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Unjustified Administration in Liberal Use of Tranexamic Acid in Trauma Resuscitation

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ABSTRACT

Background: Early administration of tranexamic acid (TXA) has been widely implemented for the treatment of presumed hyperfibrinolysis in hemorrhagic shock. We aimed to characterize the liberal use of TXA and whether unjustified administration was associated with increased venous thrombotic events (VTEs).

Methods: We identified injured patients who received TXA between January 2016 and January 2018 by querying our Level 1 trauma center's registry. We retrospectively reviewed medical records and radiologic images to classify whether patients had a hemorrhagic injury that would have benefited from TXA (justified) or not (unjustified).

Results: Ninety-five patients received TXA for traumatic injuries, 42.1% were given by emergency medical services. TXA was considered unjustified in 35.8% of the patients retrospectively and in 52% of the patients when given by emergency medical services. Compared with unjustified administration, patients in the justified group were younger (47.6 *versus* 58.4; $P = 0.02$), more hypotensive in the field (systolic blood pressure: 107 ± 31 *versus* 137 ± 32 mm Hg; $P < 0.001$) and in the emergency department (systolic blood pressure: 97 ± 27 *versus* 128 ± 27; $P < 0.001$), and more tachycardic in emergency department (heart rate: 99 ± 29 *versus* 88 ± 19; $P = 0.04$). The justified group also had higher injury severity score (median 24 *versus* 11; $P < 0.001$), was transfused more often (81.7% *versus* 20.6%; $P < 0.001$), and had higher in-hospital mortality (39.3% *versus* 2.9%; $P < 0.001$), but there was no difference in the rate of VTE (8.2% *versus* 5.9%).

Conclusions: Our results highlight a high rate of unjustified administration, especially in the prehospital setting. Hypotension and tachycardia were indications of correct use. Although we did not observe a difference in VTE rates between the groups, though, our study was underpowered to detect a difference. Cautious implementation of TXA in resuscitation protocols is encouraged in the meantime. Nonetheless, adverse events associated with unjustified TXA administration should be further evaluated.

The study was presented as a podium presentation at the 14th Academic Surgical Congress on February 6, 2019, in Houston, TX.

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Background

Hemorrhage is the leading cause of preventable death after injury; thus, early control of hemorrhage can be lifesaving.[1] The tenets of hemorrhage control include early surgical control and adequate blood product transfusion.[2] This prevents ongoing blood loss, restores volume status, and avoids the development of coagulopathy.[3] Trauma-induced coagulopathy also refers to the hyperfibrinolysis process that hinders bleeding control and clot formation and accelerates exsanguination.[4] Tranexamic acid (TXA) is a lysine analog that arrests fibrinolysis by binding plasminogen. It, hence, promotes the ability to sustain formed clots.[5,6] The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH 2) trial was a landmark international study that showed statistically significant improvement in the rates of both overall mortality and in hemorrhage-caused mortality as a result of early administration of TXA.[7] The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation study further supported these results retrospectively in the military setting.[8] These results led to the widespread incorporation of TXA in damage control resuscitation and transfusion protocols widely. Subsequently, an interest in prehospital administration also spiked. Although TXA is not included within the national scope of practice models for paramedics,[9] several prehospital medical providers nationally began administering TXA when hemorrhage is suspected, often in response to local or statewide endorsements.

Despite this widespread use of TXA, routine TXA use in the United States has called into question whether the immediate availability of blood products and operating rooms overrides any benefits derived from TXA in civilian trauma centers.[10] Additional investigations using thrombelastography have also demonstrated that nonselective administration of TXA to trauma patients with physiological fibrinolysis is associated with increased mortality.[11]

We aimed to describe the rate of nonbeneficial administration of TXA secondary the widespread use. Furthermore, we explored the association between this unjustified administration and adverse events, including venous thromboembolism incidents.

Methods

This is a descriptive study of rates of unjustified administration of TXA in trauma patients. Our trauma system's protocols, including local prehospital protocols, recommend administering TXA within 3 h of injury for signs of the presence of impending hemorrhagic shock (hypotension, clinical suspicion of major hemorrhage, with initiation of massive transfusion protocol). After constructing the study concept, we obtained an institutional review board approval before collecting the data, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and in compliance of local state law. The institutional review board waived the informed consent requirement for this study because of the retrospective nature of data collection. The trauma registry at Rhode Island Hospital started recording TXA administration, both in prehospital settings and within the hospital, in January 2016. Concurrently, the trauma division started a quality improvement protocol where all patients who received TXA had a duplex study of the lower extremities 1 wk after admission or before discharge if the length of stay was <1 wk. We queried the registry for all adult patients who received TXA between January 2016 and January 2018, either from emergency medical services (EMS) personnel in the field or from hospital personnel on arrival to the trauma center. All patients received TXA per local protocols. We excluded patients who received TXA after the first day of admission in the hospital stay as part of bleeding prevention practices in orthopedic surgery. We reviewed prehospital EMS run sheets to abstract data on the type of transporting unit. Reviewing the electronic medical records, we collected data on demographics, past medical history, including history of anticoagulation, injury pattern and severity (using injury severity score [ISS]), presence of major hemorrhage, need for operation for hemorrhage control, venous thromboembolic events, length of stay, discharge disposition, and mortality.

We defined major hemorrhage per computed tomography findings of torso injuries and bleeding, operative findings of laparotomies, thoracotomies, vascular repair, or management of soft tissue injuries, or based on orthopedic injury patterns that are associated with significant bleeding. Each medical record was reviewed by three providers—an attending trauma surgeon, a senior surgical resident, and an emergency medicine resident—to determine whether the patient, in fact, had a major hemorrhagic injury that would have benefited from TXA administration. Disagreements were resolved by discussion. If the reviewers determined that given the entirety of information available at the end of the patient's care, that the patient had no hemorrhagic injuries, then TXA administration was considered nonbeneficial for the degree of injury and that administration was labeled "unjustified." If the opposite was true, then the administration was labeled "justified." The operational definition of unjustified administration in our analysis is thus subjective.

However, as local prehospital protocols provide standing orders for TXA administration for patients "considered in paramedic judgment to be at high risk of significant hemorrhage (external or internal)," the basis for many instances of TXA administration is also subjective. Thus, we determined it was preferable to label administration as "unjustified" because unindicated might imply a protocol violation and nontherapeutic might imply that an assessment of fibrinolytic status was made, such as viscoelastic hemostatic assays. Viscoelastic assays were not routinely performed in our institution for all injured patients at the time of this analysis. In fact, we believe that all administrations were *indicated* per our local protocols. However, some might not be found eventually to be useful, or justified. In other words, none of the patients in the "unjustified" group had a major hemorrhage that TXA would have played a beneficial role in its management.

Venous thromboembolic events were determined either by surveillance duplex ultrasound, clinical findings, or other confirmatory imaging modalities. We explored incidents of

Table 1 — Characteristics of patients in the analytic sample, including demographics, past medical history, physiological parameters, and injury severity.

Characteristic	All patients	Justified administration	Unjustified administration	P value
Total patients	95	61 (64.2%)	34 (35.8%)	
TXA given by EMS	40	19 (47.5%)	21 (52.5%)	
Age (mean ± SD)	51.4 ± 21	47.6 ± 20	58.4 ± 20.8	0.02
Race				NS
White	69 (72.6%)	42 (68.9%)	27 (79.4%)	
African American	7 (7.4%)	7 (11.5%)	0 (0%)	
Other	19 (20%)	12 (19.7%)	7 (20.6%)	
Male gender	71 (74.7%)	47 (77.1%)	24 (70.6%)	NS
VTE history	4 (4.2%)	2 (3.3%)	2 (5.9%)	NS
Anticoagulation use	11 (11.6%)	7 (11.5%)	4 (11.8%)	NS
Anticoagulation reversal	8 (72.7%)	6 (85.7%)	2 (50%)	NS
Cancer history	5 (5.3%)	3 (4.9%)	2 (5.9%)	NS
Smoking	33 (34.7%)	22 (36.1%)	11 (32.4%)	NS
Alcohol use	7 (7.4%)	4 (6.6%)	3 (8.8%)	NS
Drug abuse	14 (14.7%)	9 (14.8%)	5 (14.7%)	NS
Prehospital SBP (mean ± SD)	119 ± 35	107 ± 31	137 ± 32	<0.001
Prehospital hypotension (SBP ≤ 90, %)	20 (26.3%)	18 (40%)	2 (6.5%)	0.001
Prehospital HR (mean ± SD)	94 ± 21	93 ± 24	95 ± 19	NS
Prehospital tachycardia (HR ≥ 100, %)	23 (35.9%)	16 (42.1%)	7 (26.9%)	NS
ED SBP (mean ± SD)	108 ± 31	97 ± 27	128 ± 27	<0.001
ED hypotension (SBP ≤ 90, %)	35 (37.2%)	31 (51.7%)	4 (11.8%)	<0.001
ED HR (mean ± SD)	95 ± 26	99 ± 29	88 ± 19	0.04
ED tachycardia (HR ≥ 100, %)	36 (38.3%)	28 (46.7%)	8 (23.5%)	0.03
GCS, median (IQR)	15 (9-15)	13 (3-15)	15 (15-15)	<0.001
PRBC transfusion	56 (59.6%)	49 (81.7%)	7 (20.6%)	<0.001
ISS, median (IQR)	17 (10-26)	24 (17-29)	11 (5-16)	<0.001
ED to operating room	54 (56.8%)	45 (73.8%)	9 (26.5%)	<0.001

GCS = Glasgow Coma Score; HR = heart rate; NS = nonsignificant; PRBC = packed red blood cells.

deep venous thrombosis, pulmonary embolism, myocardial infarction, and strokes. All patients followed local protocol for venous thrombotic event (VTE) prophylaxis. Chemoprophylaxis was started on first hospital day or 24 h after control of hemorrhage.

Descriptive data are presented as frequencies for categorical variables, means for parametric continuous variables, and medians for nonparametric continuous variables. We applied Pearson's chi-square test with Fisher's exact test for sparse values to test independence for categorical data. Parametric continuous data were compared using Student's *t*-test. Nonparametric data were analyzed using the Mann–Whitney test. Significance was set at $P = 0.05$. We completed all analyses using Stata/SE statistical software, version 14.0, for Windows 10 (copyright 1985-2015; Stata Corp LP, College Station, TX).

Results

We identified 144 patients in our trauma registry as having received TXA between January 2016 and January 2018. Of those, 49 were administered TXA electively by orthopedic spine surgery and were therefore excluded. Our analytical sample included 95 patients. Characteristics of our cohort are presented in Table 1. Forty patients (42.1%) received TXA by EMS before arrival to the emergency department (ED), and 55 patients were given TXA by the ED. Sixty-one patients (64.2%) had a major hemorrhage, rendering the administration justified. We could not identify a hemorrhagic injury in 34 patients (unjustified administration). Most of the unjustified administration was initiated in the prehospital setting by EMS providers (21/34 patients; Fig. 1).

Patients in the justified administration group had higher rates of hypotension and tachycardia, both in the prehospital setting and in the ED, compared with those whose TXA administration was not justified. In addition, they also required blood transfusion more often, were more likely to need operative intervention, and were found to have a higher ISS. Figure 2 illustrates the rates of justified and unjustified prehospital administration based on administering providers. Further breakdown per prehospital transportation mode is shown in Table 2. Notably, there was a significant difference in the rates of unjustified TXA administration between helicopter and ground-based EMS (14.3% *versus* 60.6%; $P = 0.03$). There was a small number of patients with VTE in each group, and

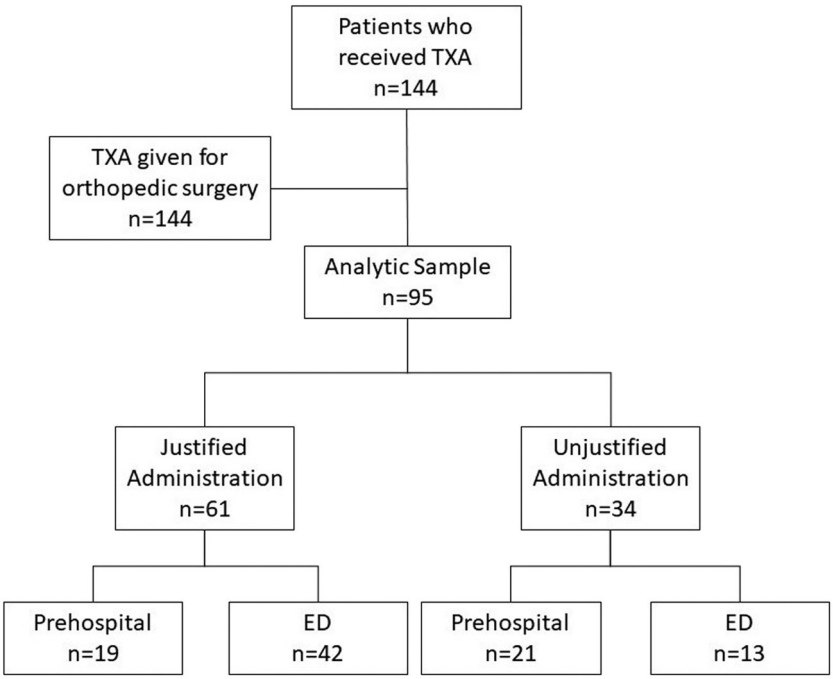

Fig. 1 – Diagram illustrating the selection of our analytic sample and comparison groups.

the difference was not statistically significant. However, the patients with justified administration had higher rate of intensive care unit (ICU) admission, longer ICU length of stay, and higher rate of in-hospital death (Table 3).

Power analysis

For the observed rates of VTE in both groups in our sample, the power was only 10.4%. To evaluate statistical difference ($\alpha = 0.05$) in VTE rates between the two groups assuming the current rates are true with a power of 80%, we would have needed about 1600 patients in our sample.

Discussion

In this early assessment of TXA administration at our center and by EMS transporting patients from our wide catchment area, we identified a significant rate of unjustified administration, especially by ground-based EMS. However, because of small sample size and low overall incidence of VTE, we were underpowered to detect a statistically significant difference in rates of VTE between the two groups.

CRASH-2 trial was a multicenter multinational study that enrolled 20,000 trauma patients to either receive TXA or placebo. The TXA group had improved rates of overall mortality and mortality from hemorrhage.[7] However, the effect size was small. The absolute risk reduction was only 0.8% for hemorrhage-caused mortality with a calculated number needed to treat of 125 patients. The CRASH-2 study did not show differences in VTE rates; however, heterogeneity in practice and data collection limited these results. Nonetheless, the reported improved mortality encouraged trauma centers worldwide to implement TXA as part of the damage control resuscitations, and TXA became an important element in massive transfusion protocols. Subsequently, CRASH-3 trial collaborators recommended TXA administration in traumatic brain injury, despite significant limitations of the trial.[12] Compared with in-hospital settings, the lack of a standardized tool, such as viscoelastic assays, that correctly identifies prehospital patients who are at risk of progressing to a severe hemorrhage with hyperfibrinolysis has resulted in protocols with low cutoffs to administer TXA. Locally, similar to many other states, EMS protocols in Rhode Island recommend TXA for any trauma patient who is hypotensive or tachycardic or if the EMS provider suspects hemorrhage.[13] These criteria, which include clinical gestalt, lack adequate specificity for identifying patients who would benefit from prehospital TXA. For example, patients with other suspected causes of hypotension such as tension pneumothorax have been treated with TXA rather than emergent needle decompression because of presenting hypotension and tachycardia that immediately improved with needle decompression followed by tube thoracostomy. In many similar cases, the indications for TXA are transient and resolve with appropriate management of the inciting cause.

Previously, a review of early integration of TXA in prehospital protocols of injured patients in the Israeli military showed a 30% rate of administration without a clear indication.[14] In the CRASH-2 trial, only 50% of the patients required blood transfusion, and patients received only two units of packed red cells on average. In other retrospective studies, there is no mention whether TXA use was appropriate. The lack of classification of unjustified administration in the

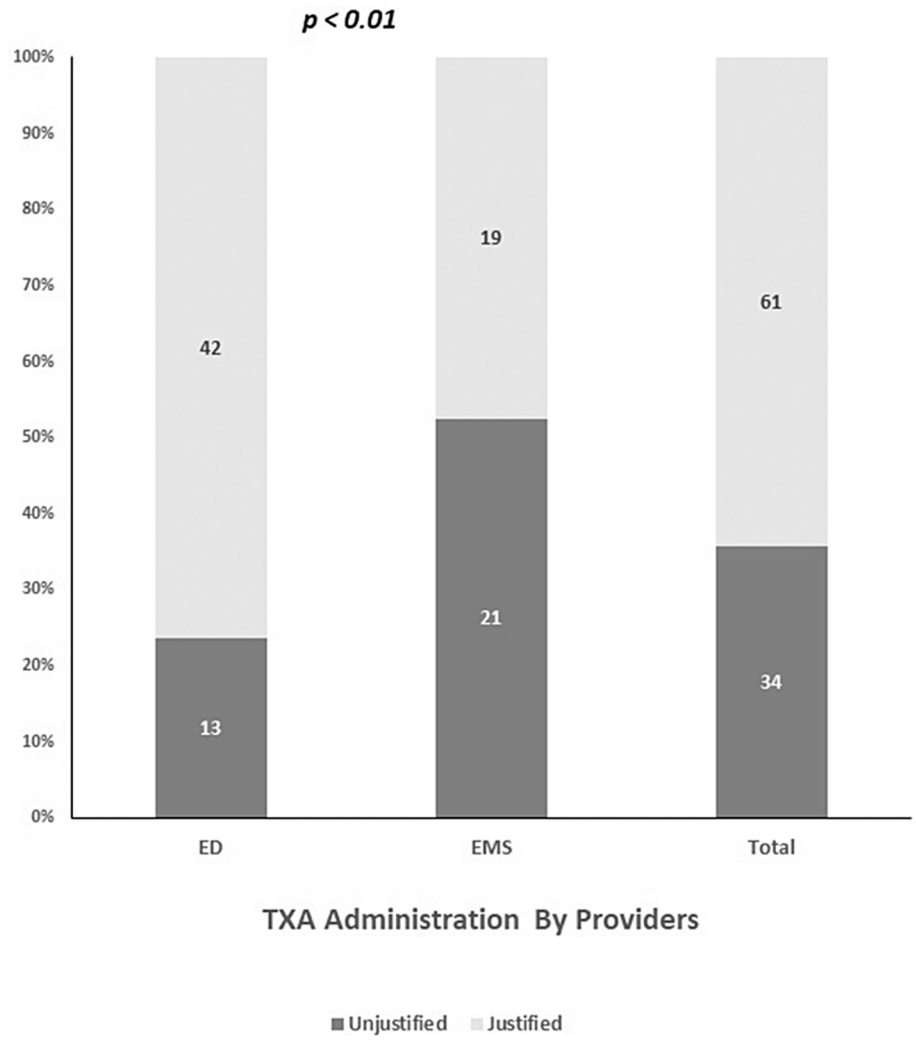

Fig. 2 – Rates of justified and unjustified administration by administering provider.

literature so far potentially adds an unmeasured confounder to the results of these studies and, therefore, to their interpretations and generalizability. This further demonstrates the importance of correct identification of patients who are at risk of severe hemorrhage with hyperfibrinolysis. The Prehospital Antifibrinolytics for Traumatic Coagulopathy & Hemorrhage trial, sponsored by the ANZICS group, looks to evaluate the efficacy of prehospital administration. They use the COAgulopathy in Severe Trauma score to help prehospital providers determine when it is appropriate to administer TXA using a score of more than 3 (*ClinicalTrials.gov Identifier: NCT02187120*). The score was previously validated to predict traumatic coagulopathy using prehospital observations in Australia.[15] However, it is not clear if this can be generalized to other patient populations such as the United States or Europe. In addition, the integration of early, rapid thromboelastogram results may represent a more precise method for identifying patients with hyperfibrinolysis who would benefit from TXA;

Table 2 – Rates of unjustified administration of TXA by provider and mode of transportation.

Prehospital provider	All patients	Justified administration	Unjustified administration
TXA given in ED	55	42 (76.4%)	13 (23.6%)
TXA given by EMS	40	19 (47.5%)	21 (52.5%)
Ground transportation	33 (82.5%)	13 (39.4%)	20 (60.6)
Helicopter	7 (17.5%)	6 (85.7%)	1 (14.3%)

Table 3 – Outcomes of TXA administration per justified *versus* unjustified administrations.

Outcomes	All patients	Justified administration	Unjustified administration	P value
DVT/PE	7 (7.4%)	5 (8.2%)	2 (5.9%)	NS
ICU admission	68 (71.6%)	50 (82%)	18 (52.9%)	0.003
ICU length of stay (d)	4 (2-8)	5 (2-15)	3 (2-5)	0.04
ED death	2 (2.1%)	2 (3.3%)	0 (0%)	NS
Hospital death	25 (26.3%)	24 (39.3%)	1 (2.9%)	<0.001

DVT = deep vein thrombosis; NS = nonsignificant; PE = pulmonary embolism.

however, this has not yet been adequately studied or validated. Although viscoelastic hemostatic assays, including rotational thrombelastometry and thrombelastography, have been studied in the setting of prehospital aeromedical transport, they failed to produce reliable results during in-flight conditions and are not routinely available for ground-based transport in the prehospital setting.[16,17] In addition, although point-of-care coagulometry has been used in physician-based EMS to reliably assess and interpret international normalized ratio during prehospital care,[18] similar capabilities are not yet available in the United States.

The role of prehospital TXA might be further limited by the impact of the timing of administration. TXA has the largest impact on mortality when administered <1 h after injury[7] but was shown to reduce mortality up to 3 h after injury. Therefore, if the correct indication cannot be reliably determined in the prehospital setting, the administration could be withheld until hospital arrival. For the majority of patients, as long as the transport time is <3 h and preferably <1 h, deferring TXA administration until ED arrival would still be beneficial. Even in rural regions where prolonged transport time might unduly delay administration, the use of online medical control through established emergency communication systems by EMS may decrease the rates of unjustified administration and subsequent potential adverse events. A further evaluation of the role of transport time and online medical control should be investigated.

Although our study did not show a difference in VTE rates, we believe that this is because of three factors. Our sample size was small, and therefore, our study had a low power to detect a difference. There is information bias since patients who turned out not to need TXA were discharged earlier; therefore, they were more likely to have a negative duplex study or develop symptoms of VTE while inpatient. It is unknown whether they developed thrombosis postdischarge and whether this was clinically significant. Finally, patients who indeed needed TXA had higher injury severity profile resulting in higher risk of VTE, likely eliminating a significant difference between the two groups. A better evaluation of the association of TXA administration with VTE requires uniformly screening all patients for VTE. At our institution, we limited this screening to patients who received TXA or if they developed symptoms concerning for VTE. Indeed, data from the University of Pittsburgh showed a threefold increase in the rate of VTE events because of TXA administration.[19]

Nonetheless, our results raise two major considerations. There is significant danger in eagerly adopting new therapies without a thorough assessment of risks. Similar trends were previously observed in the use of Drotrecogin alfa (Xigris) in sepsis and tight glycemic control in critically ill patients.[20,21] The Gartner's hype cycle is used to illustrate similar behaviors in the technology world.[22,23] Such nonmedical examples include the hype around cryptocurrency or the laboratory startup firm Theranos. All turned out to not be as lucrative as initially thought, despite large endorsements. Similarly, the hype cycle can explain the adoption of new medical treatment and the dangers of the associated inflated expectations.[24,25] In addition, this study shows the importance to consider the appropriateness of administration as a variable when retrospectively comparing outcomes between patients who received TXA and those who did not. The description of unjustified administration has not been previously reported in the literature. This might have presented a confounding in the results of some of the retrospective studies if patients received TXA without a major hemorrhage to justify it. Therefore, this should be considered in future analyses. Efforts to identify the patients who are at high risk of complications from receiving TXA, similar to the work by the investigators at the University of Colorado[11] and the University of Pittsburgh,[19] should also be encouraged.

A limitation of our study is the subjective definition of unjustified administration. Although this introduces bias, we made every effort to independently review and confirm when an unjustified administration was identified. Nonetheless, the higher ISS, need for emergent operative intervention, need for blood transfusion, presentation with shock, higher rate of ICU admission, and the higher mortality in the justified group provide some validation of our subjective assessment. We also believe that it is very valuable to address this problem both to be able to identify patients more appropriately and from a health policy standpoint, as a feedback loop to state legislators. We did not include data on prehospital transport time to avoid the risk of information bias because of missing values. Such information would be helpful in interpreting appropriateness of TXA administration. Furthermore, we did not distinguish between those who received both doses of TXA versus only the first dose only. This could serve two roles: withholding the second dose could be a surrogate to the provider's realization that the first dose was not justified. There also could be differences in the risk of VTE between those who received the two doses versus only one dose, therefore decreasing the risk concerns associated with more liberal administration of TXA in prehospital settings.

Conclusion

Widespread interest in TXA in trauma patients could lead to a high rate of an unjustified administration. The safety profile of this inadvertently unjustified administration needs to be further studied. Improving criteria for the prehospital identification of bleeding patients who would benefit from TXA should be developed and evaluated. These results are crucial to fine-tuning trauma system policies and improving the outcomes of injured patients. We strongly recommend tracking the rates of unjustified administration as a quality improvement metric in other trauma systems and centers to provide wider understanding of the problem and reduce potential negative effects.

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Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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