Aggressive calcium chloride dosing reduces early mortality in trauma patients receiving whole blood resuscitation

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BACKGROUND: Hypocalcemia has been recognized as a contributor to trauma-related mortality, yet optimal dosing of calcium during massive transfusion remains undefined. The literature suggests that ≥1 g of calcium per 2 to 4 units of blood may correct hypocalcemia, but its effect on survival is unclear. This study evaluated the association between varying calcium:low-titer O whole blood (LTOWB) ratios and 24-hour mortality to define clinically meaningful supplementation targets.

METHODS: We performed a retrospective single-center cohort study of all trauma patients receiving LTOWB and calcium, prehospital, or within 4 hours of arrival (2020–2023). Demographics, mechanism of injury, Injury Severity Score (ISS), transfusion volume, and calcium administration were collected. Calcium supplementation was defined as a continuous variable (grams/unit), mutually exclusive ranges, and threshold doses of ≥1 g per 2, 3, or 4 units of LTOWB. The primary outcome was 24-hour mortality. Multivariable logistic regression adjusted for confounders and calcium supplementation strategy.

RESULTS: Of 542 LTOWB recipients, 99 undergoing CPR were excluded; 164 received no calcium, and 273 had complete datasets for analysis. Median age was 36 (25–50) years, 72% were male, median ISS was 19 [10–28], and 55% sustained blunt trauma. Median arrival ionized calcium was 1.02 (0.79–1.14) mEq/L. Twenty-four-hour mortality was 13.6% (n = 37). On multivariable analysis, ≥1 g calcium chloride per 2 units of LTOWB independently reduced the odds of 24-hour mortality by 84% [odds ratio, 0.164 (0.034–0.796), $p = 0.025$]. Calcium chloride at this threshold neared significance for reduction in mortality ($p = 0.06$, adjusted OR = 0.221 (0.045–1.077)] when restricting the analysis to patients receiving ≥2 units of LTOWB, while gluconate had no significant associations in this cohort with greater need for LTOWB resuscitation.

CONCLUSIONS: In trauma patients receiving LTOWB, calcium chloride administered at ≥1 g per 2 units showed a consistent association with improved early survival. A ≥1:2 calcium chloride-to-LTOWB dosing protocol may be an effective and clinically relevant target for trauma resuscitation. Prospective validation is warranted. (*J Trauma Acute Care Surg.* 2026;00: 00–00. Copyright © 2026 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Retrospective cohort study; Level III.

KEY WORDS: calcium, hemorrhagic shock, trauma, low titer O whole blood, ratio

Hemorrhagic shock remains the leading cause of preventable death in trauma patients. Blood product–based resuscitation has largely replaced crystalloid-dominant strategies to mitigate trauma-induced coagulopathy and its downstream complications.[1,2] Recent literature has identified ≥1.5 L of crystalloid administration during early trauma care as an independent predictor of mortality.[3,4] The underlying mechanism of crystalloid-associated mortality centers on dilutional coagulopathy compounded by endothelial disruption and dysregulated hemostasis.[3] While studies continue to compare whole blood (WB) transfusion with component therapy using 1:1:1 ratios of packed red blood cells, plasma, and platelets, the principle of hemostatic resuscitation emphasizing permissive hypotension and early use of blood products has become the cornerstone of modern trauma management.[5,6]

Recent debate has evolved as to whether the classic "lethal triad" of trauma (coagulopathy, acidosis, and hypothermia) should be expanded to recognize hypocalcemia as a fourth pillar, transforming the paradigm into the "lethal diamond."[7] Studies by Webster et al.[8] (major trauma center in the United Kingdom, 2016) and Magnotti et al.[9] (Level I trauma center in the United States, 2011) demonstrated that over half of trauma patients present with hypocalcemia on admission. These findings suggest that calcium derangement may occur

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independently of transfusion, potentially driven by intracellular calcium shifts in ischemic tissue.[10] With activation of massive transfusion, as is often needed in exsanguinating trauma patients, chelation from citrate in blood products further exacerbates hypocalcemia.[11] Consequently, 70% to 90% of trauma patients undergoing transfusion develop hypocalcemia.[8,11–13]

Hypocalcemia has been associated with increased mortality and shorter time to death in trauma populations.[9,14,15] However, the optimal calcium replacement strategy during blood product resuscitation, particularly regarding dosing relative to transfused volume, remains undefined.[16] There is a paucity of literature analyzing calcium dosing specifically when adopting a low antibody titer O whole blood (LTOWB) based resuscitation strategy in trauma patients. The present study aims to define clinically meaningful calcium-to-LTOWB (Ca:LTOWB) dosing thresholds associated with improved 24-hour mortality in trauma hemorrhagic shock, thereby informing evidence-based calcium replacement strategies in contemporary whole blood resuscitation.

METHODS

We conducted a retrospective cohort study utilizing data from the institutional trauma registry and WB database at our level I academic trauma center. The database contains information pertaining to the study parameters for all patients who receive prehospital and in-hospital WB at our institution. All patients from 2020 to 2023 who had received LTOWB and calcium either in the prehospital setting or within 4 hours of arrival to our trauma resuscitation unit (TRU) were identified. Patients who received prehospital cardiopulmonary resuscitation (CPR) or arrived with CPR in progress to the TRU, and patients who received no calcium within the first 4 hours were excluded. Demographic data, including age, sex, mechanism of injury, and Injury Severity Score (ISS), were collected. Total calcium (grams), calcium formulation (gluconate or chloride) used, and number of units of LTOWB transfused within the first 4 hours (including prehospital and in-hospital dosing) were abstracted from the dataset.

The most common criterion to administer prehospital WB and/or WB for resuscitation in our TRU is a systolic blood pressure <90 mm Hg in the setting of trauma. Other indications for prehospital WB administration are as elaborated in prior studies.[1]

Calcium:LTOWB ratios were defined in three ways for the purpose of this study:

1. Numerical calcium:LTOWB dosing ratio (grams per unit)
2. Mutually exclusive groups of calcium:LTOWB dosing
3. Threshold groups of calcium:LTOWB dosing (nested cohorts)

To define groups 2 and 3, we used cutoff values of 1 g per 2, 3, and 4 units of LTOWB to produce 4 mutually exclusive groups and 3 threshold groups, as shown in Table 1. Threshold groups were defined as having received at least 1 g of calcium per 2, 3, and 4 units of LTOWB, respectively. By mathematical definition, the ≥1 g per 3 units cohort included patients in the ≥1 g per 2 units group, and the ≥1 g per 4 units cohort included patients in the ≥1 g per 2 units and ≥1 g per 3 units groups (Table 1).

TABLE 1. Groups of Calcium Dosing Based on Defined Ratios

Calcium:LTOWB (continuous variable)	
Grams per unit	
Calcium:LTOWB (mutually exclusive groups), g/unit	
Group 1	≥0.5
Group 2	0.33–0.5
Group 3	0.25–0.33
Group 4	≤0.25
Calcium:LTOWB (threshold groups)	
Calcium:LTOWB ratio	Patients included
≥1 g per 2 units	Only patients receiving ≥1 g calcium per 2 units of LTOWB
≥1 g per 3 units	Patients receiving ≥1 g per 2 units of LTOWB and patients receiving ≥1 g per 3 units of LTOWB
≥1 g per 4 units	Patients receiving ≥1 g per 2, 3, or 4 units of LTOWB

The primary outcome of interest was 24-hour mortality. This outcome was chosen as the time frame for determination of the calcium:LTOWB ratio was the first 4 hours of resuscitation, and early mortality was thought to best represent the outcome of the resuscitative effort centered around the period of maintenance of this ratio. The study was reviewed and approved by our institutional review board.

Statistical Analysis

Demographics of our patient cohort were represented by descriptive statistics. Continuous variables' distributions were graphically reviewed with histograms and quantile-quantile plots. Continuous independent variables were analyzed with univariate logistic regression, and categorical variables with χ^2 tests of independence. Multivariable logistic regression was used to control for confounders, based on covariates that achieved significance on univariate testing. Initial covariates tested included age, sex, mechanism of injury, and ISS. The thresholds for nested cohorts analyzed patients as two mutually exclusive groups: patients who met that specific dosing ratio versus those who did not. Similar individual odds ratios were obtained for the formulation-stratified subgroup analyses that analyzed calcium chloride and calcium gluconate cohorts separately at each of the three dosing thresholds and using calcium:LTOWB as a continuous variable. Statistical analysis was performed using Python version 3.14 and Statistical Package for Social Sciences (SPSS) Version 29.

The reporting for this study complies with the STROBE guidelines (Supplemental Digital Content 1, http://links.lww.com/TA/F330).

RESULTS

Five hundred forty-two patients received LTOWB (either prehospital or within 4 hours of arrival to the TRU) during our study period. Ninety-nine patients who received prehospital CPR or arrived with CPR in progress were excluded, leaving a total of 443 patients. One hundred sixty-four patients received no calcium, and of the remaining 279 patients, 6 patients lacked data pertaining to calcium and/or LTOWB dosing. The flow diagram representing the patient cohort is depicted in Figure 1. The demographics of our included patients (273 patients) are shown in Table 2. Forty-six percent (n = 125) of patients required emergent operative or interventional radiology intervention for hemorrhage control in our cohort. Among patients who died within the first 24 hours (n = 37), median time to death was 1.56 (0.62–5.8) hours. Of these 37 patients, 19 died due to hemorrhagic shock and 9 succumbed to traumatic brain injury. Increased age [odds ratio (OR) 1.03; 95% CI, 1.01–1.05; $p = 0.002$] and ISS (OR, 1.03; 95% CI, 1.001–1.053; $p = 0.04$) were associated with greater mortality, while female sex (OR, 1.14; 95% CI, 0.53–2.43; $\chi^2_1 = 0.11$, $p = 0.84$) and penetrating injury mechanism (OR, 1.04; 95% CI, 0.52–2.09; $\chi^2_1 = 0.01$, $p = 0.91$) were not.

Ionized calcium levels on arrival were available only for 95 patients. Among these patients, 62 patients (65.3%) were hypocalcemic on arrival (defined as an ionized calcium ≤1.1 mEq/L). 4 (4.2%) patients had an ionized calcium >1.4 mEq/L on arrival. Only 68 of the 273 patients in our cohort had ionized calcium levels at the 4-hour mark. The median [interquartile range (IQR)] 4-hour ionized calcium was 1.18 (1.08–1.28) mEq/L, and only 25% of patients were hypocalcemic at 4 hours.

The median (IQR) total transfusion volume of LTOWB within the first 4 hours was 3 (2–6) units. The four mutually exclusive groups (Table 1) of calcium:LTOWB were compared using omnibus χ^2 testing, where a statistically significant reduction in 24-hour mortality was noted between the groups ($\chi^2_3 = 9.65$ $p = 0.022$). However, post hoc testing demonstrated no significant pairwise differences, as often seen with inadequate statistical power, which may be due to low sample size and/or α adjustments in post hoc testing.[17]

Given the results with mutually exclusive groups, threshold groups (as defined in Table 1) were subsequently analyzed, and χ^2 analyses identified that calcium supplementation was significantly associated with lower unadjusted 24-hour mortality across all three dosing thresholds, with the strongest effect observed at the 1:2 threshold (Table 3). The mortality rates for patients not meeting the ≥1 g per 2, 3, and 4 unit dosing thresholds were 17.8% (n = 30/169), 20.0% (n = 23/115) and 21.1% (n = 15/71), respectively, suggesting a lower unadjusted 24-hour mortality rate with higher ratios of calcium:LTOWB supplementation. Of note, no significant differences were observed when assessing 4-hour mortality or 30-day mortality at any of the three calcium supplementation thresholds.

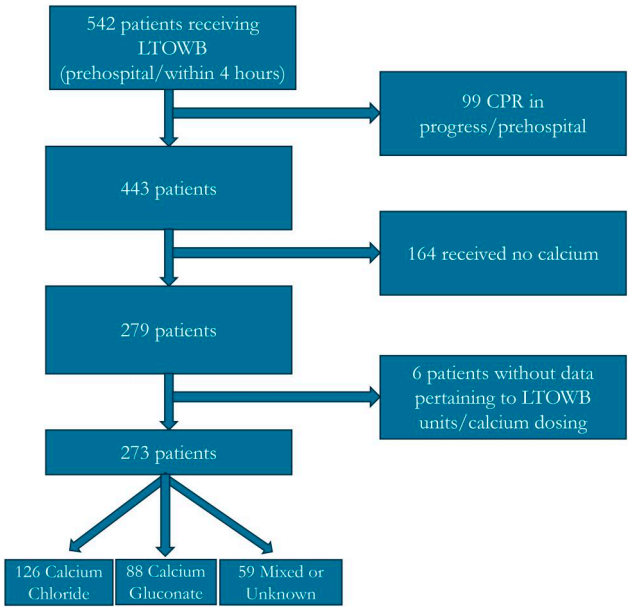

Figure 1. Flow diagram of patient cohort.

Calcium:LTOWB (grams/unit) was also analyzed as a continuous variable, which showed a crude association with mortality (OR, 0.15; 95% CI, 0.04–0.54; $p = 0.004$). Since sex and injury mechanism showed no univariate associations with mortality in our dataset, only age and ISS were selected as additional covariates for multivariable analysis. Multivariable regression (Table 4) found the 4-hour calcium:LTOWB ratio to be independently associated with decreased 24-hour mortality (saOR, 0.35; 95% CI, 0.16–0.79; $p = 0.01$), indicating that an incremental 0.59 g/unit (1 SD) increase in calcium dosing ratio was associated with a 65% reduction in the odds of 24-hour mortality. Age also showed an independent association with mortality (Standardized adjusted Odds Ratio (saOR), 1.70; 95% CI, 1.22–2.38; $p = 0.002$), while ISS did not (saOR, 1.32; 95% CI, 0.92–1.88; $p = 0.13$).

To identify the effects associated with calcium chloride versus calcium gluconate supplementation in the respective calcium:LTOWB ratios, a subgroup analysis was performed for each calcium formulation (patients who received both formulations within 4 hours of arrival were excluded from this subgroup analysis). Multivariable regressions were run using continuous calcium dosing ratio (grams per unit of respective calcium form), age, and ISS as predictors. In the calcium chloride analysis, calcium dosing ratio (saOR 0.23; 95% CI, 0.06–0.88; $p = 0.03$) and age (saOR 1.94; 95% CI, 1.22–3.08; $p = 0.005$) were independently associated with 24-hour mortality, while ISS was not (saOR 0.21; 95% CI, 0.76–1.92; $p = 0.43$). In the calcium gluconate analysis, neither calcium dosing ratio (saOR 0.11; 95% CI, 0.01–1.24; $p = 0.07$), age (saOR 0.85; 95% CI, 0.32–2.26; $p = 0.74$), nor ISS (saOR 1.20; 95% CI, 0.46–3.18; $p = 0.71$) had significant associations with mortality, which may indicate limited

TABLE 2. Demographics

Demographics	Total Cohort (n = 273)	Calcium Chloride (n = 126)	Calcium Gluconate (n = 88)
Age (median [IQR]), y	36 [25–50]	42 [28–54]	33 [25–50]
Sex, n (%)			
Male	198 (72.5)	94 (74.6)	63 (71.6)
Female	75 (27.5)	32 (25.4)	25 (28.4)
Mechanism of injury, n (%)			
Blunt	150 (54.9)	75 (59.5)	45 (51.1)
Penetrating	123 (45.1)	51 (40.5)	43 (48.9)
Injury Severity Score (median [IQR])	19 [10–28]	21 [12–30]	17 [10–26]
Arrival ionized calcium (median [IQR])	1.02 [0.79–1.14] mEq/L	1.00 [0.66–1.17] mEq/L	0.95 [0.79–1.11] mEq/L
Shock index (median [IQR])	1.09 [0.88–1.45]	1.23 [0.95–1.60]	1.04 [0.87–1.25]
24-h mortality, n (%)	37 (13.6)	26 (20.6)	5 (5.7)
30-d mortality, n (%)	57 (22.3)	34 (27)	11 (12.5)

IQR, interquartile range; mEq/L, milliequivalents per liter.

power in this regression cohort given the sample size (n = 88 with complete data) (Table 4).

Multivariable logistic regression controlling for age and ISS was repeated for threshold groups using independent regression models while analyzing each of the thresholds. This was done for all calcium forms, calcium chloride and calcium gluconate at each of the three previously defined thresholds (Table 5). These analyses identified calcium chloride dosing at a ratio of ≥ 1 g per 2 units of LTOWB to be associated with an 84% reduction in 24-hour mortality (OR: 0.164, $p = 0.025$). The formulation-stratified analysis also revealed a statistically significant association for calcium gluconate at the ≥ 1 g per 3 and ≥ 1 g per 4 units ratios (Table 5).

Similar results were noted when limiting the analysis to patients who survived > 30 minutes to mitigate survival bias [for calcium chloride at ≥ 1 g per 2 unit threshold dose, adjusted OR 0.214 (0.044–1.036), $p = 0.055$].

To account for confounders associated with the above subgroup analysis, the formulation-stratified multivariable regression analyses were repeated with our sample restricted to only the group of patients who had received ≥ 2 units of LTOWB. In this limited cohort, calcium gluconate demonstrated no significant reduction in mortality at any of the three dosing thresholds, while the mortality benefit for calcium chloride at the ≥ 1 g per 2 units dosing ratio neared statistical significance [adjusted OR, 0.22 (0.045–1.077), $p = 0.06$], likely reflecting type 2 error with a smaller sample. However, calcium chloride dosing ratio as a continuous variable was no longer significant in this restricted cohort (saOR 0.59; 95% CI, 0.33–1.06; $p = 0.08$). In addition, compared with chloride recipients, gluconate patients were younger [median (IQR) 33 (24–48) vs. 42 (28–53), $p = 0.009$], had lower ISS (median 17 vs. 21, $p = 0.03$) and required fewer transfusions by 4 hours (median 3 vs. 4 units, $p < 0.001$), suggesting these were clinically distinct populations (proportion of blunt/penetrating trauma was not significantly different between these two cohorts).

DISCUSSION

This study presents the first analysis to define a calcium-to-LTOWB ratio associated with early mortality in trauma patients. Hypocalcemia has been increasingly recognized in trauma patients on arrival to the emergency room. Our data shows how calcium supplementation at various dosing thresholds is associated with mortality in trauma hemorrhagic shock. The benefits of adequate calcium replacement were most pronounced in those receiving 2 or more units of LTOWB, potentially underscoring the multifactorial nature of trauma-associated hypocalcemia. Furthermore, formulation-stratified analyses revealed that the calcium chloride formulation at the ≥ 1 g per 2 units ratio was associated with a statistically significant reduction in 24-hour mortality, while the significance attained with lower threshold dosing ratios of calcium gluconate was completely lost when restricting the cohort to patients receiving 2 or more units of LTOWB.

Calcium plays a central role in hemostasis as a clotting factor IV and serves as an essential cofactor for activation of multiple steps in the coagulation cascade.[18] The divalent calcium ion bridges negatively charged phospholipid surfaces and vitamin K–dependent coagulation factors, facilitating complex assembly and thrombin generation.[19] Beyond its role in coagulation, calcium functions as a second messenger for platelet activation and promotes platelet aggregation.[20] Although the concept of a "lethal diamond" incorporating hypocalcemia alongside coagulopathy, acidosis, and hypothermia remains debated, mounting evidence supports its clinical relevance.[10,21,22] Multiple studies have demonstrated that hypocalcemia is associated with increased transfusion requirements, impaired hemostasis, and higher mortality among trauma patients.[8,9,15,23]

As highlighted by Webster et al.[8] and Magnotti et al.,[9] shock-related hypocalcemia frequently precedes transfusion and is subsequently exacerbated by citrate

TABLE 3. Chi-Square Analysis for 24-hour Mortality

Calcium Threshold	24-hour Mortality If Calcium Threshold Met	24-hour Mortality If Calcium Threshold Not Met	χ^2	*p*
≥1 g per 2 units (≥0.5 g/unit)	6.7% (7/104)	17.8% (30/169)	7.51	**0.01**
≥1 g per 3 units (≥0.33 g/unit)	8.8% (14/158)	20.0% (23/115)	7.72	**0.008**
≥1 g per 4 units (≥0.25 g/unit)	10.9% (22/202)	21.1% (15/71)	5.12	**0.03**

Bold values indicates statistical significance.
g/unit, grams per unit.

within stored blood products. WB stored with citrate phosphate dextrose adenine has ~1.66 g of citrate per unit.[24–26] This corresponds to ~8.7 mM of citrate per unit of WB (exact content varies depending on the citrate formulation, such as trisodium citrate in the specific blood storage solution). Schauer et al.[26] reported a mean decrease in ionized calcium from 1.25 mmol/L to 1.12 mmol/L following reinfusion of a single unit of autologous WB, illustrating the calcium-chelating effect of citrate. Calcium is chelated by citrate in an ~1:1 molar ratio (1 mM of calcium is ~40 mg of elemental calcium); therefore, each unit of WB transfused has the capacity to chelate ~8.7 mM (350 mg) of elemental calcium. While citrate metabolism by the liver is typically rapid (~3 g every 5 min), trauma patients in hemorrhagic shock often have impaired hepatic perfusion and receive transfusion rates exceeding 1 unit every 5 minutes, predisposing to citrate accumulation and profound hypocalcemia.[24]

The existence of multiple calcium formulations raises the potential for inaccurate calcium dosing in the trauma setting. One gram of calcium gluconate has ~90 mg of elemental calcium, while 1 g of calcium chloride has 270 mg of elemental calcium (three times that of calcium gluconate).[27] Given that each unit of WB can chelate around 350 mg of elemental calcium, this stoichiometric relationship provides a biochemical, albeit speculative, explanation for our findings. Specifically, a ratio of ≥1 g calcium chloride per 2 units of LTOWB can deliver sufficient calcium to offset citrate binding and was noted in this study to be independently associated with a reduction in the odds of 24-hour mortality. Likewise, other studies have also identified higher doses of calcium per blood product transfused to be associated with improved survival. Wade et al.[28] found a calcium-to-blood product ratio (determined by dividing total elemental calcium dose by number of units of packed red blood cells and plasma units administered) of >50 mg per blood product to have a statistically significant predictor of survival in trauma patients receiving massive transfusion. These results complement prior institutional data identifying hypocalcemia as an independent predictor of early mortality in trauma.[22]

While our results suggest an optimal calcium-to-LTOWB ratio to mitigate hypocalcemia-associated mortality, the potential for overcorrection leading to hypercalcemia warrants careful consideration. Hypercalcemia in bleeding trauma patients has been associated with acidosis, depressed Glasgow coma scale scores and adverse physiologic outcomes.[29] Alghanem et al.[16] conducted a retrospective study of trauma patients receiving transfusion to analyze calcium to citrate and calcium to blood ratios and determine the ratio least likely to result in hypercalcemia or severe hypocalcemia. The authors identified a threshold of 0.903 mmol of calcium administered per blood product to be statistically significant for predicting hypercalcemia, albeit with a sensitivity of

TABLE 4. Multivariable Logistic Regression for 24-hour Mortality as a Function of Calcium:LTOWB Dose Ratio (grams per unit)

Predictor	Unadjusted OR [95% CI]	Adjusted OR [95% CI]	Standardized Adjusted OR [95% CI]	*p*
All calcium forms				
Calcium dose ratio (g/unit)	0.15 [0.04–0.54]	0.17 [0.04–0.67]	0.35 [0.16–0.79]	**0.011**
Age (y)	1.03 [1.01–1.05]	1.03 [1.01–1.05]	1.70 [1.22–2.38]	**0.002**
ISS	1.03 [1.001–1.053]	1.02 [0.99–1.05]	1.32 [0.92–1.88]	0.130
Calcium chloride				
Calcium dose ratio (g/unit)	0.11 [0.02–0.77]	0.10 [0.01–0.82]	0.23 [0.06–0.88]	**0.032**
Age (y)	1.04 [1.01–1.06]	1.04 [1.01–1.07]	1.94 [1.22–3.08]	**0.005**
ISS	1.02 [0.99–1.05]	1.01 [0.98–1.05]	1.21 [0.76–1.92]	0.431
Calcium gluconate				
Calcium dose ratio (g/unit)	0.02 [0.00–1.34]	0.02 [0.00–1.47]	0.11 [0.01–1.24]	0.074
Age (y)	0.99 [0.94–1.04]	0.99 [0.94–1.04]	0.85 [0.32–2.26]	0.739
ISS	1.04 [0.96–1.12]	1.02 [0.93–1.11]	1.20 [0.46–3.18]	0.707

Bold values indicates statistical significance.
Results of three separate multivariable logistic regression models analyzing the mortality effects of (1) calcium dose ratio among entire cohort, (2) calcium dose ratio among patients receiving only calcium chloride, and (3) calcium dose ratio among patients receiving only calcium gluconate.
OR, odds ratio.

TABLE 5. Multivariable Logistic Regressions for 24-hour Mortality, by Calcium Form, Using Calcium Threshold Cutoffs

Calcium Type	Calcium Threshold	Unadjusted OR [95% CI]	Adjusted OR [95% CI]	*p*
All calcium forms	≥1 g per 2 units	**0.334 [0.141–0.792]**	**0.39 [0.159–0.94]**	**0.036**
	≥1 g per 3 units*	**0.389 [0.19–0.794]**	**0.43 [0.204–0.903]**	**0.026**
	≥1 g per 4 units**	0.456 [0.222–0.939]	0.493 [0.231–1.053]	0.068
Calcium chloride	≥1 g per 2 units	**0.177 [0.03–0.796]**	**0.164 [0.034–0.796]**	**0.025**
	≥1 g per 3 units*	0.463 [0.184–1.161]	0.481 [0.181–1.277]	0.142
	≥1 g per 4 units**	0.672 [0.278–1.624]	0.774 [0.300–1.996]	0.596
Calcium gluconate	≥1 g per 2 units	0.233 [0.025–2.17]	0.243 [0.026–2.303]	0.218
	≥1 g per 3 units*	0.079 [0.008–0.752]	0.073 [0.007–0.783]	**0.031**
	≥1 g per 4 units**	**0.038 [0.004–0.374]**	**0.037 [0.004–0.382]**	**0.006**

Results of nine multivariable logistic regression models: one for each calcium form and dosing threshold group. Overlapping groups necessitated separate regression models. *,** indicates how the results were obtained through separate regression models.

70% and specificity of 59%. However, their study specifically evaluated trauma patients receiving transfusions (not limited to WB but including component therapy) who had operative/interventional radiology intervention, classified hypercalcemia and hypocalcemia based on the first postoperative ionized calcium and did not correlate hypercalcemia with mortality.[16] Our findings build upon this work by determining the association between calcium dosing ratios and early mortality. Future studies should aim to identify thresholds at which calcium supplementation transitions from beneficial to excessive, and to determine the clinical implications of transient hypercalcemia during massive transfusion.

This study has several notable limitations. The retrospective design and reliance on single-institution data may limit generalizability. The identified ratio reflects the optimal calcium-to-LTOWB dosing within the initial 4 hours of resuscitation; whether the ≥1 g calcium chloride per 2 units LTOWB ratio remains advantageous beyond this period requires further evaluation. In addition, as LTOWB is not universally adopted, these findings may not be directly applicable to institutions employing component therapy, though ongoing multicenter trials are re-examining WB versus component-based resuscitation strategies.[6] Not all patients had an ionized calcium level drawn on arrival, and this limits an accurate tally on the proportion of our patients who were hypocalcemic on arrival. There are presently no specific guidelines that dictate the type and/or dose of calcium at our institution for trauma patients receiving WB transfusion, and variability exists in practice between providers; this study aimed to streamline our protocols for administering calcium consistently and uniformly across our trauma population. In addition, variability in the timing of laboratory assessments across clinical settings (TRU, operating room, intensive care unit) also precluded standardized postresuscitation ionized calcium measurements (and our analysis of 4-hour ionized calcium levels was limited to 68 patients who had these results). Our analyses were limited to patients who received calcium in the first 4 hours. The effect of calcium supplementation on viscoelastic parameters (such as thromboelastography) could not be evaluated since this testing is not part of our routine trauma arrival lab order set. However, as this is presently being incorporated into the panel for patients meeting our highest trauma activation criteria, these data should be available for future patient cohorts from our institution. As the median time to death in patients with 24-hour mortality was 1.8 hours, it is possible that these patients did not survive long enough to have calcium replaced in a more aggressive ratio (survival bias), and this adds to the limitations of our work. This study may be underpowered to detect modest but clinically relevant differences in mortality across dosing thresholds. With relatively few deaths in each comparator group, the observed differences, particularly for lower dosing thresholds, may reflect limited power rather than the absence of effect. Shock physiology may influence hypocalcemia and mortality; while we noted similar results with inclusion of shock index into the multivariable regression, the present study was not powered to definitively uncover significant results with expansion of our covariates in the multivariable regression. Timing of administration of WB and/or calcium may have influenced our results as our regional EMS carries and administers prehospital WB, and prior studies have demonstrated prehospital WB to improve probability of survival in trauma patients.[1] Finally, while our findings demonstrate an association between specific calcium:LTOWB dosing thresholds and 24-hour mortality, causation cannot be assumed and our data in this work are insufficient to determine whether the intervention of calcium administration corrects hypocalcemia or empirically adds synergy to resuscitation efforts. These questions represent the focus of our future prospective efforts. Despite these limitations, our findings provide a clinically relevant preliminary framework for calcium supplementation during LTOWB-based resuscitation and support ongoing efforts to optimize calcium dosing in trauma-induced hemorrhagic shock.

CONCLUSIONS

In trauma patients receiving LTOWB, calcium chloride administered at a ≥1 g per 2 units ratio optimized the reduction in 24-hour mortality. Neither calcium gluconate nor less aggressive calcium chloride dosing thresholds showed potential benefit when transfusion

thresholds exceeded 2 units of LTOWB. These findings support the adoption of a 1:2 calcium chloride-to-LTOWB dosing protocol as a clinically meaningful target during trauma resuscitation in patients receiving LTOWB, and prospective validation is warranted.

AUTHORSHIP

A.R., D.L., and P.P. participated in conceptualization, data acquisition and analysis, draft of preliminary manuscript, revision, and approval of final version. L.B., S.E., K.H., and D.G. participated in data acquisition, conceptualization, critical review of the manuscript with revision for incorporating intellectual content, and approval of the final version. J.T., B.E., and S.N. participated in conceptualization, critical review of the manuscript with revision for incorporating intellectual content, and approval of the final version. D.J. participated in conceptualization, critical review of the manuscript with revision for incorporating intellectual content, and approval of the final version.

DISCLOSURE

JTACS COI Disclosure forms for all authors have been supplied and are provided as Supplemental Digital Content, http://links.lww.com/TA/F329.

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