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Original Contribution

Evaluation of tranexamic acid in trauma patients: A retrospective quantitative analysis☆

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ABSTRACT

Introduction: Tranexamic acid (TXA) has been shown to decrease mortality in adult trauma patients with or at significant risk of hemorrhage when administered within 3 h of injury. The use and appropriateness of TXA in adult trauma patients presenting to Royal Columbian Hospital (RCH) was investigated.
Methods: This retrospective chart review utilized the British Columbia Trauma Registry to identify 100 consecutive trauma patients that presented to the emergency department at RCH between April 2012 to June 2015 and met the following indications for TXA: systolic blood pressure <90 mm Hg and/or heart rate >110 bpm and presentation within 8 h of injury. Primary outcomes included: percentage that met indications for TXA, received TXA according to the *CRASH-2* protocol, received a pre-hospital dose, and received TXA ≤1, >1 to ≤3, or >3 h from injury.
Results: During the given time period, 117 subjects (2.7%) met indications for TXA. 67 patients (57%) received TXA in any dose, with 10 subjects (8.5%) receiving TXA according to the *CRASH-2* protocol. Of the 67 patients who received any TXA, 76% did so ≤3 h. 22 patients (19%) received TXA as a pre-hospital dose.
Conclusions: <10% of adult trauma patients that met the indication for TXA received it according to the *CRASH-2* protocol. Of those patients that received TXA, 76% did so within 3 h. Further inquiry to identify reasons trauma patients are not receiving TXA as well as quality improvement initiatives in trauma care are required.
Level of evidence: III
Study type: Therapeutic

1. Introduction

Trauma is a major cause of mortality and the leading cause of death in those under 45 years old [1, 2]. Exsanguination is responsible for an estimated one-third of in-hospital mortality in trauma patients, with the most common sources being aortic, chest (heart and pulmonary) and pelvic trauma [3]. In current understanding, shock and tissue hypoperfusion occur following trauma, initiating a state of systemic anticoagulation and hyperfibrinolysis which further exacerbates hemorrhage [4, 5]. Acute coagulopathy occurs in almost 25% of trauma patients in hospital, and can increase mortality by four-fold [4-6]. It is reasonable to hypothesize then, that therapeutic agents that target fibrinolysis could potentially minimize blood loss and mortality in trauma.

Tranexamic acid[1] (TXA) is an antifibrinolytic agent that reversibly inhibits the conversion of plasminogen to plasmin, thereby preventing interaction with fibrin and breakdown of fibrin clots [7]. It is included on the World Health Organization's (WHO) list of essential medicines and is available in oral and intravenous (IV) form [8]. Current indications include heavy menstrual bleeding, hereditary blood disorders, trauma, and surgery, in which it reduces post-operative blood loss and transfusions [7, 9]. Two systematic reviews and meta-analyses in an orthopedic surgery population have shown no evidence of increased thromboembolic events or other adverse effects versus controls [9]. TXA's ability to decrease bleeding in various settings, along with its tolerability and inexpensive cost (less than $25 USD for a 1 g vial) has led

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[1] Tranexamic acid will be abbreviated as TXA.

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to investigations of its use in trauma [9, 10]. (see Appendix A for supplemental safety information).

In 2010, a randomized trial (*Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2*, *CRASH-2*) of 20,211 adult trauma patients demonstrated that TXA 1 g administered IV over 10 min followed by 1 g IV over 8 h, when compared to normal saline IV, reduced all-cause mortality at 28 days from 16% to 14.5%, (RR 0.91, 95% CI 0.85–0.97, NNT 67). This was primarily driven by a decrease in hemorrhagic death from 5.7% to 4.9%, (RR 0.85, 95% CI 0.76–0.96, NNT 125) [11]. An exploratory analysis revealed that mortality benefit was significant only when given within 3 h of injury, while unexpectedly, administration beyond 3 h increased bleeding death from 3.1% to 4.4% ($p = 0.004$, NNH 77). [12] No increase in vascular occlusive events or other serious adverse events was reported [11]. *CRASH-2* has remained the primary evidence supporting use of TXA in trauma.

Royal Columbian Hospital (RCH) is a tertiary and regional referral hospital for the Lower Mainland in British Columbia, Canada. It is a level 1-trauma center and receives over 1000 trauma cases per year. Current use of TXA in trauma patients with actual significant hemorrhage has not been previously evaluated. The objective of this retrospective analysis was to characterize the use and appropriateness of TXA for adult trauma patients. The outcomes of this study will be utilized to identify care gaps and develop quality improvement initiatives in trauma care.

2. Methods

2.1. Study design

This was a retrospective chart review of the utilization of TXA in adult trauma patients. The study was conducted at Royal Columbian Hospital in New Westminister, British Columbia.

2.2. Population

A convenience sample of 100 adult trauma patients that presented to the emergency department at RCH with actual or suspected significant hemorrhage was chosen. The end date of the sample was June 2015, as this was the most recent data available at the time of the study. We worked retrospectively from this date until sample size was reached. Patients were included if they met the indications for TXA as specified in *CRASH-2*: trauma patient >16 years of age, significant hemorrhage defined as systolic blood pressure <90 mm Hg and/or heart rate >110 bpm, and presentation within 8 h of injury. We did not include the *CRASH-2* criteria of those "at risk of significant hemorrhage (i.e. compensated hemorrhage and stable vitals)" as it was not feasible to assess this retrospectively. Patients were excluded if they had a contraindication to TXA (active myocardial infarction, clotting disorder, allergy) (See Appendix B for additional information on inclusion/exclusion criteria).

2.3. Data collection or abstraction

One investigator abstracted data from the hospital records. Baseline demographics were collected using a standardized electronic data extraction form. A request to the BC Trauma Registry (BCTR) produced a report of trauma admissions from April 2012 to June 2015 that met criteria for age, vital signs, and presentation timeline, as well as demographic information and a summation of total number of trauma admits during this period. This data was linked to hospital records, which were screened for inclusion based on whether patients were experiencing hemorrhage, and to collect outcome data. All information was recorded onto a password-protected spreadsheet by the investigator.

The study was completed under approval of the Fraser Health Research Ethics Board and in accordance with the Helsinki Declaration. As there was minimal risk to study subjects, consent was not required.

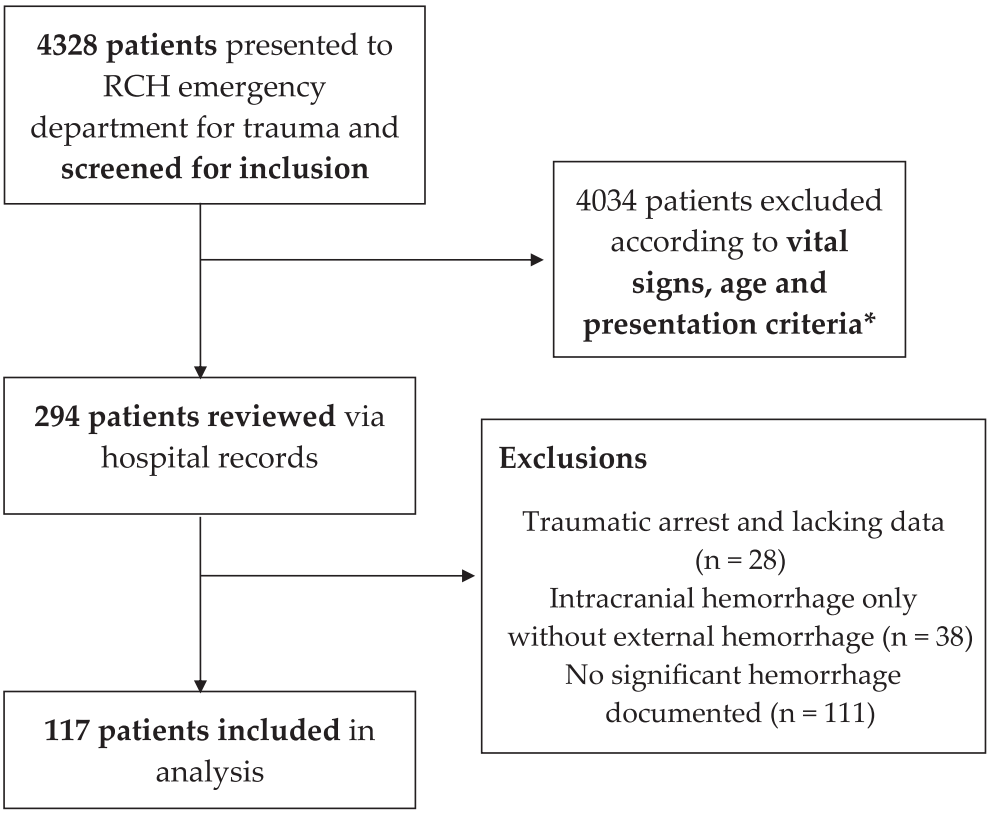

Fig. 1. Flow diagram of inclusion and exclusion of trauma population at Royal Columbian Hospital. *Excluded by initial BC Trauma Registry data request. See Methods section under '2.2 Population' and '2.3 Data collection or abstraction' for more detail on criteria.

2.4. Outcomes

The primary objective was to characterize utilization of TXA for trauma patients at a tertiary center. The secondary objective was to perform an exploratory analysis of patient outcomes including in-hospital mortality, blood transfusions (number of units packed red blood cells), vascular occlusions (deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke), and surgical interventions.

Primary outcomes included: proportion of trauma patients that met indication criteria for TXA; proportion that received both doses as per *CRASH-2* protocol (1 g IV/10 min bolus and 1 g IV/8 h infusion); proportion that received a pre-hospital dose; and for those that received TXA, proportion that received the medication within 1 h, 1 to 3 h, or >3 h from time of injury. These time categories reflect the classifications in *CRASH-2* and the subsequent analysis that showed mortality benefit only when TXA was given within 3 h of injury [11, 12]. Secondary outcomes were defined as those that occurred during hospital stay up to 28 days as documented in patient chart, which reflects the time period used in *CRASH-2*.

2.5. Analysis

Descriptive statistics (e.g. percentages) were used to report and compare primary and secondary outcomes. For those that received TXA, median time to treatment (with interquartile range IQR) and the percentages treated ≤1, >1–≤3 or >3 h from time of injury was assessed. Average volume of blood transfused (units of packed red blood cells) with standard deviation was calculated. Fisher's Exact test was used to calculate odds ratio for mortality for TXA exposure, and timing of drug administration within 3 h versus >3 h. We utilized the Pearson Chi-square test to analyze secondary outcomes.

Table 1
Baseline demographics.

	Combined (n = 117)	Tranexamic acid (n = 67)	No tranexamic acid (n = 50)
Sex			
Male	96 (82%)	54 (81%)	42 (84%)
Female	21 (18%)	13 (19%)	8 (16%)
Age (years)			
Mean (SD)	42.8 (18.9)	42.3 (17.9)	43.6 (20.4)
<25	22 (19%)	10 (15%)	12 (24%)
25–34	23 (20%)	14 (21%)	9 (18%)
35–44	21 (18%)	15 (22%)	6 (12%)
>44	51 (44%)	28 (42%)	23 (46%)
Time since injury to ER presentation (hours)			
Mean (SD)	1.2 (1.1)	1.3 (1.2)	1.2 (1.1)
≤1	69 (59%)	38 (57%)	31 (62%)
>1–≤3	40 (34%)	26 (39%)	14 (28%)
>3	8 (7%)	3 (4%)	5 (10%)
Type of Injury			
Blunt	78 (67%)	45 (67%)	33 (66%)
Penetrating	39 (33%)	22 (33%)	17 (34%)
Glasgow Coma Score on initial presentation			
Mean (SD)	11 (4.6)	11 (4.6)	12 (4.6)
Severe (3–8)	32 (27%)	20 (30%)	12 (24%)
Moderate (9–12)	14 (12%)	10 (15%)	4 (8%)
Mild (13–15)	67 (57%)	33 (49%)	34 (68%)
Not known	4 (3%)	4 (6%)	0 (0%)
Systolic blood pressure on initial presentation			
Mean (SD)	97 (41)	88 (42)	109 (38)
≤75 mm Hg	33 (28%)	22 (33%)	11 (22%)
76–89 mm Hg	21 (18%)	12 (18%)	9 (18%)
≥90 mm Hg	63 (54%)	33 (49%)	30 (60%)
Heart rate on initial presentation			
Mean (SD)	112 (35)	108 (40)	117 (28)
<77 bpm	16 (14%)	13 (19%)	3 (6%)
77–91 bpm	8 (7%)	4 (6%)	4 (8%)
92–107 bpm	9 (8%)	5 (7%)	4 (8%)
>107 bpm	84 (72%)	45 (67%)	39 (78%)
ISS (Injury Severity Score)			
Mean (SD)	26 (16)	27 (16)	25 (16)
Mild (<9)	2 (2%)	0 (0%)	2 (4%)
Moderate (9–15)	25 (21%)	11 (16%)	14 (28%)
Severe (16–25)	36 (31%)	23 (34%)	13 (26%)
Profound (>25)	54 (46%)	33 (49%)	21 (42%)

3. Results

During this period, a total of 4328 trauma patients presented to RCH emergency department (Fig. 1). For the patients that were excluded initially by the BCTR screening (n = 4034), we did not collect data on demographics, type of hemorrhage or clinical outcomes. Another 177 patients were excluded after review of hospital records. After review, 117 patients met inclusion criteria (Table 1). No patients had an identified contraindication to TXA.

Baseline characteristics were generally similar between *TXA* and *no-TXA* groups (Table 1). Mean age was 43 years old and 82% were male. Mean time from injury to presentation at emergency department was 1.2 h (SD 1.1 h). Eight patients presented beyond 3 h. The majority of patients (67 of 117; 57%) had a normal to mildly decreased GCS (13–15) on initial presentation, with most of those (42 of 67) having a GCS of 15. However more patients in the *TXA* group had a GCS score in the moderate (9–12) or severe (3–8) range. Mean systolic blood pressure and heart rate were both slightly higher in the *no-TXA* group. Mean Injury Severity Score was 26, which is considered profound trauma. A threshold of 15 is used for major trauma and constitutes a 10% risk of mortality, 75 (maximum score) has an associated 100% risk of mortality [13].

The percentage of trauma admissions that met indication for TXA was 2.7% (117/4328) (Table 2). Of the 117 included patients, 10 (8.5%) received both doses (bolus and infusion) as per the *CRASH-2* protocol. Alternate regimens were often used, such as 1 g over 30 min, 2 g over 60 min, 1.5 g bolus, and/or shorter infusion times. Eight subjects received TXA as a bolus in the operating room. Only 8 out of the 22 subjects that received a pre-hospital dose of TXA continued to receive it in hospital. Median time to receiving TXA was 1.8 h (IQR 1.05–3 h), and 76% of patients received it within 3 h.

Table 2
Primary outcomes (N = 4328[a]).

	n	%[b]
Indication for tranexamic acid	117	
Any tranexamic acid	67	57.3
Pre-hospital	22	18.8
In-hospital	52	44.4
Pre- and in-hospital	8	6.8
Bolus as per *CRASH*	55	47.0
Any bolus	64	54.7
Infusion as per *CRASH*	15	12.8
Any infusion	23	19.7
CRASH bolus and infusion	10	8.5
Any bolus and infusion	17	14.5
Timing of tranexamic acid administration	**n**	**%[c]**
Received tranexamic acid	67	
Mean time in hours (standard deviation)	3.2 (6.0)	
Median time in hours (interquartile range)	1.8 (1.05–3)	
≤1 h	16	23.9
>1 to 3 h	35	52.2
>3 h	16	23.9
>8 h	3	4.5

[a] N refers to number of subjects that presented to Royal Columbian Hospital emergency department for trauma between April 2012 to June 2015.
[b] Percentage of the 117 subjects that met indication for tranexamic acid, that received each category of dosing.
[c] Percentage of the 67 subjects that received any form of tranexamic acid, that received it within each time frame.

Table 3
Secondary outcomes during first 28 days of hospital stay.

	Overall (n = 117)	Tranexamic acid (n = 67)	No tranexamic acid (n = 50)	$\chi 2$
In-hospital mortality at 28 days	22 (19%)	14 (21%)	8 (16%)	p = 0.5
Blood transfusions	104 (89%)	61 (91%)	43 (85%)	p = 0.4
Thromboembolic events	8 (7%)	4 (6%)	4 (8%)	p = 0.7
Surgery	85 (73%)	52 (78%)	33 (66%)	p = 0.2

Table 4
Blood transfusions received during first 28 days of hospital stay.

PRBC (units)	Tranexamic acid	No tranexamic acid	Overall
Median	8	4	6
Mean (SD)	14 (17)	7 (11)	11 (15)

PRBC — packed red blood cells.

Odds ratio for mortality was not statistically significant different between *TXA* and *no-TXA* groups. Odds ratio given TXA exposure was 1.39 (0.53–3.62). Odds ratio given drug administration ≤3 h (vs >3 h) was 5.13 (0.62–42.75). Most patients received blood transfusions in addition to surgical interventions (Tables 3 and 4). Common surgeries were laparotomies and/or orthopedic in nature (Table 5). There were 8 thromboembolic events, 4 in each group. There were 3 episodes of deep vein thrombosis and 1 internal carotid artery thrombus in the *TXA* group, and 2 pulmonary embolisms and 2 episodes of deep vein thrombosis in the *no-TXA* group.

Secondary outcomes of in-hospital mortality, blood transfusions, vascular occlusions, and surgical interventions were not statistically different between the two groups (Table 3). This study was not powered to detect differences in these outcomes, however the data was analyzed for descriptive purposes.

4. Discussion

The results demonstrate that more than half of adult trauma patients meeting the indication for TXA received the medication. However, <10% received it according to the *CRASH-2* protocol. Of those that received any regimen of TXA, 76% did so within 3 h of presentation to the emergency department.

Reasons for alternate TXA regimens were not recorded in health records. One possible reason could be a change in clinical status. Perhaps patients initially suspected to be bleeding were later found not to be, or those that were hemodynamically unstable then stabilized. Another reason could be discontinuity in care. It was observed that several times, a bolus was given pre-hospital, but the infusion was not given in-hospital. Alternatively, a bolus was given in the emergency department and patients were subsequently transferred to a different service (i.e. surgery, ICU etc.) where therapy was not continued. Similarly, some infusions were started in one unit, and not continued after transfer to another ward. Another possibility is lack of familiarity among health care providers with the indication and dosing protocol for TXA in the trauma setting. As noted previously, TXA is used in various settings to prevent hemorrhage and perhaps providers were using dosing established in other situations.

Table 5
Types of surgical interventions during first 28 days of hospital stay.

Types of surgical interventions			
	Total	TXA[a]	No TXA
Neuro	7	5	2
Laparotomy	56	42	14
Orthopedic	66	40	26
Thoracic	19	13	6
Plastics	19	11	8
Vascular	14	9	5
Other	20	9	11
Total	201	129	72

[a] Tranexamic acid group.

Use of TXA experienced initial interest after *CRASH-2*. However, there has been considerable controversy and critique surrounding its use since the *CRASH-2* results were published. One of the critiques is that fibrinolytic activity was not measured, so exact mechanism of TXA in trauma cannot be certain [11, 14]. Moreover, there was no difference in transfusion requirements between groups, although increased survival may have led to more opportunity to receive transfusions [11, 14]. Most patients in *CRASH-2* were in low and middle-income countries, and <2% of patients had rapid access to blood products, surgery, and advanced critical care [9, 14]. The role of TXA in high-income countries with faster transportation times, easier access to diagnostic imaging and critical care services, and where protocols normally include fresh-frozen plasma with endogenous antifibrinolytics, is less clearly known [14]. *CRASH-2* has also been criticized for limited adverse events reporting, and other unreported data [15]. These concerns, as well as non-randomized controlled trials that later found an increase in venous thromboembolism, have perhaps led to a more tailored role in trauma, restricted to those in severe shock [15]. Two randomized trials, PATCH (Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Haemorrhage) and STAAMP (Study of Tranexamic Acid During Air Medical Prehospital Transport Trial) are currently underway in Australia and New Zealand, and the United States, respectively [16, 17].

It is difficult to conclude whether the use of alternate regimens was due to clinical status, lack of continuity in care during transfers, lack of familiarity among providers or uncertainty of benefit. However, the main concern around incomplete regimens (i.e. bolus-only, shorter infusions etc.) is that the main evidence that supports the use of TXA in trauma is *CRASH-2,* where all patients included in that study received a bolus as well as an infusion [11]. The use of alternate regimens may not confer the same mortality benefit as previously demonstrated. Another important observation is only 76% of subjects received the drug within 3 h. This is important because post-hoc analyses of *CRASH-2* have shown benefit of TXA only when given within 3 h, while there was actually an increase in hemorrhagic death if given in greater than that time period [12].

Our findings showed no difference in mortality with TXA exposure. *CRASH-2* required over 20,000 patients to find a 1.5% absolute risk reduction in mortality, therefore we did not expect this retrospective study of 117 patients to find a statistical difference [11]. Furthermore, because of the non-randomized nature of our study, we cannot make any strong conclusions about mortality given the presence of confounding. It is likely that patients that received TXA earlier in their hospital course had more severe trauma and were at higher risk of mortality. This was supported in our data with the lower GCS scores, more transfusions, and more surgical interventions in the *TXA-group*; although these differences did not reach statistical significance. *CRASH-2* similarly did not find a difference between groups in blood transfusions, thromboembolic events, and surgeries [11]. We pre-specified an analysis of these endpoints for exploratory descriptive purposes only.

We attempted to compare our results to the available literature. It is immediately noticeable that the accrual rate for our study was quite low (2.7%). This is likely due to the use of the BCTR, which also includes asphyxial, thermal, and minor traumas (i.e. falls), giving 4328 patients

as the total number of trauma admissions in the examined time period. As other studies of TXA have not reported accrual rate, it is difficult to make comparisons [12, 18]. Our baseline demographics were similar to *CRASH-2*., where patients were mainly young, male, and suffered blunt trauma [11]. The majority presented with systolic blood pressure over 90 mm Hg, and about 50% had an initial heart rate > 107 bpm. Initial GCS was mild (13–15) for 68% [11]. The mean time to presentation in our study was 1.2 h versus 2.8 h in *CRASH-2*. This could be explained by the fact that most centers in *CRASH-2* were in less developed countries with possibly more barriers to accessing health care. However, we conclude that our patients could have been included in *CRASH-2*, and perhaps would have received the same benefits TXA.

Our secondary outcomes appear to correlate with previous population data. The mortality rate of 19% was similar to *CRASH-2* (15%) [11]. Patients at our study center received more blood transfusions and surgical interventions, likely due to more ready access to these resources. While vascular occlusions have long been a hypothetical risk with TXA, our results seem to correlate with other studies that have shown that this threat is not real [9].

Our study is one of the few assessing the use of TXA in trauma patients in a tertiary center in the post-*CRASH-2* era. TXA has been integrated into hospital and prehospital ambulance services in several countries, including Canada [19, 20]. Yet, one study of its use as part of a massive transfusion protocol at an American tertiary center revealed that 38% of eligible trauma patients received the drug [21]. Other studies have examined the benefits of this drug in vastly different settings such as combat [18, 22].

There are limitations to our study. Firstly, due to its retrospective design, we were restricted to data available in hospital records, which proved difficult in assessing the significance of hemorrhage during screening. *CRASH-2* did not publish their definition of "significant hemorrhage", nor provide guidance on how patients were assessed for inclusion in regards to bleeding. Subjects were included based on the "uncertainty principle", meaning that those for which the clinician was "substantially uncertain" as to the appropriateness of an antifibrinolytic were included and randomized, while those in which it was "reasonably certain" that an antifibrinolytic was either indicated or contra-indicated were not included [11]. Other studies included patients based on whether they received blood transfusions [18]. Based on this information, we felt it was appropriate to include patients in which hemorrhage leading to hemodynamic instability was documented, or in which they received blood transfusions immediately after admission for hemorrhage, and a more reasonable indication for its administration was not apparent. We did not include those "at risk of significant hemorrhage" due to the difficulty in assessing this retrospectively, and therefore we may not have captured the true *CRASH-2* population. It is possible that if those "at risk" had also been included, the rate of appropriate drug usage may have been even lower than our results demonstrated. Moreover, TXA is commonly used as a bolus in the operating room. Many trauma patients underwent surgeries during their hospital stay, with 8 subjects receiving the drug in the operating room. Whether it was administered for trauma or a peri-operative procedure is not known, and therefore is a definite confounder.

Results of this retrospective analysis have identified care gaps and have implications for future studies. Next steps would be to identify reasons that trauma patients are not receiving TXA, as well as the rationale behind use of alternate dosing regimens. This information can be used for quality improvement initiatives in trauma care, such as revision of pre-printed orders, educational workshops for health professionals and/or quality improvement cycles, both at Royal Columbian Hospital, as well as at other trauma centers in Canada.

5. Conclusions

Less than 10% of presenting adult trauma patients that met indication for tranexamic acid at a tertiary care center received it according to the *CRASH-2* protocol. Of those patients that received tranexamic acid in any form, 76% did so within the recommended 3 h. The results have identified areas for further inquiry to elucidate reasons trauma patients are not receiving tranexamic acid, as well as possible quality improvement initiatives in trauma care centers in Canada.

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Declaration of interest

None.

Appendix A. Tranexamic acid-supplemental information

A.1. Other cautions/contraindications [23]

- History or risk thrombosis
- Acquired colour vision disturbances
- Active arterial/venous thromboembolic disease (deep vein thrombosis, pulmonary embolism, cerebral thrombosis)
- Subarachnoid hemorrhage (reduced risk for re-bleed offset by increase in cerebral ischaemia)
- Haematuria: can lead to development of clots in ureters; few reports of acute renal cortical necrosis with oliguria, and renal failure
- Oral contraceptive use

A.2. Other adverse events [23]

- Dose-related gastrointestinal symptoms
- Hypotension and dizzy
- Ocular/visual disturbances
- Hypersensitivity
- Skin
- MSK pain
- Convulsions

Cautions and contraindications listed above are as per available information on tranexamic acid use, and do not reflect the exclusion criteria for this study.

Appendix B. Inclusion/exclusion additional information

CRASH-2 also had a clinical inclusion criterion:

Included those considered "at risk of significant hemorrhage".

E.g. *compensated hemorrhage and stable vital signs bleeding stopped but might recommence following volume resuscitation* [11].

This clinical inclusion criterion is not included in this study, as the retrospective nature of our research would make this difficult to assess, and possibly confounded. By doing this, we may be excluding patients that may have benefitted from tranexamic acid treatment in our assessment of the outcomes.

CRASH-2 also excluded those with a history of cardiovascular disease, thromboembolic events, bleeding diathesis, renal failure with Cr > 250micromol/L, or those that were pregnant or on anticoagulants [11].

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