained from our trauma database. In addition, TXA administration is easily tracked in the patient's electronic medical record (Meditech) and, for the purposes of our study, was cross-referenced with the paper chart available through Sovera. Nevertheless, administration of TXA without adequate documentation may have artificially lowered the observed compliance rate. An accurate time of injury is difficult to obtain from health records. As a result, this may be a contributing factor to low compliance for cases who presented to the ED after the recommended 3-hour timeframe for TXA administration.

There were also 18 charts with incomplete data that were eliminated from the final analysis. However, the greatest limitation in the present study was the inability to discuss the decision-making process for TXA administration with the TTL after each case. Individual patient circumstances, injury patterns, response of vital signs to initial treatments, and time from injury, among

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other things, may have influenced the decision not to give TXA despite the presence of criteria for its administration.

RECOMMENDATION

TXA administration in our level-one trauma centre was low, and the reasons for this warrant further investigation. There was no formal knowledge translation strategy for TXA at our centre. Instead, the onus was on the individual clinician to be aware of the CRASH–2 results and published guidelines and incorporate them into practice. Hence, our compliance rate, while low, is consistent with the knowledge translation literature that cites the relative ineffectiveness of passive interventions and the challenges related to knowledge translation in a clinical environment.

The results of the CRASH–2 trial are not without controversy. Some trauma centres have formal protocols, whereas others leave decision making to the individual physician. Our centre has no formal guideline on TXA. We foresee engaging stakeholders in trauma care to develop an internal guideline with detailed patient, timing, and dosage factors related to TXA administration. Implementation of the guideline requires a comprehensive educational strategy, and the need to support clinicians closer to the point of decision making with such active interventions as reminders. Regardless, our study provides a baseline measure for ongoing quality-assurance audits to monitor compliance and gauge the effectiveness of strategies aimed at improving TXA administration.

CONCLUSIONS

Administration of TXA to trauma patients at risk for major bleeding was low. Quality-improvement strategies aimed at increasing appropriate use of TXA are warranted.

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