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Review Article

EVALUATION OF TRANEXAMIC ACID AND CALCIUM CHLORIDE IN MAJOR TRAUMAS IN A PREHOSPITAL SETTING: A NARRATIVE REVIEW

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ABSTRACT—Excessive blood loss in the prehospital setting poses a significant challenge and is one of the leading causes of death in the United States. In response, emergency medical services (EMS) have increasingly adopted the use of tranexamic acid (TXA) and calcium chloride ($CaCl_2$) as therapeutic interventions for hemorrhagic traumas. Tranexamic acid functions by inhibiting plasmin formation and restoring hemostatic balance, while calcium plays a pivotal role in the coagulation cascade, facilitating the conversion of factor X to factor Xa and prothrombin to thrombin. Despite the growing utilization of TXA and $CaCl_2$ in both prehospital and hospital environments, a lack of literature exists regarding the comparative effectiveness of these agents in reducing hemorrhage and improving patient outcomes. Notably, Morgan County Indiana EMS recently integrated the administration of TXA with $CaCl_2$ into their treatment protocols, offering a valuable opportunity to gather insight and formulate updated guidelines based on patient-centered outcomes. This narrative review aims to comprehensively evaluate the existing evidence concerning the administration of TXA and $CaCl_2$ in the prehospital management of hemorrhages, while also incorporating and analyzing data derived from the co-administration of these medications within the practices of Morgan County EMS. This represents the inaugural description of the concurrent use of both TXA and $CaCl_2$ to manage hemorrhages in the scientific literature.

KEYWORDS—Hemorrhage; EMS; ambulance; hemostasis; coagulation

INTRODUCTION

A significant cause of preventable death worldwide is trauma (1), and of the casualties in the prehospital setting, 91% of the deaths were associated with a source of bleeding (2). Furthermore, 20% of hemorrhagic prehospital deaths had potentially survivable injuries (3). Therefore, the management and treatment of prehospital hemorrhages are of great concern among emergency service providers along with higher-level providers, such as emergency department physicians and trauma surgeons. While both tranexamic acid (TXA) and calcium chloride ($CaCl_2$) play essential roles in managing hemorrhage, their functions are complementary rather than overlapping. Tranexamic acid prevents clot breakdown, while calcium contributes to clot formation. It is worth noting that although these agents act in different stages of the coagulation process, their combined use could potentially provide a synergistic effect in the management of traumatic hemorrhage (Fig. 1), which warrants further investigation. There is a substantial lack in the literature examining the combination of TXA and calcium in either the clinical or preclinical settings. As TXA and $CaCl_2$ are becoming more widely used in the treatment of hemorrhage, it is important to understand what literature exists and the data that support their use. Furthermore, it is vital to understand the limitations to the existing work and find avenues forward in continuing to validate treatment protocols.

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MATERIALS AND METHODS

A PubMed and MEDLINE search was conducted from January 1, 2010, to January 1, 2023, using search terms "tranexamic acid," AND "hemorrhage," AND "pre-hospital" (46 articles) to assess primary literature involving the use of TXA in the prehospital setting. The same search criteria were used for calcium use in prehospital hemorrhages by replacing "tranexamic acid," with "calcium" (23 articles). Inclusion of full text articles and exclusion of text that contained only abstracts, comments, or newsletters were excluded. Terms "subarachnoid" and "intracerebral" and "traumatic brain injury" were eliminated to remove articles focused strictly on stroke and subarachnoid hemorrhages. In addition, cardiac arrests were excluded because of the vast differences in treatment protocols and the use of calcium for cardiac arrhythmias rather than for hemorrhages. Supplemental material, editorial letters, protocols, and duplicated publications were also excluded from the search process. We also excluded articles specific to dosing, administration, and other pharmacokinetic evidence due to the research not aligning with the aim of this literature review. A schema of our study strategy is depicted in Figure 2. When searching for the use of both TXA and calcium with search terms described previously, no scientific articles were found, further highlighting the need for additional research in the prehospital administration of TXA and calcium (Figs. 3 and 4). Two authors (K.B., C.S.) conducted independent screening of articles for inclusion based on our search criteria for both agents of interest. Differing selections were resolved through discussion, and a third author (S.C.) was consulted if needed.

Deidentified patient data were obtained from Morgan County EMS through Electronic Health Records for Emergency Services (ESO) following the approval of an IRB #15960 (IUSM-Canfield). Patient health information, including patients' age, sex, and vital signs before and after treatment with TXA and $CaCl_2$ after major trauma, was assessed. Data variables including mechanism of injury, heart rates (HRs), systolic blood pressures (SBP), and end-tidal carbon dioxide ($ETCO_2$) were compared with patients treated with TXA versus TXA with $CaCl_2$. Patients who did not have an $ETCO_2$ were excluded from the results (Table 2).

RESULTS: CURRENT EVIDENCE

Tranexamic acid

Tranexamic acid is an antifibrinolytic that has been shown to stabilize blood clots by competitively binding to the lysine binding site on plasminogen and preventing its conversion to plasmin (4), thus preventing thrombolysis and resulting in reduced bleeding. Because there is less clot turnover, TXA is theorized to

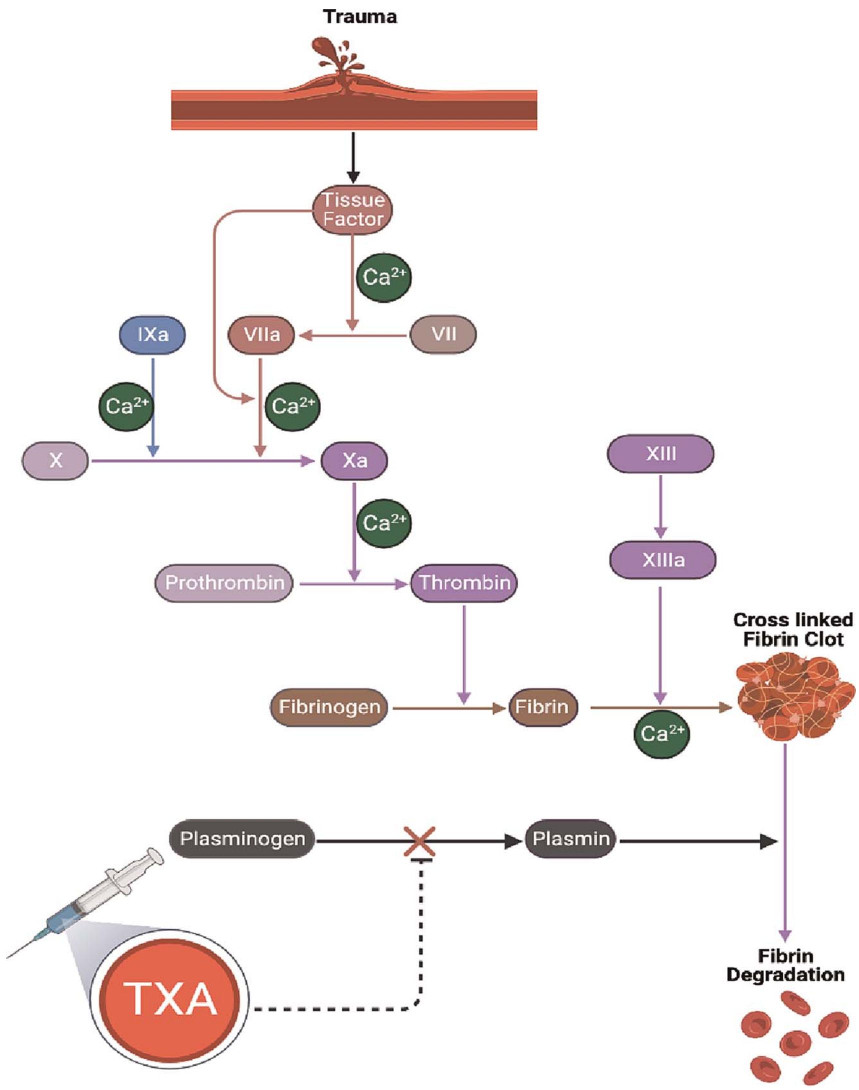

Fig. 1. **Synergistic effect of tranexamic acid and calcium on coagulation cascade in hemorrhagic traumas.** The figure illustrates the coagulation cascade highlighting the synergistic action of TXA and calcium in the process of clot formation. Tranexamic acid is shown to stabilize the fibrin clot by inhibiting the plasminogen activation, whereas calcium is depicted to enhance the efficiency of several clotting factors. Thus, the combined use of TXA and calcium is presented as a potentially effective strategy in the management of hemorrhagic traumas (created with BioRender.com). TXA, tranexamic acid.

reduce the depletion of clotting factors and reduce consumptive coagulopathy (5).

Tranexamic acid was received enthusiastically in the United States following the publication of two seminal studies, MATTERS and CRASH-2 (4). Currently, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2, or the CRASH-2 study, is the only large randomized clinical trial to date that assessed the efficacy of the use of TXA in the trauma setting. The randomized double-blinded study assessed 20,200 patients from the 274 clinical centers participating in the study. The primary outcome was in-hospital mortality after a traumatic injury. The study found that TXA given in the hospital reduced all-cause mortality with an absolute reduction of 1.5% compared with the control. The study also found that early administration of TXA (less than 1 h) after injury significantly decreased the death rate compared with when TXA was given after 3 h or more (6). When evaluating the CRASH-2 study, a direct comparison to the prehospital use of TXA should be cautioned as the study was performed in controlled hospital environments.

In contrast, the military application of TXA in trauma emergency resuscitation or the MATTERS study was a retrospective observational study in Afghanistan of the US military. The study's objective was to assess whether TXA provided benefits for combat injuries compared with control. The study found that the TXA treatment group had a lower mortality rate compared with those who did not receive TXA. In addition, the greatest benefit was observed in those who received a massive transfusion in addition to TXA. This benefit, even in the case of more severe trauma, indicated that TXA was shown to be independently associated with survival and less coagulopathy (7). One of the inclusion criteria for the study was that patients must have received at least one unit of packed red blood cells (pRBCs). These specific criteria limit its translation to the prehospital use of TXA as many EMS services do not carry blood products on their ambulances. Furthermore, the study population in the MATTERS project included wounded soldiers, limiting direct comparison with the physical characteristics of the civilian population. Nevertheless, the MATTERS study was instrumental in providing clinical evidence

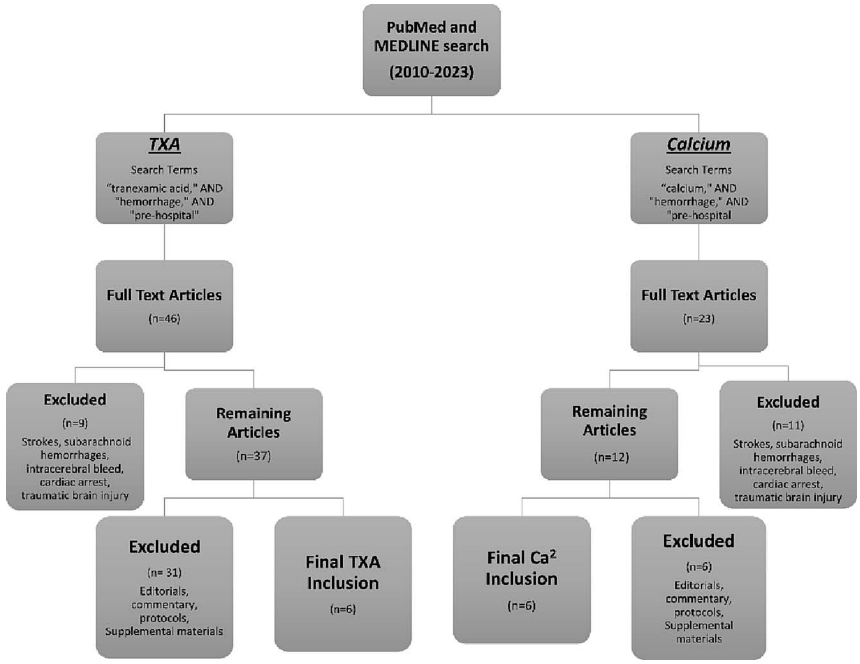

FIG. 2. **Study strategy.** Using PubMed and MEDLINE, there was 46 articles (TXA) and 23 articles (calcium that contained the inputted search words). After the exclusion of both TXA and calcium journals, there was a total of six articles each that satisfied the inclusion criteria. TXA, tranexamic acid.

of TXA while dismantling concerns of TXA use in a prehospital setting (8).

Another retrospective study that came out of Germany examined the use of TXA for prehospital civilian traumas (9). The study analyzed an EMS database that consisted of 258 patients who were treated with TXA following injury. Compared with matched controls, the patients in the TXA cohort demonstrated significantly reduced early mortality at 6 h (control: 9.3%, TXA: 1.9%), 12 h (control: 10.9%, TXA: 3.5%), and 24 h (control: 12.4%, TXA: 5.8%). However, there was no significant difference for in-hospital mortality. There were many limitations to this study, including a lack of information regarding documentation of dosages, route of administration for TXA, or the cause of death. In addition, TXA was only administered during air medical transports and not during ambulance transportation.

The use of TXA has also been shown to decrease the need for massive blood transfusion. Severely injured patients with at least one dose of TXA in the prehospital phase were compared with matched controls who did not receive TXA (10). Results of the study found that TXA patients needed significantly less pRBCs and fresh frozen plasma than their matched counterparts. Furthermore, the massive transfusion rate was significantly lower in the TXA group (5.5% *versus* 7.2%, $P = 0.015$). Thus, patients who preclinically received at least one dose of TXA required significantly fewer pRBC units when transfused, had a significantly lower rate of mass transfusion, and, overall, had a lower mortality rate.

A considerable concern with the usage of TXA in the prehospital setting is due to the unknown adverse effects of TXA administration, especially the possibility of having a cerebral vascular accident (CVA) hours to days after treatment. An ongoing multicentered combined study has assessed 128 patients in the prehospital setting who were treated with TXA and has evaluated multiple factors after administration. This includes the occurrence of adverse effects at 24 h, 48 h, and 28 days after treatment. The study found no difference in known adverse events associated with prehospital TXA administration compared with the control group (11). However, the data provided by this study only contain preliminary results; therefore, confidently ruling out TXA

Title	Author(s)	Study Design	Findings
Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study	Morrison et al (2012)	Retrospective observational study in Afghanistan of a United States military	• TXA treatment group had a **lower mortality rate** compared to those who did not receive TXA. • **Greatest benefit** was observed in those who received a massive transfusion in addition to TXA.
Tranexamic acid use in prehospital uncontrolled hemorrhage	Huebner et al (2017)	Literature Review	• Found that **1 gram of TXA is efficacious** however due to the risk of over coagulating patients, providers should withhold subsequent doses.
CRASH-2	Shakur et al (2010)	Randomized control double blinded study	• TXA reduced **all-cause** mortality during hemorrhagic traumas. • TXA showed the **greatest efficacy** when administered within 1 hour after injury.
Prehospital administration of tranexamic acid in trauma patients	Wafaisade et al (2016)	Retrospective analysis of the use of TXA for pre-hospital civilian traumas	• TXA significantly decreased mortality at 6 hours (Control: 9.3%, TXA: 1.9%), 12 hours (Control: 10.9%, TXA: 3.5%), and 24 hours (Control: 12.4%, TXA: 5.8%)
The impact of prehospital tranexamic acid on mortality and transfusion requirements	Imach et al (2021)	Retrospective cohort analysis	• TXA patients needed significantly less blood products than their matched counterparts. • Massive transfusion rate was significantly lower in the TXA group (5.5% versus 7.2%, p=0.015).
Efficacy and Safety of Tranexamic Acid in Prehospital Traumatic Hemorrhagic Shock	Neeki et al (2017)	Retrospective analysis	• No difference in known adverse events associated with pre-hospital TXA administration vs control.

FIG. 3. **The title, author(s), study design, and findings are presented for the six TXA articles that satisfied the inclusion criteria.**

Title	Author(s)	Study Design	Findings
Coagulopathy induced by acidosis, hypothermia and hypocalcemia in severe bleeding	De Robertis et al (2015)	Narrative Review	• **Greater mortality** was seen with lower calcium levels in cases of hemorrhage when compared to baseline levels (healthy: corrected total calcium >2.1mmol/L).
Hypocalcemia in trauma patients receiving massive transfusion	Giancarelli et al (2016)	Retrospective cohort over adult trauma patients in United States	• Found that mortality was seen in **49%** of patients who were in severe hypocalcemia (iCa < 0.90 mmol/L).
Ionised calcium levels in major trauma patients who received blood in the emergency department	Webster et al (2016)	Retrospective cohort over civilian trauma patients	• **89%** trauma patients who received any amount of blood products in the pre-hospital setting, demonstrated hypocalcemia.
Hypocalcemia in trauma patients	Vasudeva et al (2021)	Systematic review of 3 retrospective cohort studies	• **Hypocalcemia is independently** associated coagulopathy, hypotension, and increased mortality.
Ionised calcium levels in major trauma patients who received blood en-route to a military medical treatment facility	Kyle et al (2018)	Retrospective cohort analysis over military casualties	• Found that 70% of patients who received blood w/out calcium supplementation, resulted with hypocalcemia. • **Calcium supplementation** before or during blood transfusions in the pre-hospital setting decreased the incidence of hypocalcemia by **28%.**
Hypocalcemia in military casualties from point of injury to surgical teams in Afghanistan	Conner et al (2021)	Retrospective cohort analysis over military casualties	• Found that 55% of trauma patients were hypocalcemic before any transfusion and 75% were hypocalcemic blood transfusion.

Fig. 4. **The title, author(s), study design, and findings are presented for the six calcium articles that satisfied the inclusion criteria.**

adverse effects would be premature until further research is performed. Additional studies have demonstrated that TXA administration in the hospital setting can also increase the risk of complications. One study found that trauma patients who received TXA had a significant increase in developing venous thromboembolism compared with those who did not receive TXA (12). Another study revealed that while TXA did not significantly increase the risk of thrombotic events, doses exceeding 2 g were associated with a significantly higher risk of seizures (13). These findings emphasize the importance of a balanced evaluation of the potential benefits and risks when considering TXA use for hemorrhagic events.

Calcium

Calcium is another tool prehospital providers have used to combat hemorrhage. Serum calcium levels are regulated within a narrow range of 2.1 to 2.6 mmol/L (ionized calcium, 1.16–1.31 mmol/L) and levels less than 2.1 mmol/L (ionized calcium, <1.16 mmol/L) are defined as hypocalcemic (14). Calcium is essential for platelet function, intrinsic and extrinsic coagulation pathways, and cardiac contractility (15). Therefore, a reduction in basal calcium levels due to significant blood loss from traumatic injuries can result in decreased cardiac function, abnormal muscle activity, and impaired coagulation (16). In fact, calcium levels less than 0.8 mmol/L correlate to greater mortality in cases of hemorrhage when compared with baseline levels (healthy: corrected total calcium >2.1 mmol/L) (17).

Prehospital hemorrhage is associated with the depletion of calcium along with important coagulation factors and platelets, which has been shown to further complicate hemorrhagic shock secondary to traumatic injury (18). One review analyzed calcium levels upon arrival at the hospital and found that six of the seven studies analyzed showed a correlation between hypocalcemia and mortality (18). Hypocalcemia was observed in 55% of patients upon arriving at a trauma center after a hemorrhagic trauma, with an overall mean ionized calcium level of 1.11 mmol/L in patients who had not received prehospital blood products (19). After receiving blood product in the emergency department, 95% of patients had a decrease in serum ionized calcium levels, and the percentage with hypocalcemia increased from 55% to 89% with a mean ionized calcium level of 0.98 mmol/L (19). Current evidence suggests that low calcium is a strong predictor of trauma mortality and needs to be considered before massive blood transfusions in trauma patients (17,20–22).

The cause of hypocalcemia after hemorrhagic traumas remains uncertain, and with the lack of current literature evaluating the association between hemorrhages and calcium, there is a need for continued research to improve outcomes of trauma patients (23). One instigating factor in the development of hypocalcemia during traumas is the prehospital administration of citrated plasma. A randomized control trial evaluated the differences in calcium levels for trauma patients transported by EMS after receiving citrated plasma compared with control (normal saline with/without red blood cells). The study found that patients given citrated plasma presented to the hospital with significantly higher incidence of hypocalcemia than control (control: 35.7%, plasma: 52.6%; $P = 0.03$) (24).

Patients who experience massive blood loss after a traumatic injury often receive blood transfusions resulting in a significant risk of the transfusion causing or further worsening hypocalcemia (15). However, current literature assessing pretransfusion hypocalcemia is scarce. This becomes incredibly important when assessing calcium supplementation in the prehospital setting, especially since carrying blood products on ambulances in the United States was only recently introduced.

One of the only existing pieces of literature on this topic is a systematic review that compared 1,213 prehospital adult trauma patients who presented to the emergency department in both the United States and Australia. Ionized calcium was measured in all trauma patients upon arrival to the emergency department or trauma center to assess transfusion requirements. The primary outcome was assessing hypocalcemia and its association with hypotension, blood transfusions, and mortality. Hypocalcemia was present in 56.2% of participants arriving to the hospital after a traumatic injury before receiving any transfusions. The study also found that hypocalcemia was independently associated with prehospital hypotension, poor coagulation, and increased mortality. In addition, hypocalcemia was an independent predictor for receiving a massive transfusion (25).

The recent interest in prehospital hypocalcemia can be partially attributed to EMS agencies and other forms of prehospital medicine having the ability to carry and administer blood products (26). After the administration of blood products in the prehospital setting, it was found that 70% to 75% of trauma patients presented with hypocalcemia on arrival to the hospital (27,28). A retrospective analysis of 55 trauma patients in the United Kingdom sought to assess whether the amount of blood products transfused affected the incidence of patients becoming hypocalcemic. The study found that 89% of patients who received any amount of blood product (1 or 4 units) became hypocalcemic with a significantly reduced posttransfusion *versus* pretransfusion calcium level (0.98, 1.11 mmol/L, respectively) (19). It is important to point out that the majority of pretransfused patients were already close to or in the hypocalcemic range, suggesting that early calcium supplementation needs to be considered in the prehospital setting, especially before massive blood transfusions in trauma patients.

Primary literature assessing prehospital calcium administration for hemorrhagic traumas is extremely sparse, unless the hypocalcemia is corrected for once the patient is already in the hospital. A retrospective analysis of patients transported by the UK Medical Emergency Response Team in Afghanistan wanted to assess whether intravenous calcium, given in route to the hospital, has any effect on calcium levels when given concurrently with blood products. The results of the study found that when patients were co-treated with an average of 4 units of pRBCs or fresh frozen plasma (FFP) and 10 mL of intravenous $CaCl_2$ (10%), the incidence of hypocalcemia decreased to 28% compared with 70% when patients only received pRBCs or FFP (24).

Because of the collection of work described previously, the administration of calcium in the prehospital setting after hemorrhagic traumas is generally supported; however, there is disagreement about the best calcium-replacement protocol. For example, the European guidelines recommend 10% $CaCl_2$ for traumatic injuries outside of the hospital compared with calcium gluconate (CaGN). This is primarily due to the higher elemental presence of calcium in $CaCl_2$ (29) along with CaGN requiring hepatic metabolism to release ionized calcium, potentially reducing its bioavailability, particularly in shock (30). However, other sources recommend CaGN as the initial calcium supplementation due to the lower iatrogenic effects and lower rates of infusion reactions (24,31). This discrepancy is primarily due to a lack of clinical research directly comparing the efficacy of calcium replacement strategies during active hemorrhagic events (20,24). Regardless, it is clear that getting patients to an ionized calcium level greater than 0.9 mmol/L can have beneficial cardiovascular and coagulation effects (32). Because of the lack of primary research regarding the use of calcium in an active hemorrhagic event, additional studies are necessary to directly compare the efficacy of calcium replacement therapies.

Ongoing research

A review of EMS practices found 15 statewide protocols that allow EMS providers to administer TXA for trauma (10). One of the first adopters of prehospital TXA administration was Mayo One medical helicopters, which have had TXA available on their helicopters since 2012. In addition, Tri-State Ambulance added TXA to its protocols in December 2013 and Milwaukee County EMS in September 2014. Indiana recently began using TXA with Morgan County EMS, IN, adopting the use of TXA to their protocol in 2022. However, unlike other EMS companies, Morgan County has introduced TXA with and without co-administration of $CaCl_2$.

Morgan County EMS added TXA into their protocol because of the significant number of major traumas in their response area and an average 45-min transport time to the nearest level 1 trauma center. Per protocol, 1 g of TXA should be given for trauma patients where bleeding remains uncontrolled. The administration of 1 g of TXA en route has been shown to be efficacious; however, because of the risk of overcoagulating patients (8), Morgan County limits their providers giving more than 1 g. In addition, Morgan County EMS also added $CaCl_2$ to their hemorrhagic trauma protocol, which was heavily influenced by the Journal of Acute Care and Trauma Surgery Lethal Diamond paper. This paper suggested that the lethal triad (hypothermia, coagulopathy, and acidosis) of hemorrhagic shock be expanded to include hypocalcemia, therefore becoming known as the "lethal diamond" (33). In addition, calcium supplementation during major traumas has been associated with decreasing the risk of mortality (22,27). Due to their addition of $CaCl_2$ to the TXA protocol (Table 1), Morgan County EMS offers a preliminary glimpse into the efficacy of this combined approach.

Patient data, including age, sex, mechanism of injury, and vital signs before and after TXA/$CaCl_2$, were obtained through ESO's health electronic records. After the introduction of TXA/$CaCl_2$ to Morgan County's protocol, TXA was administered on 10 occasions, and $CaCl_2$ was co-administered to 8 of the 10 patients meeting treatment criteria (Table 2). Treatment criteria included the following: known or suspected hemorrhage after crash, blunt or penetrating trauma, age >18 years, sustained hypotension (SBP <90 mm Hg) and/or a HR of >110 beats per minute, and time of injury less than 3 h. The decision of when to add calcium with TXA for suspected hemorrhage was based on provider discretion. Patient ages (in years) ranged from 30 to 88, with seven male and three female patients. The mechanism of injury (mechanism of injury) varied among the patients, with 40% having a head injury due to a motor vehicle collision. Patient HRs in beats per minute, SBPs in millimeters of mercury (mmHg), and $ETCO_2$ are provided in Table 2.

Preliminary results show that patients who received TXA alone had a 14 mm Hg average increase in their SBP (SBP after treatment - SBP before treatment) and a 4.5 bpm decrease in average HR (HR after treatment - HR before treatment). In contrast, patients who were co-administered TXA + $CaCl_2$ had a 28 mm Hg increase in their average SBP and a 24.2 bpm decrease in HR after treatment. The change in the $ETCO_2$ was used as a determinant of intubation and was observed not to be noticeably different between the two treatments (TXA alone *vs.* TXA + $CaCl_2$) with an average increase of 8.5 and 7.7 mm Hg, respectively. Patients who were not intubated were excluded from the preliminary calculations.

Limitations

Although this narrative review provides a detailed description of the current evidence and usage for TXA and $CaCl_2$ in the prehospital setting, it is challenging to compare the two therapies. This is primarily due to a deficiency of primary literature in evaluating TXA with calcium in the treatment of prehospital hemorrhage. Furthermore, the relatively new nature of the combined TXA and calcium therapy has thus far resulted in a need for more

Table 1. **Morgan County, EMS treatment algorithm for tranexamic acid and calcium chloride administration**

Criteria	Description
A. Indications:	
1. Blunt or penetrating trauma with a risk of significant bleeding:	With systolic BP < 90 mm Hg and/or heart rate > 110 bpm.
OR	
2. Moderate to severe head injury:	With a GCS score <12 and systolic BP > 90 mm Hg.
B. Inclusion Criteria:	
1. Age >18 y	
2. Time since injury is <3 h	
3. Transport destination is a level 1 trauma center	
C. Contraindications:	
1. Time since injury is longer than 3 h	
2. GCS score of 3 with bilateral unreactive pupils	
D. TXA administration:	
1. Administer TXA 1 g over 10 min.	Mix 1 g/10 mL vial in 100 mL NS and administer *via* a dedicated IV line when possible.
E. Calcium chloride administration:	
1. Administer calcium chloride 1 g	If there is a strong evidence of a future massive blood transfusion or if requested by medical control. Slowly push 1 g over 5–10 min *via* IV or IO.

BP, blood pressure; bpm, beats per minute; GCS, Glasgow Coma Scale; IO, intraosseous; IV, intravenous; NS, normal saline.

specific literature comparing the use of TXA alone to combination therapy. In addition, the recent adoption of the combination therapy has so far yielded only a small number of patients. This limits the conclusions that can be drawn from any data analysis performed on the preliminary data.

Another limitation of this study is the type of available data regarding patient information upon arrival at the emergency department. Available data only included standard patient data contained within the ESO's health electronic records database. As such, information such as calcium levels, types of blood product given, and number of blood products given were unavailable to the researchers. In addition, estimated blood loss was not available. Going forward, it would be beneficial to consider these factors in a prospective experimental design and collect this data throughout the trial.

DISCUSSION

While both TXA and calcium are increasingly being adopted in prehospital settings, there is a clear need for further research, particularly regarding the combined use of these treatments. Future preclinical studies could include *in vivo* models of hemorrhage to study the effect of the combined administration of TXA and calcium. These models could help establish a better understanding of the optimal dosing and timing for each agent, providing a clearer rationale for their use in clinical settings. In addition, the use of animal models to explore potential adverse effects of TXA and/or calcium, such as the work by Lecker and Wang *et al.* (2019), would be worthy of exploration (34). Furthermore, examination of the drug interactions of TXA, calcium, and various other common pharmaceuticals could provide insight toward ideal treatments for individuals. Lastly, future work would also benefit greatly from the collection of blood specimens for evaluation. This would allow for the analysis of hemoglobin, levels of clotting factors, and serum calcium. This, in turn, would lend itself to a more rigorous and detailed analysis of patient status as well as enable a comparison between pretreatment and posttreatment status and values.

Building upon this preliminary work, the next stage of experimental clinical research would be increasing the sample size by extending the data collection period and collaborating with other EMS agencies, which would strengthen the validity and generalizability of the study findings. This would allow for a more rigorous analysis of patient outcomes and provide more substantial data on the impact of combined TXA and calcium administration compared to TXA alone. One of the key considerations for the use

TABLE 2. **Morgan County EMS Data**

Patient information					Pretreatment (avg)			Posttreatment (avg)		
Age	Sex	CC/MOI	TXA given	$CaCl_2$ given	SBP	HR	$ETCO_2$	SBP	HR	$ETCO_2$
30	F	MVC–head injury	Yes	Yes	116	124	49	133	116	41
80	M	MVC–head injury	Yes	Yes	77	124	15	112	102	28
56	M	MVC–head injury	Yes	Yes	130	119	26	129	94	29
46	F	Motorcycle–head injury	Yes	Yes	91	142	19	116	116	43
68	M	MVC–multisystem	Yes	Yes	141	115	27	152	74	33
88	M	MVC–multisystem	Yes	Yes	56	108	21	137	85	29
48	M	Pedestrian–multisystem	Yes	Yes	79	105	—	105	109	—
66	M	Epistaxia	Yes	Yes	148	135	—	134	131	—
82	F	Fall–multisystem	Yes	No	92	57	20	116	65	19
34	M	ATV–multisystem	Yes	No	130	146	32	134	129	50

ATV, All-Terrain Vehicle; CC, Chief Compliant; MOI, mechanism of injury; MVC, Motor Vehicle Collison.

of these agents is the severity of the patient's condition. Specifically, TXA administration should be considered in cases of severe hemorrhage, as it has been shown to be most effective in this context.

As one of the primary indications for the prehospital administration of calcium and TXA is the presence of significant bleeding, future research could be directed toward defining what exactly constitutes a severe hemorrhage. This could then serve as a more precise indicator for the administration of TXA and calcium in the prehospital setting. In a similar fashion, the timing since injury is another critical consideration that will be addressed in future studies. Tranexamic acid is most effective when administered within the first few hours after injury, and its efficacy decreases with time. Therefore, a treatment protocol should prioritize rapid assessment and initiation of treatment. However, the optimal window for the administration of calcium is still unclear and will need to be further analyzed. Calcium administration in the prehospital setting for hemorrhagic traumas follows similar indication criteria, particularly if there is a high likelihood of the patient requiring a blood transfusion. Given the lack of a universal protocol for calcium administration under these circumstances, here are the proposed criteria:

1. Significant hemorrhage: This is identified by an SBP less than 90 mm Hg and an HR greater than 100 beats per minute.
2. Potential large volume transfusion: Indication for patients who are receiving or expected to receive a large volume transfusion due to the injury.
3. Clinical symptoms of hypocalcemia: Presence of clinical symptoms such as tetany, paresthesia, seizures, QT prolongation on echocardiogram, Chvostek sign (twitching of the facial muscles in response to tapping over the area of the facial nerve), and/or Trousseau sign (carpopedal spasm caused by inflating a blood-pressure cuff to above SBP for 3 min) should raise suspicion among EMS personnel.

If hypocalcemia is suspected based on these criteria and the patient's history, administration of $CaCl_2$ is recommended. Deliver 1 g of $CaCl_2$ slowly over 5 to 10 min through intravenous (1 g/10 mL syringe) or intraosseous infusion. Patients must be placed on electrocardiogram monitoring before administering calcium, to rule out any existing cardiac arrhythmias. The monitoring should continue throughout transport. These criteria must be well defined to minimize the risk associated with TXA and calcium administration in the absence of severe hemorrhage. This aspect needs to be addressed and clearly articulated in future studies and in the development of guidelines for prehospital or hospital use of these agents.

CONCLUSION

In the setting of prehospital trauma, hemorrhage is a severe and potentially fatal complication. One increasingly popular method for addressing hemorrhage in the prehospital setting is the utilization of TXA. This is largely due to the CRASH-2 and MATTERS studies that highlighted the efficacy of TXA in reducing mortality and coagulopathy in trauma patients. Furthermore, the administration of TXA seems not to be linked to posttreatment adverse events when compared with control groups.

Another addition to traumatic hemorrhage treatment becoming ever more used is calcium. Because of its significance in the coagulation cascade, cardiac contractility, and platelet function, hypocalcemia has been linked to increased mortality and further complications in the setting of hemorrhage. With hypocalcemia being worsened by blood transfusion, many organizations support the inclusion of calcium administration in hemorrhagic treatment.

While both treatment modalities are becoming more widely implemented in prehospital settings across the nation, it is clear that more research is to be done. Calcium replacement protocols are debated among organizations because of a lack of studies comparing protocols. In addition, little to no data exist on patient outcomes when administered both TXA and calcium compared with TXA alone in the prehospital trauma setting. Our analysis of the Morgan County EMS data is a preliminary dive into this area of needed research. Though small in sample size, this preliminary work supports improved patient outcomes measured by hemodynamic variables and justifies additional studies. As the adoption of these treatment modalities continues to expand in prehospital settings nationwide, it is evident that further research is warranted. This need is underscored by the fact that our article represents the first description of co-administration of these two agents in the scientific literature. Furthermore, it provides a framework for future research endeavors to examine a relatively new and growing EMS protocol.

REFERENCES

1. Behrens AM, Sikorski MJ, Kofinas P. Hemostatic strategies for traumatic and surgical bleeding. *J Biomed Mater Res A*. 2014;102(11):4182–4194.
2. Shackelford S, Eastridge BJ. Epidemiology of prehospital and hospital traumatic deaths from life-threatening hemorrhage. Damage Control Resuscitation: Identification and Treatment of Life-Threatening Hemorrhage. 2020:31–40.
3. Davis JS, Satahoo SS, Butler FK, et al. An analysis of prehospital deaths: who can we save? *J Trauma Acute Care Surg*. 2014;77(2):213–218.
4. Stansfield R, Morris D, Jesulola E. The use of tranexamic acid (TXA) for the management of hemorrhage in trauma patients in the prehospital environment: literature review and descriptive analysis of principal themes. *Shock*. 2020;53(3):277–283.
5. Giannoudi M, Harwood P. Damage control resuscitation: lessons learned. *Eur J Trauma Emerg Surg*. 2016;42(3):273–282.
6. CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23–32.
7. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg*. 2012;147(2):113–119.
8. Huebner BR, Dorlac WC, Cribari C. Tranexamic acid use in prehospital uncontrolled hemorrhage. *Wilderness Environ Med*. 2017;28(2S):S50–S60.
9. Wafaisade A, Lefering R, Bouillon B, et al. Prehospital administration of tranexamic acid in trauma patients. *Crit Care*. 2016;20(1):143.
10. Imach S, Wafaisade A, Lefering R, et al. The impact of prehospital tranexamic acid on mortality and transfusion requirements: match-pair analysis from the nationwide German TraumaRegister DGU®. *Crit Care*. 2021;25(1):277.
11. Neeki MM, Dong F, Toy J, et al. Efficacy and safety of tranexamic acid in prehospital traumatic hemorrhagic shock: outcomes of the Cal-PAT study. *West J Emerg Med*. 2017;18(4):673–683.
12. Myers SP, Kutcher ME, Rosengart MR, et al. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. *J Trauma Acute Care Surg*. 2019;86(1):20–27.
13. Murao S, Nakata H, Roberts I, et al. Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis. *Crit Care*. 2021;25(1):380.
14. Fong J, Khan A. Hypocalcemia: updates in diagnosis and management for primary care. *Can Fam Physician*. 2012;58(2):158–162.
15. Elmer J, Wilcox SR, Raja AS. Massive transfusion in traumatic shock. *J Emerg Med*. 2013;44(4):829–838.
16. Blackney D. Prehospital administration of calcium in trauma. *J Paramed Practice*. 2022;14:279–286.

17. De Robertis E, Kozek-Langenecker SA, Tufano R, et al. Coagulopathy induced by acidosis, hypothermia and hypocalcaemia in severe bleeding. *Minerva Anestesiol*. 2015;81(1):65–75.
18. Kronstedt S, Roberts N, Ditzel R, et al. Hypocalcemia as a predictor of mortality and transfusion. A scoping review of hypocalcemia in trauma and hemostatic resuscitation. *Transfusion*. 2022;62(Suppl 1(Suppl 1)):S158–S166.
19. Webster S, Todd S, Redhead J, et al. Ionised calcium levels in major trauma patients who received blood in the emergency department. *Emerg Med J*. 2016;33(8): 569–572.
20. Giancarelli A, Birrer KL, Alban RF, et al. Hypocalcemia in trauma patients receiving massive transfusion. *J Surg Res*. 2016;202(1):182–187.
21. MacKay EJ, Stubna MD, Holena DN, et al. Abnormal calcium levels during trauma resuscitation are associated with increased mortality, increased blood product use, and greater hospital resource consumption: a pilot investigation. *Anesth Analg*. 2017;125(3):895–901.
22. Cornelius B, Ferrell E, Kilgore P, et al. Incidence of hypocalcemia and role of calcium replacement in major trauma patients requiring operative intervention. *AANA J*. 2020;88(5):383–389.
23. Aberegg SK. Ionized calcium in the ICU: should it be measured and corrected? *Chest*. 2016;149(3):846–855.
24. Moore HB, Tessmer MT, Moore EE, et al. Forgot calcium? Admission ionized-calcium in two civilian randomized controlled trials of prehospital plasma for traumatic hemorrhagic shock. *J Trauma Acute Care Surg*. 2020;88(5):588–596.
25. Vasudeva M, Mathew JK, Groombridge C, et al. Hypocalcemia in trauma patients: a systematic review. *J Trauma Acute Care Surg*. 2021;90(2):396–402.
26. Beiriger J, Silver D, Lu L, Brown JB. Transfusion Management in Trauma: What is Current Best Practice? Springer: Current Surgery Reports. 2023;11(3):43–54.
27. Kyle T, Greaves I, Beynon A, et al. Ionised calcium levels in major trauma patients who received blood en route to a military medical treatment facility. *Emerg Med J*. 2018;35(3):176–179.
28. Conner JR, Benavides LC, Shackelford SA, et al. Hypocalcemia in military casualties from point of injury to surgical teams in Afghanistan. *Mil Med*. 2021;186(suppl 1): 300–304.
29. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care*. 2019;23(1):98.
30. Kanaris C, Janjanam A. Calcium chloride versus calcium gluconate during pediatric resuscitation. Which one is better? A systemic review of the evidence. *Pediatr Crit Care Med*. 2021;22:112–113.
31. Anger KE, Belisle C, Colwell MB, et al. Safety of compounded calcium chloride admixtures for peripheral intravenous administration in the setting of a calcium gluconate shortage. *J Pharm Pract*. 2014;27(5):474–477.
32. Lier H, Krep H, Schroeder S, et al. Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. *J Trauma*. 2008;65(4):951–960.
33. Ditzel RM, Anderson JL, Eisenhart WJ, et al. A review of transfusion- and trauma-induced hypocalcemia: is it time to change the lethal triad to the lethal diamond? *J Trauma Acute Care Surg*. 2020;88(3):434–439.
34. Lecker I, Wang DS, Whissell PD, et al. Tranexamic acid-associated seizures: causes and treatment. *Ann Neurol*. 2016;79(1):18–26.