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*Original Article*

# Administration of tranexamic acid in trauma patients under stricter inclusion criteria increases the treatment window for stabilization from 24 to 48 hours-a retrospective review

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**Abstract:** Background: Since 2010, the use of Tranexamic Acid (TXA) in trauma has been brought to the forefront of severe hemorrhage treatment. However, the mixed literature illustrates the need for additional proof of efficacy and determining which patients may benefit from TXA. The purpose of this retrospective study was to evaluate a more stringent TXA inclusion criterion (heart rate ≥ 120 beats per minute (BPM) with a systolic blood pressure (SBP) ≤ 90 mmHg) as compared to the standard CRASH-2 inclusion criteria. Methods: From 2013-2016 a total of 115 patients (control, n = 62; TXA, n = 53) were included in the analysis. These patients adhered to the standard CRASH-2 and more stringent inclusion criteria; they also survived at least 8.5 hrs (minimum amount of time required for full TXA dose) from the initiation. Basic characteristics of the patients were summarized. The mortality rates between TXA and control groups were compared using two proportion z-tests. All $p$ values <0.05 were considered statistically significant. Results: There was no statistical significant difference in patient characteristics between the two treatment groups, making them more comparable ($p$ value >0.05). This study found a significant reduction of percent mortality at the 24 hr time point against the control ($p$ = 0.007). Additionally, utilizing the more strict inclusion criteria (BPM ≥ 120 and SBP ≤ 90) substantially extended time to stabilize patients to 48 hrs ($p$ = 0.029). Conclusion: By imposing the more strict criteria, TXA appears to be a better treatment option in reducing mortality rates and potentially extends the treatment time-frame for stabilizing the patient up to 48 hours.

**Keywords:** TXA, tranexamic acid, trauma, inclusion criteria, hemorrhagic shock

## Introduction

Within the lethal triad of trauma [1], coagulopathy is a common occurrence, present in nearly one in four severely injured patients arriving at the ED. Furthermore, its presence is associated with a four-fold increase in mortality [2-4].

Beginning with the landmark trial, CRASH-2 [5], in the civilian arena, and the MATTERs [6] study, in the military arena, the use of tranexamic acid (TXA) in trauma has been brought to the forefront of severe hemorrhage treatment. The CRASH-2 [7] study defined significant bleeding as either tachycardia ≥ 110 beats per minute (BPM), or systolic blood pressure (SBP) ≤ 90 mmHg, or both, in effect a combination of class II and III hemorrhagic shock [8].

From the publication of these two articles, a plethora of further studies and meta-analysis within trauma were produced (see Binz *et al.* [9] for an overview). Nevertheless, knowledge gaps and associated research priorities were identified regarding TXA within the trauma paradigm [10, 11]. In addition, in a recent United States-based survey, 47.7% of trauma surgeons did not routinely use TXA, and gave "uncertain clinical benefit" [12] as one of the reasons. Of particular interest, Pusateri *et al.* (2013) [10] labeled a "priority 1" category "Additional proof of efficacy and definition of what patients may benefit from TXA".

Thus, the purpose of this retrospective study was to evaluate a more stringent TXA inclusion criterion (≥ 120 BPM in conjunction with a SBP

**Table 1.** Demographics between the control and TXA treated groups

| Characteristics | Control n = 62 | TXA n = 53 | *p* Value |
|---|---|---|---|
| Average age | 41.9 | 41.6 | 0.93[A] |
| ± SD | 18.6 | 18.3 | |
| Sex, % Male (n) | 58.1 (36) | 79.3 (42) | 0.37[B] |
| Average injury severity score | 20.3 | 21.6 | 0.54[A] |
| ± SD | 11.7 | 11.4 | |
| Blunt vs. Penetrating injury, % Blunt (n) | 85.5 (53) | 81.1 (43) | 0.71[B] |
| Average length of stay | 13.8 | 14.7 | 0.73[A] |
| ± SD | 14.4 | 10.2 | |
| Average heart rate | 135.5 | 131.5 | 0.06[A] |
| ± SD | 13.0 | 8.2 | |
| Average systolic blood pressure | 77.0 | 77.3 | 0.87[A] |
| ± SD | 10.6 | 10.0 | |
| Venus thromboembolism % (n) | 17.7 (11) | 13.2 (7) | 0.68[B] |

[A]Continuous variable was tested using two sample t-test. [B]Discrete variable (Proportion) was tested using two proportion z-test. Abbreviation: Standard Deviation (SD).

≤ 90 mmHg) within our trauma patient population focusing upon the first 72 hrs from initial treatment. In the literature, this more stringent criterion is based upon a class III hemorrhagic shock [8] which can be indicative of patients suffering massive blood loss. Out of our total trauma admit volume only 1-3% of patients will require mass transfusion and therefore the most likely TXA candidates within this paradigm; although this can be as high as 16% in military casualties [13].

## Materials and methods

### *Data*

After approval from the Institutional Review Board, non-randomized data was abstracted from our hospital trauma registry between 2013 and 2016. Patient arrival at the hospital is determined as Day 0 and all future time points are relative to this point. CRASH-2 TXA Inclusion Criteria [5] are used by this facility and were utilized; thus all patients could have received TXA under physician discretion if: (i) >16 years old, (ii) no known hypersensitivity to TXA, (iii) no known severe renal failure, (iv) no known history of thromboembolism, (v) patient does not present with aneurismal subarachnoid hemorrhage and (vi) patient is seen (and could have been administered TXA) by qualified medical personnel within 3 hrs of injury.

Additional criteria utilized for this study: (i) All patients survived ≥ 8.5 hrs (minimum amount of time required to administer a full TXA dose), (ii) All patients received at least a single blood product. In this study, we utilized a more stringent criterion of tachycardia ≥ 120 BPM and a SBP ≤ 90 mmHg (as measured at either pre-hospital, upon admission or within the trauma bay), in essence a class III hemorrhagic shock [8]. Further, we excluded isolated injuries such as orthopedic, face and neurosurgical patients.

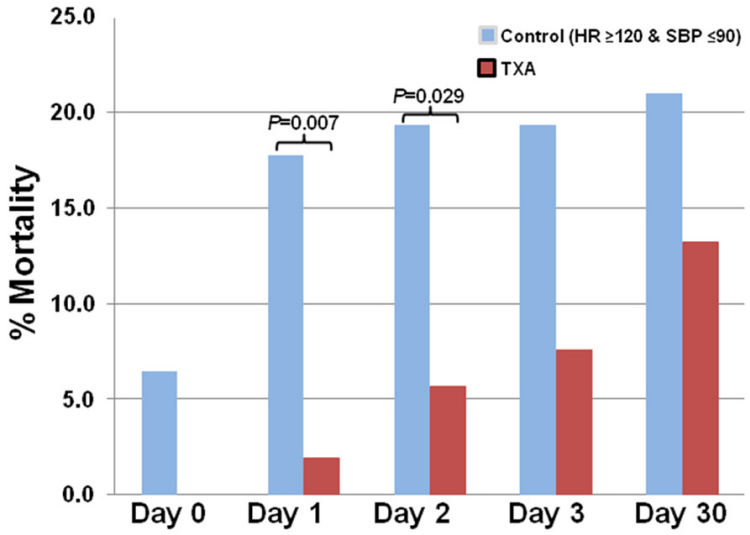
In addition, being a tertiary care facility with a large rural catchment area can prohibit some patient's arriving within our 3 hr administration window and unable to receive TXA, thus were included with the control group.

### *Statistical analysis*

All statistical analyses were performed using freely available statistical software R. Only patients meeting all criteria described above were included in the analysis. Continuous variables were summarized using mean (± SD), categorical variables were presented as relative frequencies. We tested, if mortality rate among patients receiving full TXA was significantly lower than the mortality rate in the control group (without TXA administration), by using the two proportion z-test. All $p$ values <0.05 were considered statistically significant.

## Results

**Table 1** presents basic characteristics of the participants for two groups (Control n = 62 and TXA n = 53). All basic characteristics were statistically equivalent (P>0.05) making two groups comparable. Of particular note, no significant difference was found (p = 0.54) between the ISS scores for control (20.3, SD ± 11.7) and TXA (21.6, SD ± 11.4). The mode of injury was predominantly blunt (Control, 85.5% versus TXA treatment, 81.1% (p = 0.71)) for both groups. Furthermore, the venous thromboembolism (VTE) rate between the two groups was




| % Mortality | | | |
|---|---|---|---|
| **Follow up time** | **Control N=62** | **Full TXA N=53** | ***p* Value** |
| Day 0 | 6.5 | 0.0 | 0.085 |
| **Day 1** | **17.7** | **1.9** | **0.007** |
| **Day 2** | **19.4** | **5.7** | **0.029** |
| Day 3 | 19.4 | 7.5 | 0.060 |
| Day 30 | 21.0 | 13.5 | 0.198 |

**Figure 1.** Cumulative Mortality Rates in Patients who have received a full TXA dose from 2013-2016. Sample size: Control n = 62, and TXA n = 53.

17.7% (n = 11) for the control group versus 13.2% (n = 7) for the TXA group (p = 0.68).

However, all-cause mortality (See **Figure 1**) was significantly reduced by 15.8% at 24 hrs ($p$ = 0.007) and by 13.7% at 48 hrs ($p$ = 0.029) with the initiation of TXA dosing [5] within 3 hrs of injury [14] coupled with the stricter inclusion criteria.

In addition, the predominant increase in mortality for the control group (270%) is within the first 24 hrs (up to Day 1). Conversely, the lowest mortality rate of change for the TXA group is within the first 24 hrs from time of injury and the greatest increase in mortality is observed at the day 30 point, where there is a 180% increase.

## Discussion

The goal was to examine our TXA use in trauma, determine which of our patients benefited and when. In our data, we see a difference at the 24 hr time point against the control, as previously reported [6, 15] however, using the more strict inclusion criteria (BPM ≥ 120 and SBP ≤ 90) extends survivability to 48 hrs. The overall mortality in the Control group of this study was 21%; our data is supported by the literature, with a range of 18.7%-23% [16, 17] mortality rates amongst similarly critically ill patient groups is observed. Of note, although statistical analysis calculations indicate no significant difference in heart rate between the control and treatment group ($p$ = 0.06), the authors recognize there is a 3% marginal difference. This may be due to variance in staff technique, collection times (pre-hospital, admit, and within the emergency room) or heart rate monitoring devices.

Interestingly, using a different (compared to CRASH-2) TXA dosage methodology the MATTERs study [6] found no difference in mortality between the TXA and no-TXA groups until the 48-hour point, a time at which bleeding is less likely to be the primary cause of death [18]. Morrison *et al.* (2012) suggested that a beneficial mechanism other than hemostasis may be present and although hemostasis is important at and beyond 24 hours, they proposed that attenuation of the inflammatory response may play a role in the survival benefit associated with TXA [6]. The role of TXA within the inflammatory response has been shown in the case of cardiopulmonary bypass surgery, where Jimenez *et al.* (2007) demonstrated that TXA diminishes the development of the inflammatory response and vasoplegic shock [19]. However, we see (**Figure 1**) in the control group the greatest increase in percent mortality within the first 24 hrs; whereas in the TXA treatment group we see the lowest mortality within the first 48 hrs and only see an equivalent mortality increase, to that of the control, at Day 30. Similarly, an exploratory reanalysis of the CRASH-2 trial da-

ta by Roberts *et al.* (2014) showed administration of TXA appears to reduce mortality primarily by preventing exsanguination on the day of the injury [20].

Other than those stipulated in the CRASH-2 study [5], despite the numerous studies and reviews for the use of TXA in trauma there are still no additional patient guidelines. From this we know using CRASH-2 guidelines benefits patients at day 30 by reducing all-cause mortality by 1.5% (or approximately 1 in 67) [5]. Furthermore, published work has clearly shown TXA use in trauma is not a panacea [21], nor should it be used outside of the CRASH-2 3-hour time-frame [22] and as such there are several ongoing randomized trials involving TXA [9].

## Conclusions

In essence, the introduction of the full TXA dose within these proposed, more stringent inclusion criteria described in this study potentially extends the treatment time-frame for stabilizing the patient from 24 hours up to 48 hours.

## Limitations

This study was a non-randomized, retrospective, observational, single-center study, so there may have been a selection and/or surveillance bias. Utilizing the more stringent criterion impacts our *n* number; therefore averaged across the 3 years, the data represents only 8.9% (± 2.3) of our full trauma team activations.

For non-assessed variables, the patients may not necessarily match because although there is a hospital TXA protocol, the TXA was given at the attending surgeon's discretion, other factors may have determined the need for the TXA. Nonetheless, no statistical method can truly substitute for a randomized control trial.

## Disclosure of conflict of interest

None.

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