MILITARY MEDICINE, 186, S1:300, 2021

Hypocalcemia in Military Casualties From Point of Injury to Surgical Teams in Afghanistan

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ABSTRACT

Introduction:

Hypocalcemia is a known sequela of citrated blood product transfusion. Civilian data suggest hypocalcemia on hospital admission is associated with worse outcomes. Initial calcium levels in military casualties have not previously been analyzed. The objective of this retrospective review aimed to assess the initial calcium levels in military trauma casualties at different Forward Surgical Teams (FST) locations in Afghanistan and describe the effects of prehospital blood product administration on arrival calcium levels.

Materials and Methods:

This is a retrospective cohort analysis of military casualties arriving from point of injury to one of two FSTs in Afghanistan from August 2018 to February 2019 split into four locations. The primary outcome was incidence of hypocalcemia (ionized calcium < 1.20 mmol/L).

Results:

There were 101 patients included; 55 (54.5%) experienced hypocalcemia on arrival to the FST with a mean calcium of 1.16 mmol/L (95% confidence interval [CI], 1.14 to 1.18). The predominant mechanism of injury consisted of blast patterns, 46 (45.5%), which conferred an increased risk of hypocalcemia compared to all other patterns of injury (odds ratio = 2.42, *P* = .042). Thirty-eight (37.6%) patients required blood product transfusion. Thirty-three (86.8%) of the patients requiring blood product transfusion were hypocalcemic on arrival. Mean initial calcium of patients receiving blood product was 1.13 mmol/L (95% CI, 1.08 to 1.18), which was significantly lower than those who did not require transfusion (*P* = .01). Eight (7.9%) of the patients received blood products before arrival, with 6/8 (75%) presenting with hypocalcemia.

Conclusions:

Hypocalcemia develops rapidly in military casualties and is prevalent on admission even before transfusion of citrated blood products. Blast injuries may confer an increased risk of developing hypocalcemia. This data support earlier use of calcium supplementation during resuscitation.

BACKGROUND

The metabolic and physiologic derangements seen in an exsanguinating trauma patient are well-documented. The so-called "lethal triad" of hypothermia, coagulopathy, and acidosis is a feared consequence of ongoing hemorrhage and ineffective resuscitation.[1] Massive transfusion protocols (MTPs) that replace crystalloids with blood products have been implemented in order to restore homeostasis to the injured patient and treat hemorrhagic blood failure.[2] Hypocalcemia is associated with massive resuscitation with blood products and chelation of serum calcium by the citrate in anticoagulant storage solutions.[3] Calcium plays a critical role in the coagulation cascade and thrombin generation.[3,4] Outside of the traumatically injured population, hypocalcemia is a frequent finding in hospitalized patients and correlates with severity of critical illness.[5] Studies have demonstrated that the incidence of hypocalcemia in trauma patients undergoing massive transfusion is high. Furthermore, many have demonstrated the need for vigilant calcium monitoring and aggressive supplementation.[1,4–8] MacKay et al. retrospectively reviewed calcium derangements during trauma resuscitations and demonstrated decreased mortality with ionized calcium levels within normal limits, even during massive transfusion.[9] Low ionized calcium levels at admission have been implicated in predicting the need for multiple transfusions and are associated with increased mortality in trauma patients.[7,8] These observations have led to formation of guidelines on calcium

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Presented as a poster at the 2019 Military Health System Research Symposium, Kissimmee, FL; MHSRS-19-00199.

The views expressed in this article are those of the authors and do not necessarily represent the official position or policy of the U.S. government, the Department of Defense, or the Department of the Army.

doi:10.1093/milmed/usaa267

supplementation during damage control resuscitation (DCR) in civilian trauma, as well as in military trauma throughout the full spectrum of military operations.

Before this retrospective review, the Joint Trauma System Clinical Practice Guideline (JTS CPG) for DCR recommended calcium administration after transfusing approximately four units of citrated blood products. The incidence of hypocalcemia on arrival in trauma patients has been studied within the civilian population. Studies have demonstrated between 40% and 70% of severely injured trauma patients are hypocalcemic on arrival.[1,10–12] In fact, an ionized calcium level of less than 1 mmol/L was seen in 22.9% to 56.2% in retrospective reviews of level 1 trauma patients.[8,10] Furthermore, studies have shown increased incidence of hypocalcemia in patients receiving prehospital blood product.[11] The objective of this retrospective review was to assess initial calcium levels in combat casualties at various forward deployed locations in Afghanistan and gain a better understanding of prehospital blood product administration on arrival calcium levels.

METHODS

This study is a retrospective cohort analysis of military casualties arriving from point of injury to one of two Forward Surgical Teams (FSTs) in Afghanistan from August 2018 to February 2019 split into four locations. FSTs provide DCR and surgery to bridge the time-space gap between wounding and definitive surgical care. The FSTs consisted of 10 members to include 2 surgeons; 1 nurse anesthetist; and a complement of nurses, medics, and operating room technicians. Military trauma casualties were included if they were seen at one of four FSTs. Exclusion criteria consisted of incomplete medical records, patients who received care from a surgical team before arrival, and patients who did not undergo initial lab testing on arrival. Hypocalcemia was defined as ionized calcium level less than 1.2 mmol/L using the i-STAT Point of Care Systems (Abbott Laboratories, IL). Citrated blood products used for transfusion included stored low titer group O whole blood, red blood cells (RBC), fresh frozen plasma, cryoprecipitate, and platelets. MTP was defined as greater than 10 units of low titer group O whole blood or RBCs within 24 hours. Admission calcium was recorded as well as the discharge calcium. Some patients received blood in the prehospital setting and these were analyzed separately. All FST facilities followed the JTS CPG for calcium replacement at the time: administrating one gram of calcium, either calcium gluconate or calcium chloride, after four units of citrated blood product had been transfused or if clinically indicated after lab testing.

RESULTS

There were a total of 101 patients meeting the criteria for inclusion. The predominant mechanisms of injury consisted of blast injuries (45.5%, 46/101) and penetrating injury (31.7%, 32/101) (Fig. 1). There was an average of 18 minutes from arrival in the FST to initial lab draw results. There was no significant difference in time to initial lab draw in patients who received blood products and those who did not ($P = .18$). Furthermore, there was no significant time to initial lab draw in those that were hypocalcemic on arrival compared to those who were normocalcemic ($P = .11$). A total of 38 patients (37.6%) required blood product transfusion during FST admission (Fig. 2). Of the patients who required blood transfusion, 71.1% (27/38) required at least 4 units of citrated blood products and 18.4% (7/38) required MTP.

Overall, 54.5% (55/101) of patients were hypocalcemic on arrival to the FST with a mean calcium of 1.16 mmol/L (95% confidence interval [CI], 1.14 to 1.18). Initial calcium levels ranged from 0.68 to 1.31 mmol/L. The median for the lowest calcium measured was 1.16. Patients sustaining blast injuries were significantly more likely to present with hypocalcemia (odds ratio = 2.42, $P = 0.042$). An additional 10.8% (11/101) of patients became hypocalcemic during FST admission who had arrived normocalcemic. As high as 86.8% (33/38) of patients requiring blood product transfusion were

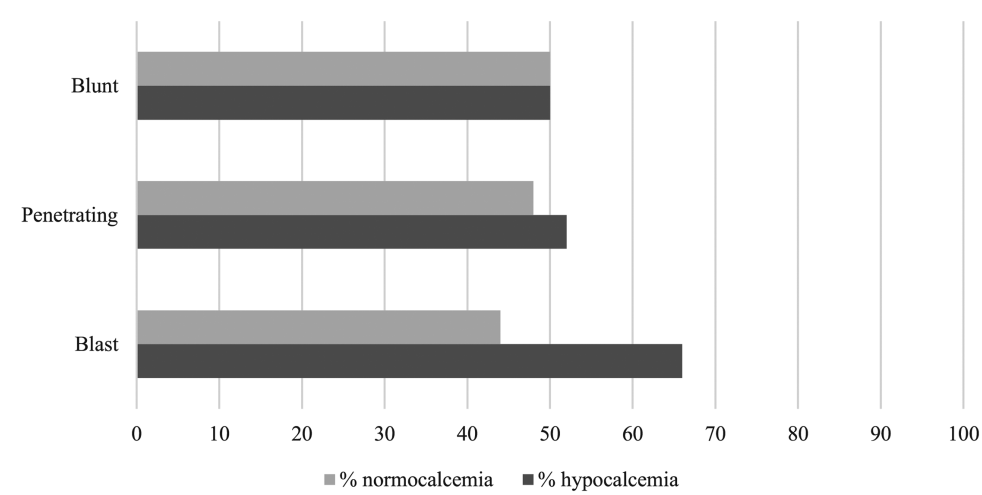

FIGURE 1. Description of the patterns of injury within the patient population and incidence of hypocalcemia for each mechanism of injury.

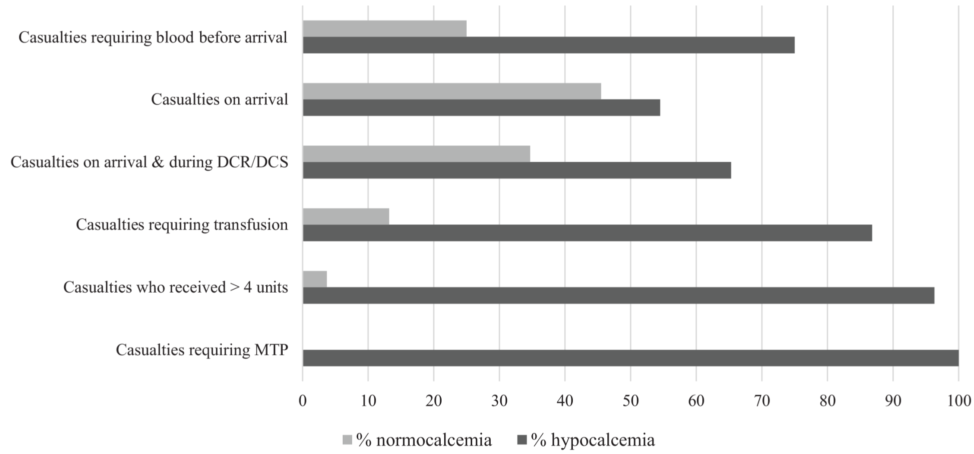

FIGURE 2. Description of patients requiring blood transfusion and incidence of hypocalcemia on arrival. DCR = damage control resuscitation; DCS = damage control surgery; MTP = massive transfusion protocol.

TABLE I. Distribution of Calcium Levels in Patient Population

Ionized calcium level (mmol/L)	Number of casualties (%) (*n* = 101)	Number of casualties that required transfusion (%) (*n* = 38)
<0.9	4 (2.9)	4 (10.5)
0.91-1.0	6 (5.9)	4 (10.5)
1.01-1.10	11 (10.9)	6 (15.8)
1.11-1.19	34 (33.7)	11 (28.9)
>1.2	46 (45.5)	13 (34.2)

hypocalcemic on arrival (Fig. 2). The initial mean calcium of patients receiving any blood product was 1.13 mmol/L (95% CI, 1.08 to 1.18). This was significantly lower ($P = 0.009$) than the initial mean calcium of patients not receiving blood products (mean 1.19 mmol/L; 95% CI, 1.17 to 1.2). Hypocalcemia on arrival was seen in 85.7% (6/7) of patients requiring MTP (mean 1.09 mmol/L; 95% CI, 0.80 to 1.4). All patients who required MTP were hypocalcemic at some point during care at the FST. Persistent hypocalcemia despite calcium supplementation was seen in 32% of patients. The distribution of calcium levels in all patients and those that received blood product is illustrated in Table I.

As high as 7.9% (8/101) of patients received citrated blood products before arrival from the point of injury or during aeromedical evacuation. A subset analysis of this group was performed. As high as 75.0% (6/8) were hypocalcemic on arrival to the FST with a mean calcium on arrival of 1.19 mmol/L (95% CI, 0.99 to 1.39). There was no significant difference in arrival calcium of the patients who received blood products before arrival compared to the rest of the cohort. The median lowest calcium for the patients receiving blood before arrival was 1.04 mmol/L.

DISCUSSION

This study evaluated the incidence of hypocalcemia in and associated factors in combat casualties arriving to forward surgical care. Previous iterations of the JTS CPG regarding calcium administration recommended supplementation following four units of citrated blood product transfusion. These recommendations were primarily based on current practice guidelines in the civilian sector. Literature based on civilian patient populations provides evidence-based approaches to care of the acutely injured patient. However, there remain many differences in the combat trauma population compared to the civilian sector. Although the majority of civilian trauma admissions are a result of blunt injury, greater than 70% of combat trauma admissions are combination of blast and penetrating mechanisms.[13] Furthermore, MTP occurs up to three times more often in combat trauma admissions.[14,15] Given these differences, it is important to describe combat trauma characteristics in order to help guide future JTS CPGs and validate the current combat clinical practice guidelines. Following this review, the JTS CPG was updated to suggest that supplemental calcium should be given after 1 unit of citrated product transfusion and continued to be monitored during ongoing resuscitation with a goal calcium of 1.2 mmol/L.

Our findings confirmed a high incidence of hypocalcemia on arrival to FSTs. In the civilian trauma population, Giancarelli et al. demonstrated incidence of hypocalcemia in their cohort as 97.4%, with the incidence of severe hypocalcemia (<0.9 mmol/L) at 71%.[3] Hypocalcemia has been defined in the civilian literature as anywhere from 1 to 1.16 mmol/L.[1,3–9] There is literature to suggest that laboratory defined hypocalcemia is not necessarily a useful marker in describing the deranged calcium homeostasis in trauma. Furthermore, data suggest calcium concentrations that deviate significantly from normal during large volume resuscitations result in higher mortality.[9] Although there is little data on whether correcting calcium levels to normal levels improves survival, it is clear that there is an inverse concentration-dependent relationship with mortality in traumatically injured patients.[7] With these findings in mind, this study defined hypocalcemia as ionized calcium less than 1.2 mmol/L. Also, this was the median

TABLE II. Amount of Product Resuscitation and Incidence of Hypocalcemia

Number of units of blood products transfused	Number of casualties	Number (%) of casualties with hypocalcemia	Number (%) of casualties who received calcium
1	3	2 (67%)	0 (0%)
2	6	3 (50%)	1 (17%)
3	2	2 (100%)	1 (50%)
4	6	6 (100%)	2 (33%)
5	1	1 (100%)	1 (100%)
6	2	2 (100%)	2 (100%)
7	1	1 (100%)	1 (100%)
8	1	1 (100%)	1 (100%)
10	3	3 (100%)	2 (67%)
12	1	1 (100%)	1 (100%)
13	1	1 (100%)	1 (100%)
14	1	1 (100%)	1 (100%)
15	1	1 (100%)	1 (100%)
16	2	2 (100%)	2 (100%)
18	2	1 (50%)	2 (100%)
19	1	1 (100%)	1 (100%)
25	1	1 (100%)	1 (100%)
31	1	1 (100%)	1 (100%)
50	1	1 (100%)	1 (100%)
70	1	1 (100%)	1 (100%)
	38 casualties	**33 casualties**	**24 casualties**

value of the reference range in the point of care testing used by the FSTs. In our study, greater than 50% of all trauma patients were hypocalcemic on arrival. The distribution of calcium levels within our patient population is described in Table I. As expected, incidence of hypocalcemia increased as citrated blood product was transfused (Table II). As high as 86.8% of patients that required any amount of blood product transfusion were hypocalcemic on arrival. Furthermore, there was a significant correlation in patterns of injury and incidence of hypocalcemia. Our findings demonstrated blast injuries were over twice as likely to present with hypocalcemia (Fig. 2). Similar observations were identified in regard to the early coagulopathy of trauma, previously thought to result from resuscitation practices, but identified to be present on admission and related to injury severity and associated mortality.[16] There are likely a number of underlying mechanisms responsible for the physiologic cause of hypocalcemia in the traumatically injured patient, which should be an area for further investigation.

Prehospital blood product transfusion is increasingly utilized in the civilian sector. Rehn et al. demonstrated that the use of prehospital transfusion has been shown to reduce RBC, fresh frozen plasma, and platelet consumption in severely injured patients.[17] Our study demonstrated that 75% of patients who received prehospital blood products were hypocalcemic on arrival. This group was also at risk for developing significantly lower calcium during their admission compared to patients that did not receive prehospital blood products. These findings highlight the importance of monitoring calcium levels in the acutely injured patient. In the past, calcium has not been routinely supplemented with initial product transfusion. However, there is evidence to suggest that early calcium supplementation in combat casualties can provide significant increases in ionized calcium levels. Kyle et al. analyzed the effect of supplementing calcium with prehospital blood product transfusion in military trauma patients. They found admission calcium levels of patients that received calcium with prehospital blood had a significantly higher ionized calcium that those that did not receive calcium.[18] This provides valuable insight into resuscitation of combat casualties and the need for early use of supplemental calcium. Despite calcium supplementation, patients undergoing blood product resuscitation remain at risk for hypocalcemia. Giancarelli et al. supplemented patients receiving four units of blood product or more with three times the recommended amount of calcium (6 g calcium gluconate) with little change in repeat ionized calcium levels.[3] Our review demonstrated that over 30% of patients who received supplemental calcium remained hypocalcemic. These findings suggest that the optimal supplemental calcium dose and timing is not determined.

This study highlights the need for intensive calcium monitoring and potential need for early supplementation in combat casualties. As the role of calcium in hemorrhage and resuscitation is being further elucidated, severe hypocalcemia must be avoided secondary to its impact on mortality in trauma patients. Based on the high incidence of hypocalcemia in military trauma patients, this study suggests that the threshold for calcium supplementation should be lower than previously suggested to avoid complications of hypocalcemia.

This retrospective review has several limitations. First, this was a pilot analysis in a small sample and requires validation in a larger data set. Second, the frequency of lab monitoring and timing of calcium supplementation was not well-documented, particularly the timing of subsequent ionized calcium levels in relation to blood product resuscitation or the time in which calcium was supplemented during the resuscitation. Such data could provide insight into the frequency at which calcium should be measured and the amount of calcium required for supplementation during initial resuscitation. Finally, patient mortality, further transfusion, or calcium supplementation required after the patients were discharged/transferred from the FST are unknown.

In summary, military trauma patients are at high risk for developing hypocalcemia regardless of blood product transfusion. Prior guidelines for calcium supplementation did not account for hypocalcemic patients who received less than four units of blood product, but did not exhibit signs of hypocalcemia. Earlier calcium supplementation should be considered. This analysis supports vigilant calcium monitoring in all military trauma patients early in their course of resuscitation. Avoidance of severe hypocalcemia in the deployed setting is imperative given its association with increased mortality. Further study is needed in trauma patients to determine the incidence of hypocalcemia early after injury, the association of hypocalcemia with mortality, the optimal timing and dose of calcium supplementation, and the potential benefit and associated risk of prehospital calcium supplementation.

ACKNOWLEDGMENTS

We would like to sincerely thank the Soldiers of the 8th Forward Resuscitative Surgical Team and 67th Forward Surgical Team for their dedication to the mission and tremendous ability to care for the injured patient.

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