Prevalence of Trauma-Induced Hypocalcemia in the Prehospital Setting

Matt D. Brandt, MD[1]; Cody Liccardi[2]; Jennifer Heidle[3];
Timothy D. Woods, MD[4]; Crystal White, RN[5]; J. Randolph Mullins, MD[6];
Jami Blackwell, RN, MBA[7]; Lamanh Le, PharmD[8]*; Kara Brantley, PharmD[9]

ABSTRACT

Background: Recent data published by the Special Operations community suggest the Lethal Triad of Trauma should be changed to the Lethal Diamond, to include coagulopathy, acidosis, hypothermia, and hypocalcemia. The purpose of this study is to determine the prevalence of trauma-induced hypocalcemia in level I and II trauma patients. **Methods:** This is a retrospective cohort study conducted at a level I trauma center and Special Operations Combat Medic (SOCM) training site. Adult patients were identified via trauma services registry from September 2021 to April 2022. Patients who received blood products prior to emergency department (ED) arrival were excluded from the study. Ionized calcium levels were utilized in this study. **Results:** Of the 408 patients screened, 370 were included in the final analysis of this cohort. Hypocalcemia was noted in 189 (51%) patients, with severe hypocalcemia identified in two (<1%) patients. Thirty-two (11.2%) patients had elevated international normalized ratio (INR), 34 (23%) patients had pH <7.36, 21 (8%) patients had elevated lactic acid, and 9 (2.5%) patients had a temperature of <35°C. **Conclusion:** Hypocalcemia was prevalent in half of the trauma patients in this cohort. The administration of a calcium supplement empirically in trauma patients from the prehospital environment and prior to blood transfusion is not recommended until further data prove it beneficial.

KEYWORDS: *hypocalcemia; trauma; ionized calcium; Diamond of Death; Lethal Triad*

Introduction

Trauma is a leading cause of death, and recent data suggest that hypocalcemia management plays a significant role in trauma resuscitation. A literature review published in 2019 by the Special Operations community suggested the Lethal Triad of Trauma should be changed to the Diamond of Death, to include coagulopathy, acidosis, hypothermia, and hypocalcemia. Hypocalcemia, especially in the hypovolemic trauma patient population, is an emerging problem.[1] Studies dating to the 1980s confirm that hypocalcemia is one of the most common electrolyte disorders in intensive care unit (ICU) and trauma patients; it is also associated with poor patient outcomes.[2] Calcium plays a vital role in membrane receptor activation, hormone release, transfer of fluids between compartments, cardiac conductivity, and coagulation.[2] A deficiency in calcium has been associated with increased morbidity and mortality, as well as poor coagulation, among other pathologies.[1]

Calcium measurement is often reported as either total serum calcium or ionized calcium. The total serum calcium concentration is divided into protein-bound (30–55%), diffusible to organic and inorganic anions (5–15%), and ionized calcium (50%). Available literature suggests that using total serum calcium to predict ionized calcium is not accurate, especially in critically ill patients.[3] A recent chart review at our institution showed that there was a low correlation of total adjusted calcium to ionized calcium levels when Payne's formula is used to account for albumin. Because of the result of this review, ionized calcium has been used in class I and II trauma patients at our institution.[4] Class I trauma team activation includes full team response and the trauma surgeon responding to the trauma bay within 15 minutes of notification. Class II trauma team activation includes partial team response and the trauma surgeon responding upon the emergency physician's request (see Supplement 1 for Trauma Classification Criteria).

Many studies have explored hypocalcemia in hypovolemic trauma patients who received blood transfusion(s) and reported high mortality and morbidity rates in this patient population.[5–9] Vivien et al., Cherry et al., Magnotti et al., Webster et al., and Vasudeva et al. assessed ionized calcium levels in trauma patients and reported that up to 70% of patients were hypocalcemic upon arrival to the ED before receiving any blood products.[10–14] Despite the lack of data on the impact of calcium in the prehosital setting, there has been discussion of giving calcium supplemention in this enviroment to prevent further hypocalcemic events.[15,16]

The primary goal of this study was to determine the prevalence of ionized hypocalcemia in trauma patients in the prehospital setting prior to blood transfusion. Secondary outcomes such as prevalence of coagulopathy, acidosis, and hypothermia, and the relationship of injury severity score (ISS) and hypocalcemia were also reviewed in this study.

Methods

Study Design

This observational cohort study was completed retrospectively at a single-center, level I trauma facility and SOCM training site affiliated with the Joint Special Operations Medical Training Center at Fort Bragg, NC. It includes patients from a trauma services registry presenting between September 2021 and April 2022 to the ED as a class I or class II trauma. All

*Correspondence to Lamanh.le@coxhealth.com

[1]Dr Matt D. Brandt, [2]Cody Liccardi, [3]Jennifer Heidle, [4]Dr Timothy D. Woods, [5]Crystal White, [6]Dr J. Randolph Mullins, [7]Jami Blackwell, [8]Lamanh Le, and [9]Kara Brantley are all affiliated with CoxHealth, Springfield, MO.

laboratory data and radiographic imaging were abstracted from the Cerner Electronic Medical Record (EMR).

Patients

Patients from September 2021 to April 2022 were identified via the trauma services registry. Patients' ionized calcium (iCa) levels were collected upon admission to the ED. Patients were excluded from the study if they received blood products prior to ED arrival, had incomplete data regarding calcium values, deceased within 24 hours of ED arrival, or were pregnant.

Ionized Calcium Measurement

Ionized calcium was obtained from venous blood draw and placed in green top tubes. All samples were run with a NOVA machine. The reference iCa level at our institution is 1.13–1.32mmol.

Outcomes

The primary purpose of this study is to determine the prevalence of hypocalcemia in trauma patients upon admission to the ED. Hypocalcemia was defined as ionized calcium levels (iCa) <1.13mmol/L. Secondary outcomes assessed in this cohort were coagulopathy, acidosis, and hypothermia. The correlation of ISS distribution and hypocalcemia is also reported.

Statistical Analysis

Descriptive statistics were utilized to illuminate data collected from chart reviews and are reported in terms of mean, median, and percentages.

Results

Of the 408 patients screened, 370 were deemed eligible for inclusion for final analysis. A total of 38 patients were excluded: 27 received blood products, two were pregnant, three died within 24 hours of admission, and six had inadequate laboratory data (Figure 1). Patient characteristics included age, trauma level (I and II), mechanism of injury, ISS, initial blood pressure, ionized calcium levels, initial prothrombin time (PT), INR, pH level, lactate level, and temperature (Table 1).

FIGURE 1 *Patient selection.*
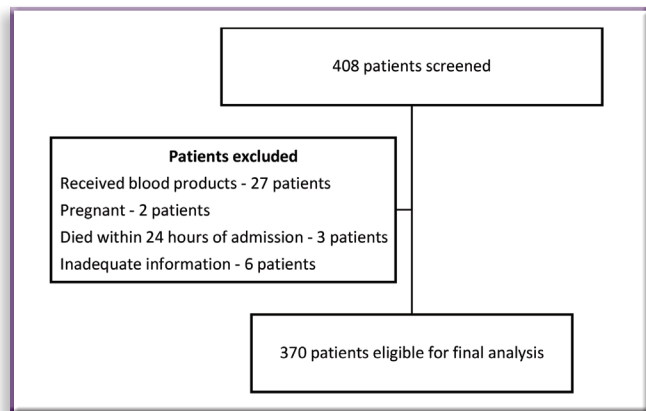
Hypocalcemia was identified in 189 (51%) patients. Severe hypocalcemia, defined as iCa <0.9mmol/L, occurred in two (<1%) patients. Normocalcemia was identified in 176 (47.6%) patients, and hypercalcemia occurred in three (<1%) patients. The primary outcome of this study was to assess the prevalence of hypocalcemia, which occurred in half (51%) of the

TABLE 1 *Patient Characteristics*

Variables	Sample Size, n = 370
Age, years, mean	51
Trauma Level	
Level 1, n (%)	111 (30)
Level 2, n (%)	264 (70)
Mechanism of injuries	
Trauma, n (%)	359 (97)
GSW, n (%)	10 (2.7)
Other/Unknown	6
ISS[1]	
1–5, n (%)	147 (49)
6–10, n (%)	55 (18.4)
11–15, n (%)	32 (10.7)
16–20, n (%)	28 (9)
21–25, n (%)	20 (6.7)
26–30, n (%)	8 (2.7)
31–35, n (%)	6 (2)
36–40, n (%)	1 (<1)
>40, n (%)	1 (<1)
Initial SBP <90mmHg, n (%)	11 (3)
Ionized calcium level, range	0.57–1.59
Initial PT[2], range	9.9–41.7
Initial INR[2], range	0.9–4.43
Initial pH[3], range	6.93–7.55
Lactic[4], range	0.3–9.9
Temperature[5] in °C, range	29.2–39.6

ISS = injury severity score, SBP = systolic blood pressure, PT = prothrombin time, INR = international normalized ratio, GSW = gunshot wound.
1: n = 298 for ISS, 2: n = 286 for PT and INR, 3: n = 147 for pH, 4: n = 253 for lactic acid, 5: n = 358 for temperature.

trauma patients who presented to the ED. The final analysis included 10 (2.7%) patients who presented after a gunshot wound injury, and nine (90%) patients in this subgroup were found to be hypocalcemic (Table 2).

TABLE 2 *Prevalence of Hypocalcemia*

Calcium Status	Sample size, n (%), iCa range	GSW, n (%), iCa range
Normocalcemia	176 (47.6)	1 (10)
Hypocalcemia	189 (51) (0.76–1.12)	9 (90) (0.99–1.12)
Severe Hypocalcemia	2 (<1)	NA
Hypercalcemia	3 (<1)	NA

Normocalcemia iCa 1.13–1.32 mmol, hypocalcemia iCa <1.13 mmol, severe hypocalcemia iCa <0.9 mmol, hypercalcemia iCa >1.32 mmol GSW = gunshot wound.

In addition to hypocalcemia, we also evaluated the other elements of the Diamond of Death—coagulopathy, acidosis, and hypothermia. In the hypocalcemia group, our data showed that 25 (8.7%) patients had INR not within normal limit (WNL) of 0.8–1.13; of those patients, six (2%) experienced coagulopathy as defined INR >1.5. Twenty-two (15%) patients presented with initial pH <7.36 with only one case of severe acidosis or pH <7.2. Seventeen (6.7%) patients had lactic level greater than 2, and six (1.7%) patients experienced hypothermia or temperature <35°C (Table 3).

Figure 2 portrays ISS distribution in hypocalcemic trauma patients. Over 70% of patients in the hypocalcemia group presented with ISS of 1–15, which is categorized by Bolorunduro et al. as mild and moderate.[17] In this study, no direct relationship between ISS and hypocalcemia was found.

TABLE 3 *Secondary Outcomes*

Variables	Hypocalcemia Group, n (%)	Entire Cohort, n (%)
Abnormal INR[1], n (%)	25 (8.7)	32 (11.2)
INR >1.5, n (%)	6 (2)	9 (3)
Acidosis[2], n (%)	22 (15)	34 (23)
Severe acidosis, pH <7.2	1 (<1)	2 (1.4)
Elevated lactic[3], n (%)	17 (6.7)	21 (8)
Hypothermia[4] (Temp. <35°C), n (%)	6 (1.7)	9 (2.5)

Normal lab ranges: INR 0.8–1.13, PT 9.0–13.5, iCa (mmol/L) 1.13–1.32, pH 7.36–7.46, and lactic acid 0.4–2.00.
1: n = 286 for PT and INR, 2: n = 147 for pH, 3: n = 253 for lactic acid, 4: n = 358 for temperature.

FIGURE 2 *ISS distribution of hypocalcemic trauma patients.*

ISS categories[18]:
<9: mild
9-15: moderate
16-24: severe
≥25: profound
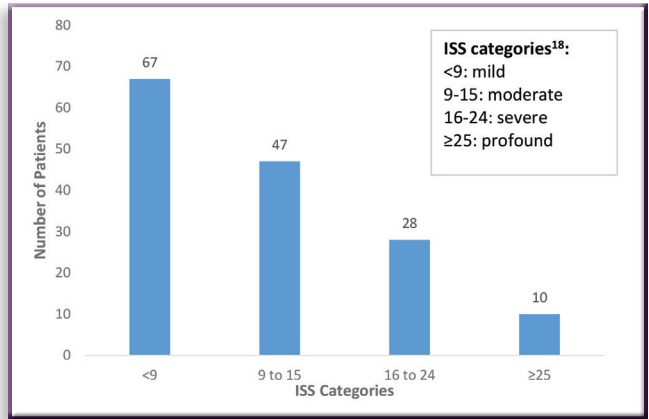
ISS = Injury Severity Score.

Discussion

Hypocalcemia was not considered a major contributing factor in trauma-related deaths until recently. In 2019, the Trauma Triad was updated to include hypocalcemia and has been renamed the Lethal Diamond.[1,2] It is crucial to understand how hypocalcemia interacts with other components of the Lethal Diamond. First, calcium is a necessary ion in hemostasis and coagulation cascade. It plays a significant role in platelet adhesion and intrinsic function of factors II, VII, IX, X, and proteins C and S in the coagulation cascade. Second, declining calcium level results in lowering pH, which leads to increased clot formation time. Third, hypothermia decreases the metabolism of citrate in the liver, which contributes to accumulation of citrate and subsequent hypocalcemia. A healthy liver can metabolize approximately 3g of citrate every 5 minutes. However, liver injuries due to trauma or critical illness reduce citrate metabolism, and citrate begins to accumulate and chelate with free ionized calcium in serum, leading to hypocalcemia.[2] Numerous studies over the past 30 years have observed high mortality rates in trauma patients with hypocalcemia, and the correlation of blood transfusion and hypocalcemia in hypovolemic trauma patients is well-established.[5–9] However, the relationship of calcium hemostasis in severe injuries and the impact of a calcium supplement prior to blood transfusion is poorly defined.[18]

This retrospective analysis completed at a single-center, level I trauma, and SOCM training facility had similar outcomes in comparison to previous literature, in which ionized calcium was utilized (Table 4). Of the 370 trauma patients included in the final analysis, 189 (51%) patients had an iCa level of <1.13mmol/L, and among these patients, only two patients experienced severe hypocalcemia. These patients did not receive any blood products prior to their ED arrival. Interestingly, the data of this cohort also showed that nine (90%) patients in the gunshot wound group experienced hypocalcemia, as indicated in Table 2. Zero patients in the GSW group received a blood transfusion, and these patients were normotensive in the ED. Hypovolemic shock could be one of the causes of hypocalcemia. However, a larger sample size is needed to confirm this relationship.

Other elements of the Diamond of Death—coagulopathy, acidosis, and hypothermia—were also assessed in this cohort. Only six (2%) hypocalcemic patients had acute traumatic coagulopathy defined as INR >1.5 (Table 3). Our findings differ from those found by Vasudeva et al. This group of authors reported that there was an independent association between hypocalcemia and acute traumatic coagulopathy, and INR levels were 1.3 and 1.7 in normocalcemic and hypocalcemic groups, respectively, with a *p*-value of 0.03.[12] With respect to acidosis, 22 (15%) of the hypocalcemic patients had pH <7.36 with one case of severe acidosis. Vivien et al. reported a direct relationship between iCa level and arterial pH level with a correlation coefficient of 0.76.[13] Finally, six (1.7%) patients in the hypocalcemic group had initial temperature of <35°C. Unfortunately, the direct relationship between calcium and hypothermia is not clearly understood.

Recently, Blackney et al. and Leech et al. recommend starting empiric calcium treatment in hypovolemic trauma patients in whom blood transfusion is anticipated.[15,16] However, there is insufficient evidence to support the use of supplement calcium in trauma patients prior to blood transfusion.[14] In our cohort, only 14 (7.4%) patients required blood transfusion upon their presentation to the ED. Literature has shown that mortality is higher in patients with an abnormal calcium level either from primary injury or overcorrection.[18] Due to the lack of evidence describing the relationship of calcium dysregulation in severely injured patients, the impact of transfusion and calcium supplementation, empiric calcium treatment in hypovolemic trauma patients should not be initiated in the prehospital setting until more evidence is available.

This study has several limitations. First, this is a retrospective and observational study completed at a single-center facility. Second, laboratory ranges were preset ranges according to the facility and may vary in comparison to other level I trauma centers. This study was completed during winter months,

TABLE 4 *Ionized Hypocalcemia in Trauma Patients Among Different Studies*

	Vivien et al.[13] (2005)	Cherry et al.[11] (2006)	Magnotti et al.[10] (2011)	Webster et al.[14] (2016)	Vasudeva et al.[12] (2019)	This study (2022)
Sample Size (n)	212	396	591	55	226	370
Study Site	France	Pennsylvania, USA	Tennessee, USA	UK	Australia	Missouri, USA
Hypocalcemia, %	74	23	56	55	50	51

which may have contributed to changes in coagulopathy as well as the number of trauma patients seen at this time of year. This study was completed utilizing chart review, which could contain human error.

Conclusion

Half of trauma patients presenting from an out-of-hospital setting were hypocalcemic, with severe hypocalcemia identified in two patients. The results of this retrospective chart review agree with current literature regarding identifying the correlation between hypocalcemia and trauma patients. The administration of calcium supplementation empirically in trauma patients in the prehospital setting is not recommended until further data prove it beneficial.

Author Contributions

CL conceived the study concept. TW, MB, JM, and CW opted to proceed with the study. JH, JB, CW, and CL coordinated and collected the data. LL analyzed the data. JH and CL disseminated results. KB and LL wrote the first draft. All authors read and approved the final manuscript.

Disclosure

None.

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None.

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SUPPLEMENTAL 1
TRAUMA CLASSIFICATION CRITERIA

Class 1 Trauma Team Activation:

Major trauma patient with life- or limb-threatening injury
- SBP at any time <90 and/or clinical evidence of shock (altered level of consciousness [LOC], heart rate [HR] >120 with clinical signs of shock)
- Age-specific hypotension and/or clinical evidence of shock (altered LOC, decreased peripheral pulses, delayed cap refill)
  - 0–12 month SBP should be <70
  - 1–10 year SBP should be 70+ (age in years × 2)
  - 10+ SBP should be <90
  - Consider shock if blood products were given or if ≥40mL/kg crystalloid bolus administered to maintain vital signs
- Child ≤2 years with cardiopulmonary resuscitation (CPR) in progress
- Respiratory rate <10 or >29
- Penetrating injury to head, neck, torso, extremities proximal to elbow and knee (T-shirt/boxer shorts area)
- Flail chest, intubation at scene, airway compromise or obstruction, suspected tension/hemo/pneumothorax
- Orthopedic injuries:
  - Two or more proximal long-bone fractures (femur/humerus)
  - Extremity trauma with loss of distal pulse
  - Amputation proximal to wrist or ankle
  - Pelvic fracture (not to include hip fractures)
- GCS ≤8
- Open or depressed skull fracture
- Paralysis or signs of spinal cord/cranial nerve injury
- Any hemorrhage control issue:
  - Active or uncontrolled hemorrhage
  - Bleeding controlled by a tourniquet
- Facility transfer with patient requiring blood or blood pressure support
- Severe burn with or without associated trauma:
  - Partial or full thickness (2nd or 3rd degree)
  - Adult burn >20% body surface area (BSA)
  - >50 years with >10% BSA
  - Pediatric burn >15% BSA
  - Signs of inhalation injury

Class II Trauma Activation:

Blunt or penetration injury to areas other than the Class I activation criteria:
- >65 years and currently taking an anticoagulant (not aspirin)
- Amputation distal to the wrist or ankle
- Crush, degloving, or mangled extremity
- Open long bone fracture
- Two or more distal bone fractures
- Pregnant woman with blunt abdominal trauma not meeting other Class I criteria (does not include patients with injuries isolated to the fetus)
- Prolonged LOC
- Altered mental status
- GCS 9–14
- Neurological deficit associated with spinal cord injury (SCI) transferred from an outlying facility
- Fall ≥20 feet
  - Pediatric fall ≥10 feet
- Motor vehicle crash (MVC), high speed >40 mph
  - MVC >30 mph with unrestrained children <8 years
- MCI (any incident with 5 or more patients) or other ATV-like vehicle crash >20-mph
- Burns, partial and full thickness, with or without associated trauma, that do not meet other Class I criteria
  - Pediatric burns <15% not meeting other class I criteria
- Resuscitated drowning victim

Trauma team activation upgrades should be considered for the following co-morbidities in trauma patients ≥65 years of age:
- Anticoagulant use and bleeding disorders
- End-stage renal disease; patients requiring dialysis
- Adults ≥65 years of age with SBP <110mmHg and/or HR >90