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ORIGINAL RESEARCH

Pre-Hospital Calcium Administration Reduces Incidence of Hypocalcemia and Mortality in Trauma Patients

Oluwafolaranmi E Sodade[1], Katherine A Kummer[2], Cindy L Austin[1], Brian B Draper[3]

[1]Trauma & Burn Research, Mercy Hospital, Springfield, MO, 65804, USA; [2]Trauma Department, Mercy Hospital, St. Louis, MO, 63141, USA; [3]General & Trauma Surgery, Mercy Clinic, Springfield, MO, 65804, USA

Correspondence: Oluwafolaranmi E Sodade, Trauma & Burn Research, Mercy Hospital, 1235 E Cherokee, 5H, Springfield, MO, 65804, USA, Email fola.sodade@mercy.net

Background: Extensive literature has established how critical calcium is to countless physiological pathways; however, the consequences of trauma-induced hypocalcemia, if not pro-actively managed, are often overlooked. Data suggests that timely calcium administration may be advantageous in correcting hypocalcemia and preventing unfavorable clinical outcomes. There is limited data examining the impact of pre-hospital calcium administration in trauma patients transported from the injury scene by air ambulance. Our Lifeline air transport service initiated a pre-hospital calcium administration protocol in October 2021.

Objective: To determine the efficacy of the pre-hospital calcium protocol on ED ionized calcium (iCa) values and clinical outcomes.

Methods: A single-center, retrospective cohort analysis of 87 trauma patients transported from the scene via Lifeline air services was conducted. Cohort 0 had 54 patients who received pre-hospital blood products without calcium, and Cohort 1 had 33 patients who received blood products and calcium. Eleven patients were excluded from final analysis due to missing iCa values.

Results: Cohort 1 had significantly higher iCa values (4.92 ± 0.74 vs 4.24 ± 0.76 mg/dL, p-value = 0.007) and lower incidences of hypocalcemia (multivariate OR: 0.03 [95% CI: 0.002, 0.27]) when compared with Cohort 0. Hospital mortality rates appeared lower in Cohort 1 compared to Cohort 0, though this difference did not reach statistical significance (p-value = 0.38). Clinical data points including ICU and hospital length of stay were similar. Twelve patients were hypercalcemic on ED arrival: nine in Cohort 1, and three in Cohort 0. This could be attributed to variable injury severities, comorbidities, type and volume of blood products, and calcium overtreatment.

Conclusion: The administration of pre-hospital calcium significantly reduced episodes of hypocalcemia and severe hypocalcemia.

Keywords: trauma-induced hypocalcemia, hypercalcemia, pre-hospital blood products administration, calcium supplementation, ionized calcium on ED arrival

Introduction

Calcium is an integral element in multiple organ systems and pathways, assisting in skeletal mineralization, mediating cell responses to hormones, platelet adhesion, coagulation, and contractility of myocardial and smooth muscle cells.[1,2] Citrate, a calcium chelating anion, is applied in the manufacturing, collection and storage of blood products as an anticoagulant. The hepatic breakdown of infused citrate in massive transfusions may cause citrate toxicity, leading to disruption of calcium-dependent pathways, hypocalcemia, inhibition of clot formation, and increased mortality.[3,4]

Acute coagulopathy in trauma patients after sustaining blood loss and worsened by transfusion can lead to low ionized calcium (iCa) levels, with the risk of hypocalcemia and significantly increased incidences of organ dysfunction, morbidity and mortality.[5–7] The critical implication of hypocalcemia in trauma is connected to components of a lethal triad which includes acidosis, coagulopathy, and hypothermia. Due to the indirect and direct negative effects of hypocalcemia on each section of the triad, there have been suggestions of a proposed lethal diamond, which supports calcium as a fourth potential component.[8–10]

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Current data suggest that early administration of calcium may be advantageous in the management of trauma patients who receive blood products and are at risk of hypocalcemia, which has been independently associated with acute traumatic coagulopathy.[7,11] Although published literature has established the benefit of maintenance of ionized calcium levels in trauma patients, professional guidelines from organizations such as the American College of Surgeons Trauma Quality Program and the German Trauma Society TraumaRegister DGU state only that hypocalcemia should be prevented in patients receiving massive transfusion;[12,13] the European Task Force for Advanced Bleeding Care in Trauma recommends the use of calcium chloride over calcium gluconate, but does not discuss administration details such as timing or dosing.[14] The American College of Surgeons Advanced Trauma Life Support Manual briefly states that calcium administration should be based upon serum calcium levels.[15] The 2019 clinical practice guideline from the Joint Trauma System regarding damage control resuscitation gives a specific calcium administration regimen, recommending that one gram of calcium be given i.v./i.o. following the first transfused blood product and after every fourth blood product thereafter. It does, however, also caution providers against giving calcium chloride peripherally, citing a risk of skin necrosis.[16] Given these limited guidelines, the development of an institutional protocol for calcium administration in patients receiving massive transfusion is a complicated task. This is especially challenging in the prehospital setting, for which recommendations are even less clear.

Pre-hospital transfusion of blood products is becoming increasingly recognized as a beneficial approach to early treatment of critically ill patients with hemorrhagic conditions. Though it may also occur in patients without pre-hospital blood transfusion,[17] a study by Mooreet al found that the incidence of hypocalcemia is significantly higher in those who received two units of plasma.[18] Work by Cherryet al showed higher risks of pre-hospital hypotension, base deficit, and mortality among trauma patients with iCa ≤ 1.[19] Publications specifically addressing the utility of pre-hospital calcium administration remain limited, and its effects on outcomes are not yet definitively recognized.

Our Lifeline air transport service initiated a calcium administration protocol in October 2021. Based on existing literature, we hypothesized that patients who were administered replacement calcium enroute to the hospital would have iCa levels within the normal range and better clinical outcomes when compared with patients who did not have pre-hospital calcium replacement. The objective of this study is to determine if the timeliness of calcium administration on our air ambulance en route the hospital was effective in maintaining a relatively normal iCa level in the emergency department (ED) and improving overall clinical outcomes.

Materials and Methods

A retrospective cohort analysis of adult patients, ages 18 and above, transported from the scene of injury between January 1, 2018, and August 31, 2024, by Lifeline air transport services was conducted. This study period encompasses the range for which relevant patient data was available at the time of data collection; data for all patients who met inclusion criteria during the study period was recorded. Cohort 1 was made up of patients who received blood products with calcium administered by the Lifeline air transport service enroute to the Level 1 trauma center. Patients who were transferred from other facilities or transported via personal vehicles or ground medical transport services were excluded. The policy of pre-hospital calcium administration was implemented by Lifeline in 2021; the study period included not only the years following implementation but also the prior three years to ensure that sufficient patients with recorded [iCa] who had not received pre-hospital calcium would be captured. The specific calcium administration protocol used by Lifeline providers is to push 1g calcium chloride i.v. over the course of two minutes for any adult patient undergoing blood product resuscitation.

For this study, normal blood calcium levels were defined to be between 4.8–5.2 mg/dL, corresponding to 1.2–1.3 mmol/L. This was based upon the reference range utilized by our electronic medical record software. Hypocalcemia and hypercalcemia were defined as any level outside this normal range of iCa: < 4.8 mg/dL hypocalcemia, and > 5.2 mg/dL hypercalcemia. Severe hypocalcemia is defined as any value less than 4.0 mg/dL (1.0 mmol/L).

Statistical methods included the calculation of odds ratios or mean differences and 95% confidence intervals to describe the effect of pre-hospital calcium administration on outcomes. Both univariate and multivariate linear regression models were employed. If a subject was missing a value for ED [iCa], they were removed from only those analyses

utilizing this value but remained included in comparisons of length of stay and mortality. Values were deemed significant if the *p*-value was less than 0.05.

Results

Summary

Eighty-seven datapoints met the inclusion criteria and were included in the descriptive analysis. Of these, 33 out of 87 trauma patients (37.9%) received both blood product transfusions and calcium administration during the prehospital period (Cohort 1). The remaining 54 patients (62.1%) received only blood products without calcium replacement (Cohort 0). All 33 patients in the calcium cohort received calcium chloride. Upon arrival at the hospital, the calcium statuses of the patients were as follows: 57.4% (50/87) hypocalcemic, 16.1% (14/87) normocalcemic, 13.8% (12/87) hypercalcemic, 12.6% (11/87) no iCa measured. Eleven patients in Cohort 0 were severely hypocalcemic (85%) (iCa less than 4.0mg/dL) compared to two patients only (15%) in Cohort 1.

iCa (mg/dL) Level in ED

Table 1 and Figure 1 compare the effects of prehospital calcium administration on admission iCa levels in trauma patients treated in the ED. The data indicates that patients who received calcium replacement alongside blood product transfusion during the pre-hospital period exhibited higher mean iCa levels with a lower standard deviation..

The univariate mean difference between the two groups is 0.68 (95% CI: 0.31, 1.04), indicating that patients who received pre-hospital calcium administration along with blood product transfusion had significantly higher iCa levels upon hospital admission compared to those who received only blood product transfusion (*p*-value = 0.0004).

A multiple linear regression model was used to further evaluate the impact of pre-hospital calcium administration on ED calcium levels (measured in mg/dL) while adjusting for demographic characteristics, type of injury, pre-existing comorbidities, type, and volume of pre-hospital blood products used and IV fluid administration. Using a significance threshold of 0.05, the multivariate mean difference is 0.79 (95% CI: 0.22, 1.36) with a *p*-value of 0.007.

These findings demonstrate that pre-hospital calcium administration has a statistically significant impact on iCa levels in trauma patients upon ED admission.

Hospital LOS

Table 2 compares the hospital length of stay (LOS) between trauma patients who received pre-hospital calcium administration and those who did not. The data show that the mean LOS for patients without pre-hospital calcium administration is 15.94 ± 20.33 days, while the mean LOS for patients who received calcium is 15.27 ± 14.88 days.

The univariate mean difference in LOS between the two groups is −0.67 days (95% CI: −8.39, 7.05), indicating no significant difference in LOS based on pre-hospital calcium administration (*p*-value = 0.86).

A multiple linear regression model was used to further assess the impact of pre-hospital calcium administration on LOS, adjusting for demographic characteristics, ISS, type of injury, pre-existing comorbidities, type and volume of pre-hospital blood products IV fluid administration, type and volume of hospital blood products, and hospital calcium administration. The multivariate mean difference was −5.79 days (95% CI: −19.02, 7.44), with no statistically significant association (*p*-value = 0.39).

Table 1 Comparison of Calcium Level Between Groups of Patients with and without Pre-Hospital Calcium Administration

Pre-Hospital Calcium Administration	Sample Size	Mean (mg/dL)	Standard Deviation (mg/dL)	Univariate Mean Difference with 95% CI	Multivariate Mean Difference with 95% CI
0	49	4.24	0.76	0.68 (0.31, 1.04)	0.79 (0.22, 1.36)
1	27	4.92	0.74		

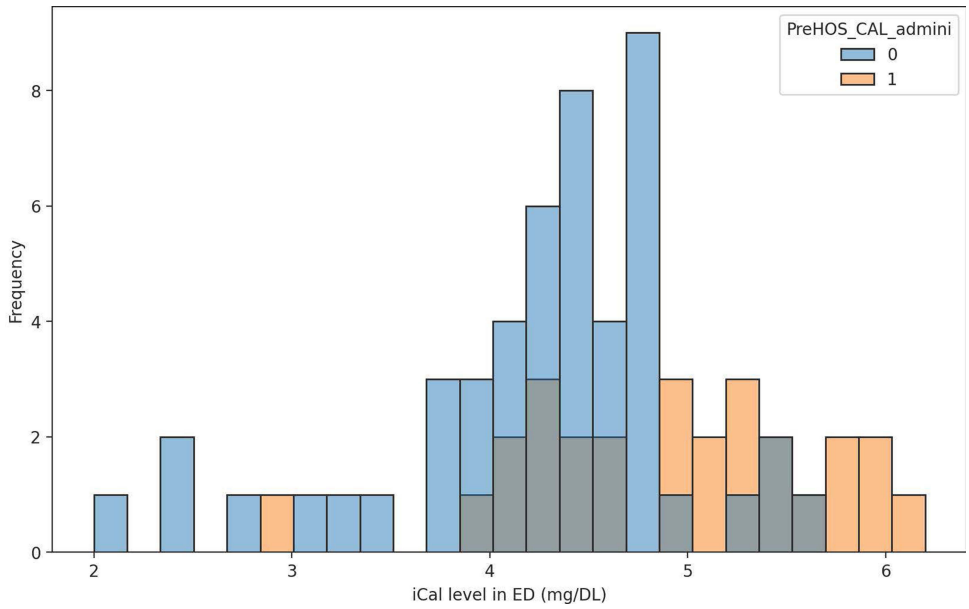

Figure 1 Histograms Comparing iCa Level in ED between groups of patients with (Cohort 1) and without (Cohort 0) Prehospital Calcium Administration.

These findings suggest that pre-hospital calcium administration does not have a significant impact on hospital LOS in trauma patients.

Incidence of Hypocalcemia

Hypocalcemia is defined as iCa levels below 4.8 mg/dL. The data indicates that 13.7% of trauma patients (12/87) exhibited hypercalcemia in the ED, while 12.6% of patients (11/87) were found to have hypocalcemia.

Table 3 compares the occurrence of hypocalcemia in trauma patients with and without pre-hospital calcium administration. Among patients who received only blood product transfusion, 79.6% (39/49) were hypocalcemic. In contrast, among those who received both pre-hospitalcalcium and blood product transfusion, 40.7% (11/27) were hypocalcemic.

The univariate odds ratio (OR) for hypocalcemia in patients who received pre-hospital calcium compared to those who did not was 0.18 (95% CI: 0.06, 0.50), indicating statistically significant association (p-value = 0.001).

Table 2 Comparison of Hospital LOS Between Groups of Patients with and without Pre-Hospital Calcium Administration

Pre-Hospital Calcium Administration	Sample Size	Mean (mg/dL)	Standard Deviation (mg/dL)	Univariate Mean Difference with 95% CI	Multivariate Mean difference with 95% CI
0	54	15.94	20.33	−0.67 (−8.39, 7.05)	−5.79 (−19.02, 7.44)
1	33	15.27	14.88		

Table 3 Comparison of Hypocalcemia Rates and Odds Ratios Between Trauma Patients with and without Pre-Hospital Calcium Administration

Pre-Hospital Calcium Administration	Sample Size	Subjects with Hypocalcemia	Univariate Odds Ratio with 95% CI	Multivariate Odds Ratio with 95% CI
0	49	39	0.18 (0.06, 0.50)	0.02 (0.002, 0.19)
1	27	11		

A multivariate logistic regression model was used to assess the impact of pre-hospital calcium administration on hypocalcemia, while adjusting for demographic characteristics, ISS, type of injury, pre-existing comorbidities, type, and volume of pre-hospital blood products, prehospital IV fluid administration. The multivariate odds ratio was 0.02 (95% CI: 0.002, 0.19), suggesting a statistically significant reduction in the odds of hypocalcemia with pre-hospital calcium administration (p-value = 0.001).

These findings indicate that pre-hospital calcium administration significantly reduces the likelihood of hypocalcemia in trauma patients.

Incidence of Hypercalcemia

Hypercalcemia is defined as iCa levels above 5.2 mg/dL. Table 4 compares the occurrence of hypercalcemia in trauma patients with and without pre-hospital calcium administration. Among patients who received only blood product transfusion, 6.1% (3/49) were hypercalcemic. In contrast, among those who received both pre-hospital calcium and blood product transfusion, 33.3% (9/27) were hypercalcemic.

The univariate OR for hypercalcemia in patients who received pre-hospital calcium compared to those who did not was 7.67 (95% CI: 1.86, 31.58), indicating statistically significant association (p-value = 0.003).

A multivariate logistic regression model was used to assess the impact of pre-hospital calcium administration on hypocalcemia, while adjusting for demographic characteristics, ISS, type of injury, pre-existing comorbidities, type, and volume of pre-hospital blood products and pre-hospital IV fluid administration. The multivariate OR was 188 (95% CI: 3.83, 9246), suggesting a statistically significant increase in the odds of hypercalcemia with pre-hospital calcium administration (p-value = 0.008).

These findings indicate that pre-hospital calcium administration significantly increases the likelihood of hypercalcemia in trauma patients.

ICU/Hospital and 30-Day Mortality

The data shows that the ICU/hospital mortality rate among trauma patients is the same as the rate observed within 30 days of hospital admission. Table 5 compares the rates of ICU/hospital mortality and the associated ORs in trauma patients with and without pre-hospital calcium administration. Among patients who did not receive pre-hospital calcium, 29.6% (16/54) died, whereas only five deaths occurred in patients who received pre-hospital calcium (15% [5/33]). It reveals that patients who received calcium administration appeared to show a lower mortality rate in the ICU/hospital compared to those who did not. However, the univariate OR for mortality in patients who received pre-hospital calcium

Table 4 Comparison of Hypercalcemia Rates and Odds Ratios Between Trauma Patients with and without Pre-Hospital Calcium Administration

Incidence of Hypercalcemia				
Pre-hospital Calcium Administration	**Sample Size**	**Subjects with Hypercalcemia**	**Univariate Odds Ratio with 95% CI**	**Multivariate Odds Ratio with 95% CI**
0	49	3	7.67 (1.86, 31.58)	188 (3.83, 9246)
1	27	9		

Table 5 Comparison of Hospital, ICU, and 30-Day Post-Admission Mortality Rates and Odds Ratios Between Trauma Patients with and without Pre-Hospital Calcium Administration

Pre-Hospital Calcium Administration	**Sample Size**	**Subjects with Hypocalcemia**	**Univariate Odds Ratio with 95% CI**	**Multivariate Odds Ratio with 95% CI**
0	54	16	0.42 (0.14, 1.30)	0.46 (0.05, 3.98)
1	33	5		

compared to those who did not was 0.42 (95% CI: 0.14, 1.3), indicating no statistically significant association (p-value = 0.20).

A multivariate logistic regression model was used to assess the impact of pre-hospital calcium administration on ICU/hospital mortality, while adjusting for demographic characteristics, ISS, type of injury, pre-existing comorbidities, type and volume of pre-hospital blood products, pre-hospital IV fluid administration, type and volume of hospital blood products and hospital calcium administration. The multivariate OR was 0.46 (95% CI: 0.05, 3.98), suggesting no statistically significant impact of pre-hospital calcium administration on mortality rates (p-value = 0.48).

These findings indicate that pre-hospital calcium administration does not have a statistically significant effect on the likelihood of mortality in trauma patients.

Discussion

To the best of our knowledge, this is the first review of trauma patients measuring the impact of pre-hospital calcium administration transported by Lifeline air transport services from the scene of injury to ED admission. The first cohort of patients who received blood products and supplemented calcium enroute the hospital, associated with lower incidences of hypocalcemia and an overall significant increase of iCa on ED admission, when compared with the second cohort of patients who similarly received blood products but without calcium supplementation. These findings are relevant after adjustment by a multivariate logistic regression model to demographic characteristics, type of injury, pre-existing comorbidities, type and volume of pre-hospital blood products, and pre-hospital IV fluid administration.

Our finding showed that eleven (85%) of patients in Cohort 0 presented with severe hypocalcemia which is consistent with multiple studies that traumatic injuries coupled with necessary transfusion of blood products are associated with worsening hypocalcemia.[2,6,7,9] Similarly, a study by Giancarelli et al (2016) reviewed 156 patients and showed that 97% of trauma patients who received massive transfusion experienced hypocalcemia, with 71% of those experiencing severe hypocalcemia, (less than 0.90 mmol/L).[20]

Despite not meeting statistical significance, our results showed a higher percentage of mortality (76%) in Cohort 0 when compared to Cohort 1 (24%), corroborating several studies indicating a higher mortality rate in trauma patients who had a lower level of iCa, regardless of age or injury severity.[19–22]

The negative effects of blood calcium variations are critical to address in trauma patients. Mild hypocalcemia may be tolerable, but severe hypocalcemia and hypercalcemia should be prevented. Hypercalcemia has been associated significantly with mortality upon ED admission, following pseudo-hypocalcemia leading to either overcorrection or over-treatment. Administering the correct dose response of calcium supplementation to blood products is crucial.[23]

These results showed that 33.3% (9/27) patients who received pre-hospital calcium supplementation along with blood products were significantly more likely to experience upon arrival to the ED. This outcome highlights the importance of serial ionized calcium testing, importantly, in the prehospital settings to prevent the risks associated with the fixed, non-guided administration regimen.

Published work by Helslootet al demonstrated a parabolic relationship between iCa level and mortality in which patients with [iCa] $\geq$ 1.3 mmol/L had an increased risk of death within six hours of presentation and higher incidence of coagulopathy than normocalcemic individuals.[12] This is a key consideration as coagulopathy is a component of the lethal triad and is known to influence trauma outcomes. Similar results were presented by Becker et al, who reported an odds ratio of 17.5 for 30-day mortality in the hypercalcemic cohort.[24] Further research is warranted to determine the optimal parameters for pre-hospital calcium administration.

The hospital LOS was similar in both cohorts which is reflective of the confounders including the varying levels of injury severities, co-morbidities and age disparities.

Limitations

A study by Spinella et al showed that trauma patients transfused at least one unit of a blood product; FFP and RBC amounts were independently associated with increased survival and decreased survival, respectively.[25] Our study, despite identifying and recording the different blood products administered in the pre-hospital (Lifeline) settings, did not analyze the eventual outcomes of these groups separately.

Early coagulopathy increases transfusion requirements and incidences of organ dysfunction; the recognition of this coagulopathic state has care implications for shocked patients and the management of massive transfusion.[5] This, however, could not be determined in the pre-hospital setting since diagnosis requires a laboratory assessment of clotting times and could be a factor leading to overtreatment and eventual hypercalcemia noted in nine patients in Cohort 1. Recognizing this major limitation, we recommend a titration regimen based on real-time iCa testing in future projects.

Due to foreknowledge regarding the limited number of patients presenting under the circumstances required for inclusion, the study design involved inclusion of all eligible subjects within the study period, rather than performance of a priori power calculation. Therefore, our limited sample size may restrict the interpretability of the results. The retrospective nature of the study also limits wider applicability.

Currently, there are varying guidelines for the correction of hypocalcemia during ongoing trauma resuscitation; extensive work needs to be done as regards repletion by specific blood product. The physiological effects of variability of citrate in blood products, storage metabolism, decreased clearance and prolonged circulation have direct interaction with coagulopathy, academia, hypothermia, and hypocalcemia.[12,26] Factors other than hypocalcemia were not addressed in our study.

Conclusion

Overall, prehospital calcium management significantly increased the iCa level at ED admission, reduced the incidence of hypocalcemia and severe hypocalcemia, but also significantly increased the risk of hypercalcemia. Future studies are needed to identify standardized, potentially test-based administration regimens to balance its benefits and risks.

Ethics

This study was reviewed and approved by the Mercy Institutional Review Board and determined as Exempt from the Common Rule under 45 CFR 46.104. All the guidelines in the Declaration of Helsinki were followed. A waiver of consent and HIPAA authorization was approved specifically for the use of protected health information to confirm study eligibility and confirmation of clinical information that cannot be obtained by available de-identified information. Patient data were confidential and secured in a master key which was deleted upon study completion.

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Disclosure

The authors report no conflicts of interest in this work.

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