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ORIGINAL ARTICLE

Poor adherence to Tranexamic acid guidelines for adult, injured patients presenting to a district, public, South African hospital

Mauvais adhérence aux directives relatives à l'acide tranexamique chez les patients adultes blessés se présentant dans un hôpital de district public sud-africain

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ABSTRACT

Introduction: In South Africa's high injury prevalent setting, it is imperative that injury mortality is kept to a minimum. The CRASH-2 trial showed that Tranexamic acid (TXA) in severe injury reduces mortality. Implementation of this into injury protocols has been slow despite the evidence. The 2013 Western Cape Emergency Medicine Guidelines adopted the use of TXA. This study aims to describe compliance.
Methods: A retrospective study of TXA use in adult injury patients presenting to Khayelitsha Hospital was done. A sample of 301 patients was randomly selected from Khayelitsha's resuscitation database and data were supplemented through chart review. The primary endpoint was compliance with local guidance: systolic blood pressure <90 or heart rate >110 or a significant risk of haemorrhage. Injury Severity Score (ISS) was used as a proxy for the latter. ISS >16 was interpreted as high risk of haemorrhage and ISS <8 as low risk. Linear regression and Fischer's Exact test were used to explore assumptions.
Results: Overall compliance was 58% (172 of 295). For those without an indication, this was 96% (172 of 180). Of the 115 patients who had an indication, only eight (18%) received the first dose of TXA and none received a follow-up infusion. Compliance with the protocol was significantly better if an indication for TXA did not exist, compared to when one did ($p < 0.001$). Increased TXA use was associated only with ISS >15 ($p < 0.001$).
Discussion: TXA is not used in accordance with local guidelines. It was as likely not to be used when indicated than when not indicated. Reasons for this are multifactorial and likely include stock levels, lack of administration equipment, time to reach definitive care, poor documentation and hesitancy to use. Further investigation is needed to understand the barriers to administration.

ABSTRACT

Introduction: Dans l'environnement sud-africain caractérisé par une forte prévalence de blessures, il est impératif que la mortalité liée aux blessures soit maintenue à un minimum. L'essai CRASH-2 a indiqué que l'acide tranexamique (ATX) réduisait la mortalité en cas de blessures graves. L'adoption de cette procédure dans les protocoles de gestion des blessures a été lente, en dépit des données probantes. Les Directives de médecine d'urgence du Cap occidental 2013 ont adopté l'utilisation de l'ATX. L'étude vise à décrire la conformité.
Méthodes: Une étude rétrospective de l'utilisation de l'ATX chez les patients adultes souffrant de blessures et se présentant à l'hôpital de Khayelitsha a été réalisée. Un échantillon de 301 patients a été sélectionné de manière aléatoire dans la base de données de réanimation de Khayelitsha et les données ont été complétées par un examen des dossiers. Le principal paramètre était la conformité aux directives locales: une tension artérielle systolique <90, un rythme cardiaque >110 ou un risque d'hémorragie significatif.

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L'Indice de gravité des blessures (IGB) a été utilisé à titre d'approximation pour ce dernier. Un IGB >16 a été interprété comme un fort risque d'hémorragie et un IGB <8 comme un faible risque. La régression linéraire et la méthode exacte de Fisher ont été utilisées afin d'étudier les hypothèses.
Résultats: Le taux de conformité générale s'élevait à 58% (172 sur 295). Pour ceux ne présentant aucune indication, ce taux s'élevait à 96% (172 sur 180). Sur les 115 patients présentant une indication, seulement huit (18%) avaient reçu la première dose d'ATX et aucun n'avait reçu d'injection subséquente. Le respect du protocole était considérablement meilleur si aucune indication d'ATX n'existait, par rapport à son existence ($p < 0{,}001$). Une augmentation de l'utilisation de l'ATX n'était associée qu'à un IGB> 15 ($p < 0{,}001$).
Discussion: L'ATX n'est pas utilisé conformément aux directives locales. Il était tout aussi susceptible de ne pas être utilisé lorsque cela était indiqué que lorsque cela ne l'était pas. Les raisons en sont multiples et incluent probablement la disponibilité en stock, le manque de matériel d'administration, le temps pour atteindre le lieu de prise en charge définitif, l'absence de documentation et l'hésitation à l'utiliser. Des enquêtes supplémentaires sont nécessaires pour comprendre les barrières à l'administration.

African relevance

- Low- and middle-income countries are heavily burdened by morbidity and mortality caused by trauma.
- Tranexamic acid has been shown to reduce trauma-related mortality.
- This study shows that Tranexamic acid is not administered appropriately when indicated.

Introduction

Globally low- and middle-income regions are burdened by morbidity and mortality due to serious injury [1]. South Africa is no exception, however, matters related to injury morbidity and mortality locally have been largely unexplored. The National Burden of Disease study by Bradshaw, et al. in 2000 found that injuries were South Africa's third leading cause of death (or 12% of all deaths) [2]. Little has changed since then; Statistics South Africa reported in 2013 that injuries contributed to 10% of all deaths – much higher than what would be expected in a high-income country [3]. Unsurprisingly, injury burden at emergency centres (EC) are high. In Cape Town, South Africa's second largest city, as much as 36% of adult presentations are injury related [4].

Coagulopathy, hypothermia and acidosis are considered the three key mechanisms whereby injury leads to death [5]. Coagulopathy has been of particular interest recently due to the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) findings and its recommendation of Tranexamic acid (TXA) use for serious injury [6]. TXA is a synthetic derivative of the amino-acid lysine. It works as an antifibrinolytic agent by binding to plasminogen and blocking the interaction of plasminogen with fibrin, thus preventing lysis of the fibrin clot [7]. In 2010, the CRASH-2 trial provided good evidence that TXA in severely injured patients saves lives, with a relative risk reduction of close to 10% in all-cause mortality, and 15% in haemorrhage related mortality [6]. In the study, injured, adult patients were randomised to receive TXA if they had a systolic blood pressure (SBP) less than 90 mmHg, a heart rate (HR) greater than 110 and/or were at a high risk of significant bleeding. Administration within three hours of the injury showed the largest benefit [6].

The CRASH-2 trial recruited 20,211 patients from 274 hospitals in 40 countries. Of particular interest was that a significant number of participants were drawn from low- and middle-income regions including South Africa. It was the largest ever injury-related, randomised control trial in history and its findings have largely been accepted as fairly robust [6]. The Military Application of TXA in Injury Resuscitation study subsequently confirmed CRASH-2′s findings in a more severely-injured, military sample; it found that TXA administration resulted in more than 6% absolute reduction in mortality compared to controls, despite higher Injury Severity Scores in the TXA-arm [8].

Paradoxically, the uptake of TXA recommendations in global, clinical injury guidelines has been rather slow. For example, the 2012 version of the Advanced Injury Life Support guidance did not include TXA [9]. Using data from the World Health Organisation and the CRASH-2 findings, it was shown that 1189 additional lives could be saved annually in South Africa if TXA was administered within three hours [10]. It was for this reason that the Western Cape Emergency Care guidelines (South Africa) included TXA use for serious trauma in its 2013 guidelines, and is stocked in all local ECs [11]. The aim of this audit was to review the appropriateness of TXA use at a single district, public hospital's EC using the provincial guidelines as a reference standard.

Methods

Data were obtained through a retrospective analysis of an existing database and supplemented through a retrospective chart review. The audit received ethical approval from the human research ethics committee, University of Cape Town. It was conducted at the EC of Khayelitsha hospital – a district, public hospital on the outskirts of Cape Town. Khayelitsha hospital is a 240-bed hospital with a 24-h EC. Its workforce consists of emergency medicine consultants, permanent medical officers, community service medical officers and emergency medicine specialist trainees. The suburb of Khayelitsha houses around 400,000 people, of which 55% live in informal settlements and 74% earn a monthly income of USD 220 or less [12].

The database used for primary data collection was established during the month of November 2014. This database captures various clinical variables via a smartphone application on all patients managed within the resuscitation area of Khayelitsha hospital EC. All patients older than 13-years, who presented with an injury during twelve, randomly selected weeks (randomised using Excel: Microsoft Office, 2016, Redmond, USA) were extracted from this database. A nursing register of patients treated in the resuscitation area was crosschecked to ensure all patients over the selected data collection periods were included. Any missing data were captured through subsequent chart review. Key variables collected included time of arrival, age, SBP and HR at triage, detailed list of injuries, administration of TXA and method of administration. The Abbreviated Injury Score (AIS) was derived from injury variables, and used to calculate the Injury Severity Score (ISS) for each subject. Patients with partially missing data were included for analysis except where analyses involved the specific missing variable.

The main outcome measure was appropriate use of TXA, dependant on the presence or absence of one or more of the three indications for TXA use: SBP $\leq$ 90 mmHg, HR $\geq$ 110, and patients

deemed to be at significant risk of haemorrhage. As it was not possible to retrospectively quantify a significant risk of haemorrhage objectively, we decided *a priori*, to assess the risk of haemorrhage by using the ISS (a measure of severity) as a subjective measure of risk of haemorrhage. The ISS has previously been associated with a need for blood products [5,13]. Patients with an ISS $\leq$8 (low severity) were deemed at low risk of haemorrhage, whilst patients with an ISS $\geq$16 (high severity) were deemed at significant risk of haemorrhage. For the purposes of this audit, an ISS ranging from 9 to 15 (moderate severity) was deemed appropriate whether TXA was used or not. Appropriate TXA use was defined as documented administration of 1 g TXA over ten minutes followed by 1 g given over eight hours. Microsoft Excel was used for analysis. Summary statistics were used to describe all collected variables, including 48-h and 7-day mortality. Overall, compliance with the protocol was calculated for each of the three TXA indications and expressed as proportions. Associations between the indications and TXA administration were tested using linear regression and the Fisher Exact test (STATA: Statacorp, 2015, Texas, USA).

Results

The database yielded 301 injured patients of which six had to be excluded; three patients were incorrectly classified as injured; two patients lacked all required variables and one patient absconded prior to being seen. For the remaining 295 patients, 207 (70%) presented between the hours 20:00 and 08:00; of which 159 (77%) presented between the hours 20:00 and 04:00. The sample consisted of 87% (258/295) male patients. The median values for the remaining variables were: age 27 years (inter-quartile range (IQR) 23–34), HR 92 beats per minute (IQR 80–107), SBP 123 mmHg (IQR 108–140) and ISS 5 (IQR 4–10). Three further patients were excluded from compliance calculations for individual indications as the injury severity was not captured.

Fig. 1 describes the audit's main findings. Overall compliance to the TXA guideline was 58% (172/295). Of the 115 patients who had one or a combination of indications, 21 (18%) received a first dose of TXA. Of the 21 patients who received a correct, first dose of TXA, none received the follow-on infusion. Of the 180 patients who did not have an indication, 172 (96%) did not receive TXA. Tranexamic acid was used significantly more appropriately if an indication did not exist, compared to when one did ($p < 0.001$).

Patients presenting with HR > 109, were less likely to receive TXA (6%, 3 of 50) when compared to SBP < 90 (26.7%, 4 of 15) and ISS >15 (20%, 5 of 25) although this difference was not statistically significant ($p = 0.08$). Linear regression analysis of these subgroups showed that only an ISS >15 was significantly associated with appropriate TXA administration ($p < 0.001$). When subdividing the sample according to ISS, those with an ISS >15 were

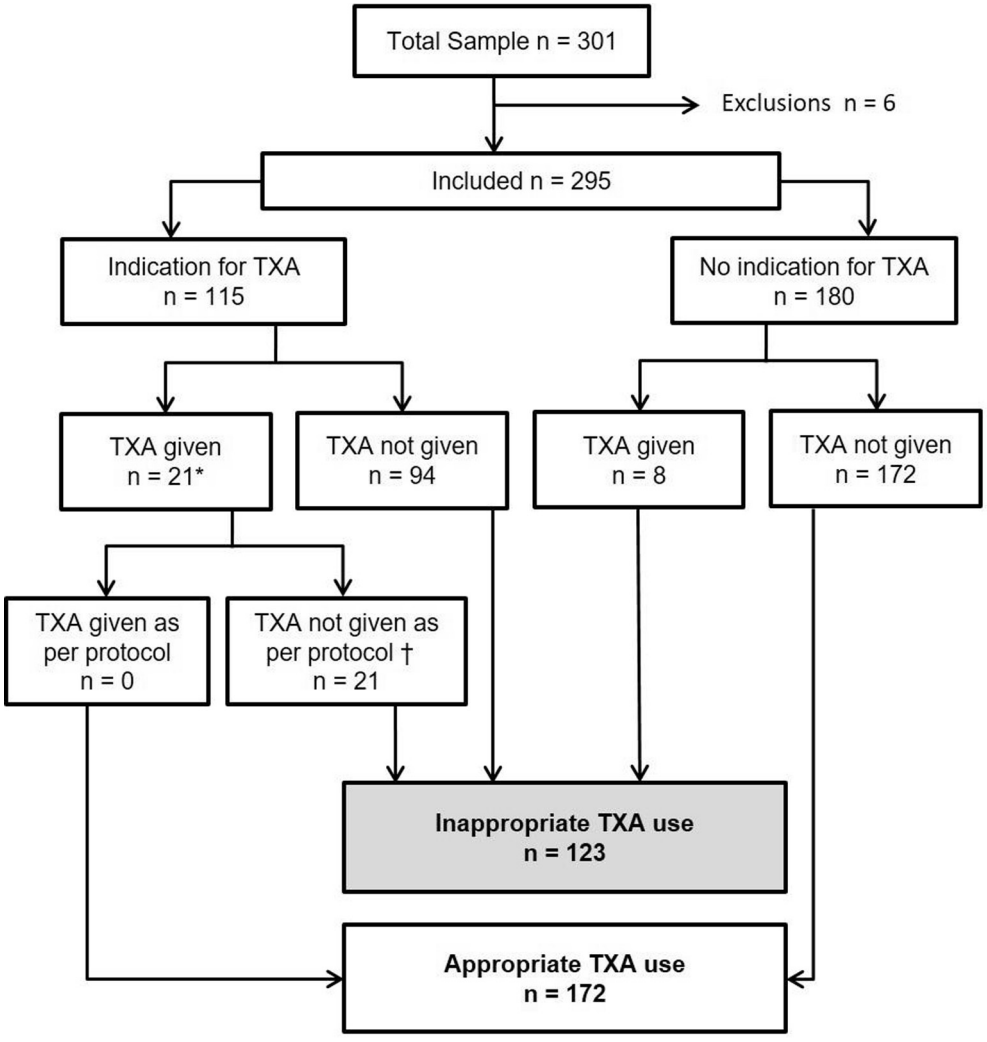

Fig. 1. Audit findings of appropriate TXA use. TXA, Tranexamic acid; *, Includes four patients with only Injury Severity Scores between 9 and 15 that received TXA; †, 1 g stat followed by 1 g over eight hours.

Table 1
Compliance for individual indications (n = 292).

Indication	Patients with indication n (%)	Correctly received TXA n (%)
HR only	50 (17)	3 (6)
HR and SBP	2 (1)	0
HR and ISS	10 (3)	4 (40)
All patients with HR	63 (22)	7 (11)
SBP only	15 (5)	4 (27)
SBP and ISS	7 (2)	0
All patients with SBP	25 (9)	4 (16)
Only ISS	25 (9)	5 (20)
All patients with ISS	42 (14)	9 (21)
HR, SBP and ISS	1 (0)	0

HR, heart rate; SBP, systolic blood pressure; ISS, Injury Severity Score; TXA, Tranexamic acid.

more likely to receive TXA (20%, 5/25), when compared to ISS between 9 and 15 (6.2%, 4 of 65) and ISS <9 (6.8%, 8 of 117) although this difference was not statistically significant (p = 0.17). The 48-h and 7-day mortality were similar, 1.4% (4 of 295). Table 1 presents the patients who appropriately received the first TXA dose. Not a single patient received the follow-on dose. Of the 42 patients with ISS ≥16 as an indication for TXA, nine had head injuries that contributed significantly to the calculation of the ISS. One of these received TXA.

Discussion

Tranexamic acid was not appropriately administered for a significant number of patients who were likely to have indications for use. This was mainly due to TXA not being given for the indications outlined in the local clinical guidelines. Where it was given, only the first dose was given, but no follow-on infusion. The findings suggest that TXA was either not stocked for use, patients took too long to reach the hospital, clinicians were hesitant to use it or clinicians did use it, but simply failed to document this. It was beyond the remit of the retrospective design to correct the findings for stock-levels of TXA at the time of the patient's treatment. Although possible, it seems unlikely that TXA could have been out-of-stock for such a large proportion of the data collection period. The time taken to reach hospital could be a possible reason for the poor adherence; although the EC is situated in an urban area close to a city ambulance base it serves a reasonably sized area, with challenging access as well as a number of primary care referral centres. Anecdotally, delays are commonly experienced. Lack of resources, such as an infusion pump, may have contributed to the lack of administration of the follow-on dose. Although all of these reasons would have influenced TXA use, it would seem unusual to have been the cause of non-usage so often over the data collection period. Unfortunately, there are no data to support any of these assumptions.

The audit suggests a certain degree of hesitancy to TXA's use. The difference between the Western Cape and Advanced Trauma Life Support guidelines might have contributed to this hesitancy [9,11]. Although disappointing, these results are in keeping with TXA use for injury reported elsewhere. A 2015 review, assessing compliance of the 2013 European injury guidelines (that also include TXA use for the CRASH-2 indications) revealed that only 66% of respondents used TXA [14]. And in a tertiary American centre, only 38% of eligible patients received TXA after it was specifically implemented as part of a massive transfusion protocol [15]. Given that Khayelitsha Hospital's EC forms part of a training network for emergency specialist trainees who rotate through another seven emergency medicine specialist-run ECs around the city of Cape Town, it is important to establish whether the findings of this audit are a city-wide phenomenon.

The mortality in this audit was low. This should however, not be seen as a reason why TXA could be omitted. As stated previously, the benefit is of a relative reduction of mortality of around 10% [6]. This means that for every ten injured patients that died not receiving TXA, only nine would have died had they received it. It follows that the impact will be greater if calculated over a longer time and/or citywide. It has to be borne in mind that this study represents the findings of an audit aimed at service improvement. The findings likely reveal the potential for further research to optimise this aspect of trauma care throughout all the city's public ECs.

Abnormal vital signs were significantly less associated with TXA use compared to severe injury as per an ISS >15. Whereas vital signs are objective measures of severity, estimating the risk of severity (and thereby the risk of haemorrhage) is fairly subjective. One of the limitations of this audit was the inability to objectively evaluate the retrospective risk of haemorrhage. Given the association between ISS and haemorrhage, this proxy use of ISS provided a reasonable solution to estimating the risk retrospectively [5,13]. It is important to note, however, that ISS was only calculated for the purposes of this retrospective study. We are not suggesting in any way to incorporate ISS into the protocol of TXA use. Another limitation regarded the small sample – the size renders it impossible to make generalisations of TXA administration for both an extended time interval and TXA use in other public ECs in the region. It would however be disingenuous to disregard the findings, seeing that in all likelihood it suggests a citywide shortfall in injury care. A useful addition to future audits would be time from injury to EC. Although originally included in the proposal, poor record keeping excluded the inclusion of a time variable. Future studies should either be prospective or care needs to be taken to select a retrospective sample that includes this variable. Finally, the use of blood products was not recorded. However, since the use of blood products is commonly used as a prompt for TXA use, future audits should include the use of blood products alongside an evaluation of TXA use.

The mortality benefit of appropriate TXA use is fairly certain and as previously stated has been estimated to substantially reduce mortality due to injury locally [10]. When considering the relatively low cost of TXA compared to other modalities of injury care (i.e. imaging and blood products), it seems imprudent to ignore the findings of this small audit. These suggest barriers to TXA use. The Western Cape Guidelines have taken a step in the right direction including the CRASH-2 findings in the local guideline. This audit has shown that there is likely to be room for improvement regarding TXA use for severely injured patients. Further research is now needed to explore the barriers suggested. Stock levels and administration equipment should be relatively straight forward to address. Substantial prehospital delays to definitive care might suggest that the initial TXA dose be licensed for use by appropriate prehospital providers, as is done elsewhere [16]. Improved record keeping would also go a long way to improve data capture and thus quality of retrospective research. Although currently lacking, an injury surveillance registry will allow clinicians to track quality metrics such as TXA use in order to drive quality of care and evidence-based practice.

Conflicts of interest

Stevan Bruijns is an editor for the African Journal of Emergency Medicine. All peer reviews are performed blinded and the author was not involved with the editing of this paper. The authors declare no further conflict of interest.

Dissemination of findings

SL disseminated findings to the staff at the study site. Results were presented as a poster at the African Conference for Emergency Medicine in Cairo, 2016.

Author contribution

DH and SB conceived the original idea of the study. LH constructed and maintained the database from which the sample was drawn. SL assisted with the implementation of and maintenance of the database. JW did the data collection and analysis. JW drafted the manuscript with input from SB and DH. SB,DH and SL revised the manuscript. JW, LH, SB,DH and SL approved the final version that was submitted.

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