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Original Article

A retrospective analysis of calcium levels in pediatric trauma patients

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Abstract: Traumatic injury is a major cause of morbidity and mortality in pediatric patients. Hemorrhage is a known but treatable component of these outcomes. Evidence exists that major trauma patients are at high risk for hypocalcemia but the rate of pediatric occurrence is not documented. The purpose of this study was to determine the incidence of hypocalcemia in pediatric trauma patients, as well as to investigate any correlation between hypocalcemia and the need for transfusion and operative intervention. After IRB approval a retrospective analysis was conducted of all pediatric trauma patients seen in our Adult Level One, Pediatric Level Two trauma center. Significance testing for mortality was performed using Pearson's χ^2 test. For the remaining numeric variables, association was determined one-way analysis of variance (when comparing all classes) or Welch's two-sample t-test (when comparing subsets based on calcium or mortality). In any event, significance was determined using $\alpha=0.05$. A total of 2,928 patients were identified, 1623 were excluded, primarily due to incomplete data. Patients were predominantly male following blunt trauma. Initial calcium levels were 8.73 mg/dL, 95% CI [4-10.9] and 8.97 mg/dL, 95% CI [6.42-13.1] when correcting for albumin levels. Acute declines were noted when comparing initial and corrected serum calcium levels in patients requiring transfusion (7.99 mg/dL and 8.72 mg/dL) and operative intervention (8.54 mg/dL and 8.91 mg/dL). 456 (34.9%) patients required operative intervention, 138 (10.6%) required transfusion and 29 (2.2%) required massive transfusion. Patients in our cohort arrived with calcium values on the low end of normal, with a trend towards hypocalcemia if operative intervention or blood transfusion was required. This has been previously associated with increased mortality. Patients requiring operative intervention and transfusion are at increased risk for hypocalcemia and recognition of this potential is key for improved outcomes.

Keywords: Hypocalcemia, pediatric, trauma, transfusion

Introduction

Traumatic injuries are a major cause of morbidity and mortality in pediatric patients. Over twelve thousand people aged 0 to 19 years die from unintentional injuries annually in the United States, with a large portion of these being due to blunt and penetrating traumas [1]. Hemorrhage is a known potential consequence of these events and may be significant enough to progress to traumatic shock. In addition to achieving source control of ongoing bleeding, the goals of managing traumatic shock are to maintain perfusion to end organs via oxygen delivery and ensure appropriate cardiac output [2]. Such trauma patients are at an increased risk of developing hypocalcemia through colloid-induced hemodilution, severe shock and ischemia-reperfusion. In addition, the binding of calcium with citrate, which is present in blood products as an anticoagulant, can further potentiate hypocalcemia when a patient receives multiple units of blood product or undergoes massive transfusion protocol [3, 4].

Calcium is an important component of coagulation, platelet aggregation, thrombus formation and cardiac contractility. Derangements in calcium levels can worsen outcomes in patients already at risk of developing hemodynamic instability due to the well-established "lethal triad" of acidosis, hypothermia, and coagulopathy [5]. There is even suggestion of adding hypocalcemia and transitioning to the "lethal diamond". In adult trauma patients, hypocalcemia is associated with increased need for blood products as well as increased mortality in trauma. Magnotti also reported 50% of adult trauma patients will have hypocalcemia at time of presentation, further compounding this effect [6].

While evidence suggests that major trauma patients are at high risk for hypocalcemia, the rate of hypocalcemia in the pediatric population specifically, as well its effect, is not well documented. Review of the literature demonstrated limited studies which supports the notation of further need for investigation in this area. One study of 435 pediatric trauma patients showed the incidence of hypocalcemia to be 41% and 46% in those receiving submassive and massive transfusions, respectively [7]. Another study from 1988 showed decreases in calcium and occasional episodes of clinically significant decreases in mean arterial pressure with rapid transfusion of fresh frozen plasma in pediatric burn patients [8].

The purpose of this study was to further determine the incidence of hypocalcemia in pediatric trauma patients, as well as to investigate any correlation between hypocalcemia, the need for transfusion, and operative intervention in the first twenty-four hours of presentation.

Methods

After IRB review, the study was determined to be no greater than minimal risk and exempt from continued review (STUDY00001462). Subsequently, the institutional trauma registry was queried for all pediatric (<19 years) trauma patients over an 8-year period (January 1st 2012-December 1st 2019). Data fields obtained by the trauma registrars included age, sex, blunt vs. penetrating, Injury Severity Score (ISS), Glasgow Coma Scale (GCS), initial hospital vital signs, length of stay and hospital mortality.

From this initial query the electronic records of identified patients were used to identify laboratory data to include initial serum calcium, ionized calcium (if available), serum albumin and International Normalization Ratio (INR). Additional data was obtained if the patient required operative intervention in the first 24 hours (operating room/interventional radiology), received calcium, the type and amount of blood products transfused in the first 24 hours and if the Massive Transfusion Protocol (MTP) was activated. All pediatric trauma patients were included in the study, exclusion criteria were receiving calcium prior to hospital arrival, pregnancy and incomplete data. This included a diverse patient population ranging from trauma transfers with isolated orthopedic injuries to polytrauma patients undergoing initial resuscitation. The registry includes patients expiring upon arrival and those amenable to more conservative management.

Study classes

The primary outcome of this study was to determine the incidence of hypocalcemia and severe hypocalcemia in pediatric trauma patients. The secondary outcome of this study was to determine the impact of hypocalcemia on rate of transfusion, operative intervention and mortality, these outcomes were used for subgroup analysis. Calcium levels throughout the study utilize albumin corrected calcium levels to substitute for the lack of ionized calcium levels. Descriptive statistics were done for the entire sample (1305 patients) and sub group analysis was done for patients with a corrected serum calcium less than 9 mg/dL, the facility low calcium limit (625 patients), required operative intervention (456 patients) or received a transfusion (135 patients). There is no age correction for pediatric patients though it is accepted that serum calcium levels are lower at birth but peak at age 15-25. 536 of the study patients were above age 14 and accounted for a significant number of the hypocalcemic and mortality patients. Arterial blood gases (Ionized Calcium) are not routinely obtained on pediatric trauma patients so serum calcium, serum albumin and corrected calcium were utilized for analysis [9]. The rate of transfusion was evaluated on the basis of standard 350 milliliter (ml) units for blood and plasma and one pooled (6 pack) unit of platelets, all delivered with-in the first 24 hours from hospital arrival. Operative intervention was determined on the basis of surgical or interventional radiology with-in the first 24 hours. Mortality was evaluated by the number of days from the time of trauma to death if it occurred during the initial admission, subsequent admissions were not evaluated (**Figure 1**).

Statistical analysis

Patients were first divided into classes based on outcome measures. They were also categorized as hypocalcemic or not based on whether or not their corrected serum calcium fell below 9. Significance testing for mortality was performed using Pearson's χ^2 test. For the remaining numeric variables, association was determined one-way analysis of variance (when comparing all classes) or Welch's two-sample t-test (when comparing subsets based on calcium or mortality). For other categorical data, Pearson's χ^2 test was used. In any event, significance was determined using α=0.05. Data analyses were performed using a combination of tools, including Perl 5.30, R 3.6.1. and an add-on xlsx package for R (version 0.6.5).

Results

Demographic data

There were 2,928 pediatric patients entered into the trauma registry over 8 years. Of those, 1623 were excluded primarily due to incomplete laboratory data for analysis; isolated orthopedic injuries that didn't have laboratory samples obtained (n=1575), arrived without signs of life (n=48) and pregnancy (n=3). The patients (**Table 1**) were predominately male 67.5% (881/1305) with an average age of 11.24 years (1 month-18 years). The mean ISS of the entire cohort was 12.14 (1-75) and 1089 (83.3%) were seen after blunt injury. As would be expected patients requiring transfusion had a higher ISS, percentage of penetrating injuries and lower GCS. The remaining samples had a similar ISS and mortality rate though the hypocalcemic and intervention cohorts were slightly higher. The overall in hospital mortality was 3.8% (49/1305) with an average ISS of 34.8 (25-75) among those that died. Due to the age range and associated hemodynamic variability encountered throughout the sample the value of heart rate, blood pressure and shock index was negated.

Laboratory findings

We hypothesized hypocalcemia would be associated with increased morbidity and mortality. Initial calcium levels were 8.73 mg/dL, 95% CI [4-10.9] and 8.96 mg/dL, 95% CI [6.42-13.1] when correcting for albumin levels (**Table 2**). Acute declines were noted when comparing the overall sample with patients that died and those requiring blood transfusion. Though not consistently obtained ionized calcium levels were on the lower end of the normal range mean =1.1 mmol/L, 95% CI [0.84-1.36] and 41 (3.13%) received supplemental calcium either in the form of calcium chloride or calcium gluconate. The mean INR was noted to be elevated in all groups; overall-1.22, calcium less than 9-1.26, operative intervention-1.25 and transfusion-1.56. This finding has been previously established as a predictor of mortality in pediatric trauma patients [10].

Outcome

Length of stay was higher in the cohorts with lower calcium values (transfused, operative intervention and calcium <9) (**Table 3**). Low titer whole blood, with a lower citrate level, is now used in trauma patients over age 14 but was not utilized during the study period. The hypocalcemic patients also required increased amounts of transfusion when compared to the overall population. Of note when looking at the MTP patients, those that received calcium replacement had a higher ISS 31 vs 20, lower corrected calcium 8.48 mg/dL vs 8.53 mg/dL and higher volume of transfusion (mean =19.25 vs 3.38 units). Thus, higher acuity (MTP/ISS) patients had their calcium replaced more frequently but without clear mortality benefit (50% vs 66%). Also, of note, the patients that received calcium also received an actual massive transfusion as opposed to just an activation. The calcium replacement group only had 1 patient that didn't receive a large volume transfusion versus 9 in the non-calcium replacement group.

The institutional high limit for serum calcium is 10.2 mg/dL. In the overall sample there were 29 patients with a corrected calcium level greater than 10.2 mg/d, with a mean corrected calcium level of 11.4 mg/dL. Their mean ISS

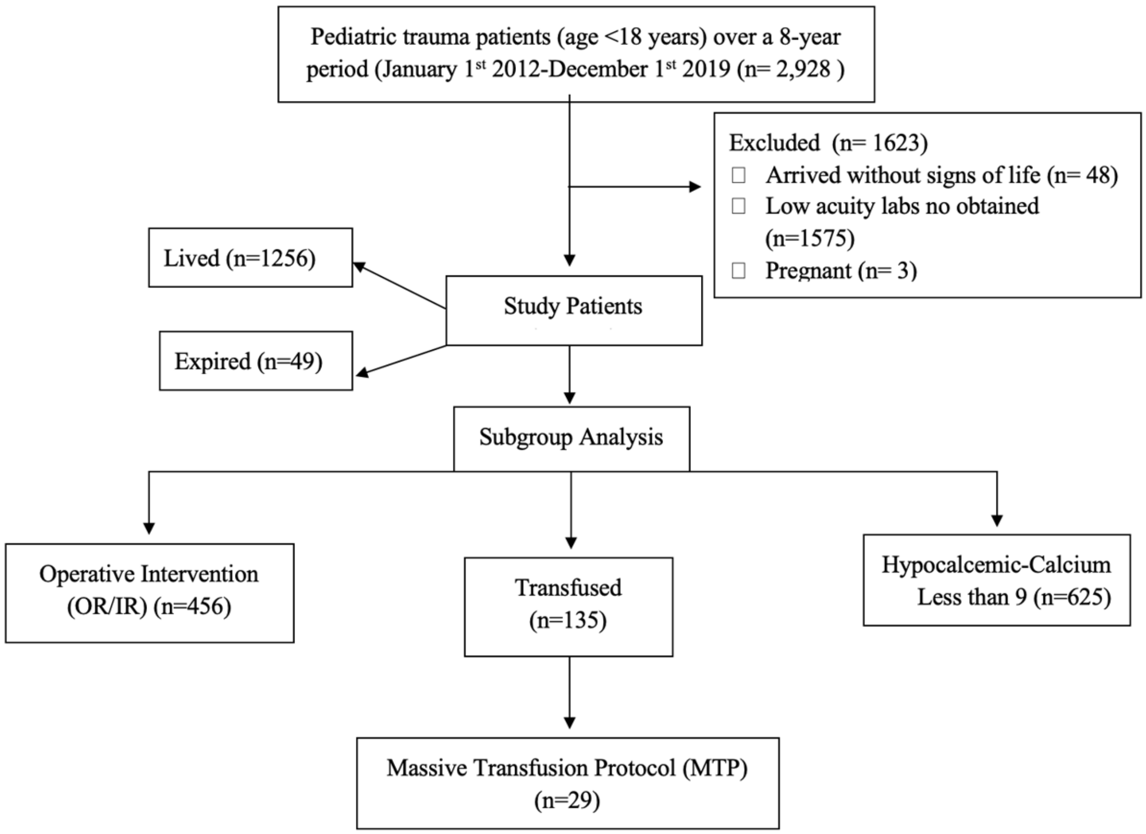

Figure 1. Study flow diagram.

was 7.8, much lower than any of the other groups evaluated and there were no mortalities in the group. The had a short mean length of stay at 3.2 days and all presented with a GCS of 14-15 decreasing the likelihood of neurologic injuries as the primary complaint. Only one of these patients received a blood transfusion, none required MTP activation or calcium replacement (**Tables 4**, **5**).

Discussion

The primary outcome of this study was to determine the incidence of hypocalcemia and severe hypocalcemia in pediatric trauma patients. The secondary outcome of this study was to determine the impact of hypocalcemia on rate of transfusion, operative intervention and mortality. This study is the first to look directly at calcium values in pediatric trauma patients and its effects on morbidity and mortality.

Our research suggests that there is an association between hypocalcemia and mortality, as the average calcium value in our cohort of patients that lived was 8.97 mg/dL, while the average calcium value was 8.64 mg/dL in the cohort that died. There were a total of 625 patients that presented with initial calcium values of less than 9, and of these 625 patients, a total of 347 (39.5%) required operative intervention. Despite a large number of hypocalcemic patients requiring the OR/IR, only 34 patients (5.4%) were given calcium supplementation. Abnormal calcium values have gained increasing attention in trauma literature [11]. Several studies have suggested the significance of hypocalcemia on patient outcomes though knowledge regarding calcium replacement appears to be lacking [12, 13].

Based on our data, there is an association between hypocalcemia and increased mortality. Early administration of calcium supplementation could have a positive outcome on both morbidity and mortality, while potentially reducing the amount of blood required for transfusion as well. As seen in our data collection,

Table 1. Mean epidemiologic and hemodynamic characteristics

	ISS	Blunt	Lived
Overall	12	1089 (83.3%)	1256 (96.2%)
Transfused	23	87 (64.4%)	109 (80.7%)
Calcium <9	15	501 (80.1%)	592 (94.7%)
Required OR-IR Intervention	14	341 (74.8%)	435 (95.4%)

ISS-Injury Severity Score.

Table 2. Hemodynamic characteristics **Table 3**

	SBP	HR	GCS
Overall	123	106	13
Transfused	110	121	10
Calcium <9	124	105	13
Required OR-IR Intervention	124	108	13

GCS-Glasgow Coma Scale, SBP-Systolic Blood Pressure (mmhg), HR-Heart Rate.

patients did trend towards hypocalcemia if they required operative intervention, which was also associated with increased mortality. As a result, it can be extrapolated that early correction and replacement of calcium in pediatric trauma patients could have a positive effect on the morbidity and mortality of this specific subgroup of patients.

Regionally, the incidence of blunt trauma is likely influenced by the frequency of motor vehicle collisions as our trauma center catchment area encompasses a large network of open highways and interstates with speed limits in excess of 60 miles per hour. In terms of generalizability, it is reasonable to assume some variability in these ratios, but examination of the central question regarding incidence and degree of hypocalcemia after blood product administration in trauma was not expected to be impacted.

Treatment of hypocalcemia in pediatric trauma patients can be complex and age dependent [14]. Intravenous treatment with calcium salts is ideal but may be limited by tenuous vascular access and the patient's hemodynamic status [15]. Infiltration of calcium solutions can cause severe tissue necrosis. As most patients in our study receiving calcium replacement trended towards adulthood, intravenous access may be less of a concern. Nonetheless, patency of vascular access is essential and if in doubt, intraosseous infusion should be considered. One study suggests the use of 10% calcium gluconate for neonatal and infants but there is limited evidence supporting the use of calcium chloride in this population [16]. Several studies support the use of calcium chloride in ages birth to 18 and are focused on treatment of citrate induced chelation and acute cardiocirculatory failure, both conditions that may occur in severe trauma [17]. Interestingly, younger pediatric patients seem to benefit the most from calcium replacement in non-traumatic situations [18].

Citrate chelation has long been recognized as a contributing factor to hypocalcemia [19]. This is worsened in balanced blood product resuscitations which have become a cornerstone of damage control resuscitation. It is currently unknown if the pathophysiology of trauma predisposes patients to hypocalcemia or if it's a side effect of treatment but it is clear that it worsens outcomes [20]. A study from the United Kingdom found that 55% of trauma patients presenting to the accident center were hypocalcemic prior to the administration of blood products [21]. In our study, the predominance of hypocalcemia in the transfused population was second only to the subgroup of known hypocalcemic patients.

Literature in patients with primary hyperparathyroidism found that serum calcium may be an appropriate screening tool for hypocalcemia but ionized calcium levels provide a more sensitive marker of disease severity [22]. Due to changes in the original testing process and estimation of albumin levels using the Payne method there may be inaccuracies in calculation of corrected serum calcium, though more concerningly they seem to overestimate calcium levels [23-25]. These findings indicate that ionized calcium values are beneficial for pediatric trauma patients and should be obtained if possible, including utilization of a venous sample.

Our study has several limitations, including its retrospective nature and the required exclusion of a significant number of patients due to incomplete data. Patients in this incomplete data spectrum were on opposite ends of the

Table 3. Corrected calcium levels

	Calcium Level (Range)	Std Dev	*P* Value
Overall	8.73 mg/dL (6.42-13.1)	0.6	<0.01
Lived	8.97 mg/dL (7.1-13.1)	0.6	<0.05
Died	8.64 mg/dL (6.42-9.6)	0.77	0.11
Transfused	8.72 mg/dL (6.96-12.4)	0.59	<0.05
Calcium <9	8.55 mg/dL (6.42-8.9)	0.32	<0.05
Required OR-IR	8.91 mg/dL (6.96-12.4)	0.64	<0.05

Table 4. Length of Stay, Mortality and Transfusion Data

	RBC	FFP	PLT
Overall	3.26	3.1	1.35
Transfused	3.21	3.1	1.37
Calcium <9	3.71	3.4	1.39
Required OR-IR Intervention	3.51	3.5	1.37
P Value	<0.01	<0.01	0.18

RBC-Red Blood Cell, FFP-Fresh Frozen Plasma, PLT-Platelet, blood products are expressed in units.

Table 5. Length of stay and mortality

	LOS	Mortality %
Overall	6.55	3.8
Transfused	15.1	19
Calcium <9	8.46	5.3
Required OR-IR Intervention	9.48	4.6
P Value	<0.01	

Length of Stay (LOS) is expressed in days.

curve. Most were low acuity isolated orthopedic injuries but there were also patients that were moribund upon hospital arrival and also never had labs drawn. Higher acuity patients may have already received transfusions which would have decreased their initial calcium levels. Laboratory data outside the initial admission period (24 hours from the time of injury) were excluded. The lack of routine ionized calcium measurements also impacted the study and necessitated the use of corrected serum calcium as our primary measurement. Serum magnesium levels may be low in patients with hypocalcemia, magnesium levels are not collected at our institution as part of routine chemistry panels [26]. It would be necessary to have a higher rate of ionized calcium results collected on all arrived to arrive at more definitive conclusions. There was no standardization for which patients had labs drawn though if patients did not have a complete set of labs to include calcium and albumin they were excluded. This could be accomplished by encouraging a shift in current practices, adding the order to the standard trauma laboratory study panel, or by simply expanding the study to include a larger number of centers.

The data are from a single institution; however, with a sample size of 1305 patients, it represents a larger data set than any other previously reported studies. Accruing large numbers of high acuity pediatric trauma patients at any one institution can be challenging, and this necessitated a longer data collection period. The implementation of the current electronic medical records was utilized for convenience sampling. During this extended data collection there were multiple changes in care modalities to include the implementation of tranexamic acid, prehospital transfusion, and increased adoption of damage control resuscitation. Finally, our study merely measured the incidence of hypocalcemia in pediatric trauma patients and correlation with a limited number of outcome measures. Though previous studies have suggested hypocalcemia is associated with negative results we did not evaluate the role of calcium replacement on improved outcomes.

Conclusion

The focus of this study was to review calcium values at the time of presentation. Our study highlights the significance and importance of calcium in pediatric trauma patients. Further studies looking at trends of calcium values over the course of admission are warranted and could provide additional insight into the role of calcium in pediatric trauma patients. The data collected in our study indicates that more emphasis on correction of hypocalcemia is required and could reduce overall morbidity and mortality.

Patients in our cohort arrived with calcium values on the low end of normal, with a trend towards hypocalcemia if operative intervention or blood transfusion was required. This has been previously associated with increased mortality. As such, these patients face compounded risks of pathophysiologic and iatrogenic processes secondary to trauma including coagulopathies and dysrhythmias. Patients requiring operative intervention and transfusion are at increased risk for hypocalcemia and recognition of this potential is key for improved outcomes. The future study of hypocalcemia in pediatric trauma patients should ideally involve multiple institutions working in collaboration. Further study could also focus on dosage and timing of calcium administration as it corresponds to citrate burden. It would be interesting to see not only its impact on mortality but also on observed hemodynamic changes. End points of future studies wound likely need to be expanded beyond retrospective study alone to detect any benefits. Additionally, efforts should be made to evaluate the role of calcium replacement on morbidity and mortality. Given the relationship between transfusion, hypocalcemia, and increased mortality, consideration should be given to routine measurement of early ionized calcium levels in injured pediatric patients requiring transfusion and early replacement as indicated.

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Disclosure of conflict of interest

None.

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