



Original Article

Parenteral calcium administration and outcomes in critically ill patients with hypocalcemia: A retrospective cohort study

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ABSTRACT

Background: Hypocalcemia is common among patients admitted to the intensive care unit (ICU). The administration of calcium in critically ill patients with hypocalcemia remains debated, as previous data on outcomes are conflicting, and subgroup analyses are lacking. This study aimed to investigate the association between parenteral calcium administration and clinical outcomes in critically ill patients who had hypocalcemia with and without sepsis.

Methods: This retrospective cohort study included individuals who developed hypocalcemia during the first 7 days of admission to a mixed medical-surgical adult ICU at a University-affiliated teaching hospital. Patients who were not receiving renal replacement therapy, and were admitted to the ICU for at least 48 h between October 1, 2015 and September 24, 2020, were included. The primary outcomes included all-cause 180-day mortality and time-to-shock resolution. Subgroup analyses were conducted in sepsis and nonsepsis patients with mild or moderate hypocalcemia, based on median splits. Proportional hazard regression analyses were performed to identify the association between parenteral calcium administration and outcome parameters.

Results: Among the 1100 patients who met the inclusion criteria, 427 (38.8%) patients were admitted for sepsis and 576 (52.4%) patients received parenteral calcium. Patients who received and did not receive parenteral calcium demonstrated no significant difference in 180-day mortality (adjusted hazard ratio [aHR] = 1.18, 95% confidence interval [CI]: 0.90 to 1.56). Intravenous calcium administration reduced the probability of a shorter time to shock resolution (adjusted odds ratio = 0.81, 95% CI: 0.70 to 0.94). Subgroup analyses in patients with and without sepsis indicated no significant association between calcium administration (aHR = 1.63, 95% CI: 0.99 to 2.69) and 180-day mortality (aHR = 1.06, 95% CI: 0.74 to 1.51). Notably, parenteral calcium was associated with an elevated risk of 90- and 180-day mortality in patients who had sepsis and mild hypocalcemia (aHR = 1.88, 95% CI: 1.02 to 3.47 and aHR = 1.79, 95% CI: 1.07 to 3.00, respectively).

Conclusions: Intravenous calcium administration did not provide survival or shock resolution benefits in ICU patients with hypocalcemia, and may even be harmful. Further research, including randomized controlled trials, are needed to confirm these findings.

Introduction

Calcium is an essential nutrient that fulfills many vital roles in the human body. These include regulation of hormone secretion, glycogen metabolism, nerve conduction, muscle contraction, blood homeostasis, and cell division.^[1] Approximately half of the calcium in the serum is bound to proteins and anions, while the other half is available as ionized calcium (iCa).^[1,2] Serum iCa is commonly measured in patients admitted to the

intensive care unit (ICU), as calcium levels change with alterations in albumin levels and acid–base status.^[1,2]

Hypocalcemia, a condition characterized by low blood calcium levels, is widely prevalent among patients admitted to the ICU.^[1,2] Studies suggest that it is induced by catecholamines and systemic inflammation in patients with critical illness.^[1,3–6] It is associated with poor outcomes, particularly in those in whom iCa levels fail to normalize during the early stages of critical illness.^[7–13] However, sev-

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eral studies demonstrated no independent association between low iCa levels and mortality.^[5,6,14,15] In addition, most patients admitted to the ICU do not experience health problems that are directly related to a hypocalcemic state (i.e., seizures, tetany, and cardiac arrhythmias).^[1,2] Nevertheless, ICU physicians routinely administer calcium in an attempt to correct hypocalcemia.^[2,3,16] This practice is driven by studies which suggest that correction of hypocalcemia may improve hemodynamics in critically ill patients by enhancing left ventricular function and vascular resistance.^[3,17,18] Critical care guidelines also recommend the administration of intravenous calcium in cases of significant hemorrhage which is accompanied by hypocalcemia or hyperkalemia-related changes on the electrocardiogram (ECG).^[19,20] However, the efficacy of this practice has never been confirmed in clinical trials. In addition, there is evidence to suggest that calcium supplementation may be harmful.^[3] Calcium administration has been shown to worsen organ dysfunction and survival rates in murine models of sepsis. This may be attributed to a worsening of sepsis-induced calcium imbalance owing to a direct shift of additional calcium into the cells.^[21–23] The imbalance over-activates calcium/calmodulin-dependent protein kinase pathways, increases mitochondrial dysfunction, and generates reactive oxygen species, leading to cell injury and vascular leakage.^[21–26] In this context, increasing evidence shows that clinical outcomes may be better in patients with sepsis who receive calcium-channel antagonists before hospital admission; this may be attributed to the fact that these drugs prevent excessive shifting of extracellular calcium into the cells.^[27–29]

Previous studies have focused on the association between calcium administration and short-term mortality.^[15,24,30,31] However, the harmful effects that manifest in the longer term (i.e., oxidative stress, mitochondrial dysfunction, and cell damage) may have been overlooked;^[21,25] this was evident from the findings of a recent clinical trial in cardiac arrest patients that had to be terminated prematurely.^[32] Although calcium supplementation is common during ICU admission, only one retrospective cohort study has shown benefit;^[30] several others have demonstrated either no effect or harm.^[15,21,24,31] Notably, the pathophysiological mechanisms involved in calcium dysregulation may be more profound in patients with sepsis; however, calcium administration may improve hemodynamics in patients without sepsis. We therefore aimed to investigate the association between parenteral calcium administration (PCA) and clinical outcomes, including long-term mortality and time to shock resolution, in critically ill hypocalcemic patients with and without sepsis.

Methods

Study design and setting

This retrospective cohort study was conducted at the Gelderse Vallei Hospital, a university-affiliated teaching hospital located in Ede, The Netherlands. The hospital has two mixed medical-surgical adult ICUs with 12 and 5 beds, respectively. Both ICUs are managed by the same medical staff; this ensures the use of similar patient management protocols in both units. The study cohort included patients who were admitted to the ICU between October 1, 2015 and September 24,

2020. The Institutional Review Board of the Gelderse Vallei Hospital, Ede, approved the study titled “Hypophosphatemia and hypocalcemia: course, supplementations and associations with outcome in the general intensive care population” (approval number: 2101–012) on February 4, 2021. The study was conducted in compliance with the principles of the Helsinki Declaration of 1975 and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.^[33]

Inclusion and exclusion criteria

All patients who were aged at least 18 years, stayed in the ICU for at least 48 h, and had available data for at least one iCa measurement were included. As concurrent citrate infusions reduce iCa concentrations in patients receiving renal replacement therapy (RRT),^[34] these patients were excluded to solely focus on endogenous hypocalcemia. In cases of readmission during the same episode of hospital stay, data from only the first instance of ICU admission were evaluated.

Data collection

Data pertaining to clinical parameters (age, sex, body mass index, and pre-existing comorbidities) were obtained from the local electronic patient data management systems, namely, MetaVision® (iMDsoft, Tel Aviv, Israel) and NeoZIS® (MI Consultancy, Katwijk, The Netherlands). The data regarding Acute Physiology and Chronic Health Evaluation IV (APACHE IV) scores, diagnosis at admission, and Barthel index were obtained from ICU admission records. Daily laboratory results and Sequential Organ Failure Assessment (SOFA) scores were recorded for the first 7 days of ICU admission. Data regarding the duration of vasopressor therapy and ventilator support throughout ICU admission were also collected. Dates of death were obtained from the electronic patient record system, Xcare® (Nexus, Viaanen, the Netherlands), which is linked with the Dutch population register. All collected data were anonymized and stored on a secure computer system.

Subgroups

The study cohort was divided into sepsis and non-sepsis groups based on clinical assessment by the attending intensivist at the time of ICU admission. Assessment was typically performed based on the Sepsis-3 criteria, which pertain to new-onset organ dysfunction (increase in SOFA score by 2) in patients with known or suspected infection.^[35] This was documented in the National Intensive Care Evaluation system, ensuring consistent recording across all cases. Patients were also divided into subgroups based on the presence of hyperkalemia (potassium ≥ 5.5 mmol/L) or clinically significant hemorrhage (excluding cerebral hemorrhage).

Hypocalcemia

Hypocalcemia was defined by serum iCa levels of <1.15 mmol/L, according to the local laboratory reference values (iCa: 1.15–1.30 mmol/L). The measurements were obtained from arterial blood (ABL90 Flex Plus Analyser, Radiometer Medical ApS, København, Denmark) as part of routine

daily measurements. The minimum value on the day of ICU admission was used to determine the presence of hypocalcemia on that day. As per a previous study, patients who developed hypocalcemia during the first 7 days of ICU admission were split into moderate and mild hypocalcemia groups based on quartiles of the minimum baseline iCa values in the entire cohort.^[9] Patients with mild and moderate hypocalcemia during ICU admission were assigned to the moderate hypocalcemia group.

Calcium administration

Thresholds and (contra-)indications for calcium administration were not included in local protocols during the study period. Calcium was therefore not routinely administered in cases of hypocalcemia; it was administered at the discretion of the attending physician, usually via the intravenous route, as a 2000 mg bolus dose of calcium gluconate. If deemed safe, and if the patient was receiving it before hospital admission, 500 mg of calcium carbonate was administered once daily. For the analyses, patients who received intravenous calcium gluconate on the day of diagnosis of hypocalcemia were assigned to the PCA group; the others were assigned to the control group. The total dose of intravenous calcium (in grams) administered during the first 7 days of ICU admission was recorded.

Outcomes

The primary outcome was all-cause 180-day mortality. Secondary outcome parameters included the duration of mechanical ventilation and vasopressor therapy and length of stay in the ICU (ICULOS) and hospital (HLOS). The period from initiation until 24 h after cessation of vasopressor therapy was considered as the time to shock resolution. Data regarding ICU-, hospital-, 28-day, and 90-day all-cause mortality were recorded.

Statistical analysis

Categorical variables have been presented as counts and percentages, whereas continuous variables are presented as means±standard deviations or medians and interquartile ranges (IQRs) depending on normality. Normality was tested using the Kolmogorov–Smirnov test and visual inspection of plots. The Student's *t*-test was used for normally distributed data, and the Mann–Whitney *U* test was used in other cases; categorical variables were tested using the chi-squared test.

Cox regression analysis was performed to evaluate the association between PCA and the outcome parameters. Possible confounders were identified using a stepwise approach and the number of covariates were matched based on the one-in-ten rule. The same model was run by replacing PCA with combined enteral and parenteral administration. Covariates were excluded in the case of multicollinearity (as in the case of Spearman's correlation coefficient of 0.7) or violation of the proportional hazard assumption. In cases where multivariable analysis demonstrated a significant association between PCA and 180-day mortality, additional multivariable models were generated for 28- and 90-day mortality. Survival function plots were generated, and a two-sided *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 29.0 (IBM Corporation, Armonk, NY, USA; 2022) software.

Results

Study population

A total of 1468 patients were admitted to the ICU for the first time between October 1, 2015 and September 24, 2020. After excluding those who received RRT (*n* = 119) and did not have available data regarding iCa measurements (*n* = 29), 1320 patients were included for evaluation (Figure 1). A total of 12,599

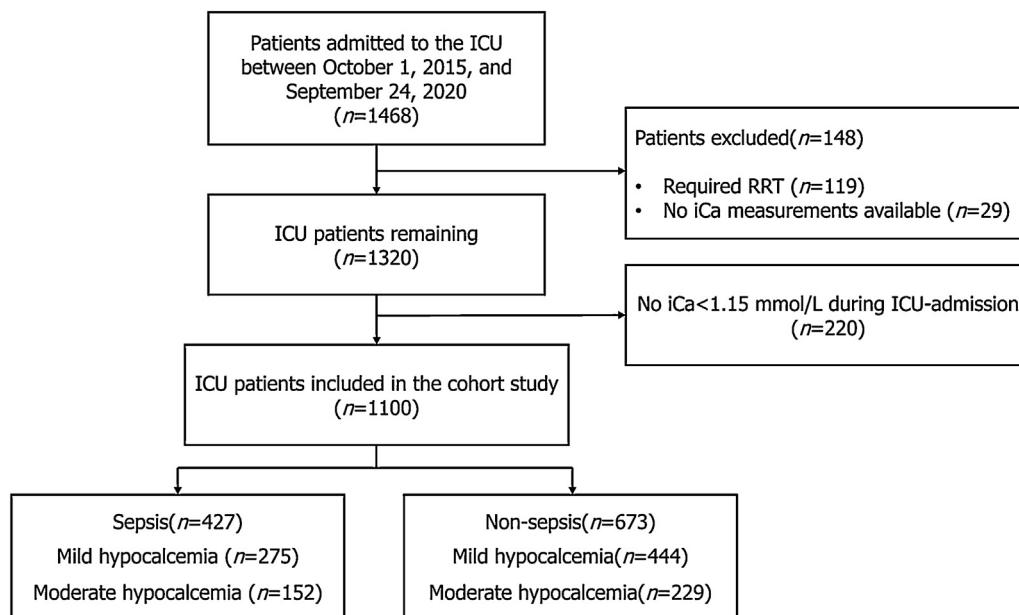


Figure 1. Flowchart of the study cohort after selection based on the inclusion and exclusion criteria and distribution into subgroups. Mild hypocalcemia = iCa 1.06–1.14 mmol/L; moderate hypocalcemia = iCa <1.06 mmol/L. iCa: Ionized calcium; ICU: Intensive care unit; RRT: Renal replacement therapy.

individual iCa measurements were available from the included patients. The median baseline iCa value in the entire cohort was 1.10 (IQR: 1.06–1.15) mmol/L. Based on this range, iCa levels of <1.06 mmol/L and 1.06–1.14 mmol/L were considered as moderate and mild hypocalcemia, respectively. Hypocalcemia was observed during the first 7 days of ICU admission in 1100 (83.3%) patients; these patients were included in the analysis. The patients with hypocalcemia had a median age of 70 (IQR: 59–77) years; 649 (59.0%) were male, and 427 (38.8%) were admitted to the ICU due to sepsis.

PCA

Among the 1100 patients with hypocalcemia, 576 (52.4%) received PCA. Of these patients, 60.4% (348/576) calcium was administered within 24 h of ICU admission; 45.8% (264/576) and 24.7% (142/574, as 3 patients in the PCA group were no longer in the ICU on day 3 of admission) of patients in the PCA group received calcium on days 2 and 3 (of ICU stay), respectively. The median dose of intravenous calcium received during the first 7 days of ICU admission was 2000 (IQR: 2000–6000) mg. Patients with mild hypocalcemia had a lower frequency of

receiving PCA (36.0% vs. 73.2%, $P < 0.001$), and the cumulative PCA dose within the first 7 days of ICU admission was lower than that in those with moderate hypocalcemia (median=2000 mg, [IQR: 2000–4000] vs. median=4000 mg, [IQR: 2000–6000], $P < 0.001$). A total of 27 (4.7%) patients received concurrent enteral calcium with PCA, whereas 24 (4.6%) patients received only enteral calcium without PCA. Table 1 shows the patient characteristics at baseline and at ICU admission in those who received and did not receive PCA for hypocalcemia. Among 73 patients with hyperkalemia (potassium ≥ 5.5 mmol/L), 40 (54.8%) patients received PCA.

Outcome data

Data regarding all-cause 180-day survival was available for all patients included in the primary analysis. A total of 255 (23.2%) patients who developed hypocalcemia died within 180 days of ICU admission. Supplementary Table S1 shows a comparison of the baseline characteristics between survivors and nonsurvivors. In the group of patients who received PCA, 153 (26.6%) patients died within 180 days after ICU admission; in contrast, 102 (19.5%) patients died in the control group (hazard

Table 1
Baseline characteristics of study patients.

| Baseline variables | Total (n=1100) | No intravenous administration (n=524) | Intravenous administration (n=576) | P-value |
|---------------------------------------|------------------|---------------------------------------|------------------------------------|---------|
| Age (years) | 70 (59–77) | 68 (56–76) | 71 (61–78) | 0.003 |
| Sex, female | 451 (41.0) | 224 (42.7) | 227 (39.4) | 0.361 |
| BMI on admission (kg/m ²) | 26.5 (23–30) | 26.8 (23.5–30.5) | 26.3 (23.0–30.1) | 0.167 |
| APACHE IV-score | 69 (48–84) | 67 (52–84) | 74 (61–91) | <0.001 |
| SOFA-score | 5 (3–7) | 6 (3–8) | 7 (5–9) | <0.001 |
| Barthel-index | 20 (16–20) | 20 (18–20) | 20 (18–20) | 0.596 |
| Comorbidities | | | | |
| COPD | 257 (23.3) | 135 (25.7) | 122 (21.2) | 0.073 |
| DM | 275 (25.0) | 123 (23.5) | 152 (26.3) | 0.265 |
| Baseline blood tests | | | | |
| CRP (mg/L) | 96 (18–214) | 80 (15–211) | 108 (24–216) | 0.075 |
| Albumin (g/L) | 26 (21–32) | 28 (23–34) | 25 (20–29) | <0.001 |
| Creatinine (μ mol/L) | 82 (61–123) | 83 (64–123) | 100 (71–151) | <0.001 |
| Arterial pH* | 7.32 (7.24–7.40) | 7.34 (7.25–7.41) | 7.31 (7.23–7.39) | 0.025 |
| Arterial lactate† | 2.2 (1.4–3.7) | 1.8 (1.2) | 2.6 (1.6–4.3) | <0.001 |
| Glucose (mmol/L)‡ | 8.5 (7.3–10.3) | 8.2 (7.2–10.0) | 8.9 (7.36–10.5) | 0.005 |
| Baseline electrolytes | | | | |
| Minimum iCa (mmol/L) | 1.09 (1.05–1.13) | 1.12 (1.09–1.14) | 1.03 (1.07–1.10) | <0.001 |
| Maximum iCa (mmol/L) | 1.16 (1.12–1.20) | 1.17 (1.13–1.21) | 1.15 (1.10–1.20) | <0.001 |
| Sodium (mmol/L)§ | 138 (135–141) | 138 (135–141) | 138 (135–141) | 0.692 |
| Magnesium (mmol/L)§ | 0.72 (0.61–0.83) | 0.75 (0.64–0.85) | 0.70 (0.59–0.81) | <0.001 |
| Potassium (mmol/L)§ | 3.9 (3.6–4.4) | 3.9 (3.6–4.3) | 4.0 (3.6–4.4) | 0.123 |
| Phosphate (mmol/L)§ | 1.05 (0.84–1.33) | 1.05 (0.86–1.29) | 1.05 (0.81–1.39) | 0.528 |
| ICU admission type | | | | |
| Elective surgical | 99 (9.0) | 43 (8.2) | 56 (9.7) | 0.290 |
| Emergency surgical | 213 (19.4) | 72 (13.7) | 142 (24.6) | <0.001 |
| Medical | 782 (71.1) | 407 (77.6) | 375 (65.1) | <0.001 |
| ICU admission reason | | | | |
| Sepsis | 427 (38.8) | 185 (35.3) | 242 (42.0) | 0.023 |
| Hemorrhage§ | 48 (4.4) | 11 (2.1) | 37 (6.4) | <0.001 |
| Cardiac arrest | 20 (1.8) | 7 (1.3) | 13 (2.3) | 0.281 |

Categorical variables are presented as number (percentages) and continuous variables as median (interquartile range).

Missing data was observed in the following baseline characteristics (n): BMI (26), APACHE-IV (5), SOFA-score (4), Barthel-index (60), CRP (12), Albumin (28), Creatinine (12), Arterial pH (10), Arterial Lactate (12), Glucose (131), Sodium (12), Magnesium (51), Potassium (21) and Phosphate (49).

* Minimum value on admission day.

† Maximum value on admission day.

‡ Mean value on admission day.

§ Excluding cerebral hemorrhage.

APACHE IV: Acute Physiology and Chronic Health Evaluation IV; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-reactive Protein; DM: Diabetes mellitus; iCa: ionized calcium; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment score.

ratio [HR]=1.49, 95 % confidence interval [CI]: 1.16 to 1.92). On multivariable analysis, PCA was not found to be associated with 180-day mortality (adjusted HR [aHR]=1.18, 95 % CI: 0.90 to 1.56; Figure 2, Supplementary Table S2).

Sepsis and non-sepsis

Supplementary Tables S3–S6 show the differences in baseline characteristics between patients who received and did not receive PCA (in the four subgroups). PCA was associated with increased 180-day mortality in both groups of patients with and without sepsis (HR=1.63, 95 % CI: 1.09 to 2.43 and HR=1.28, 95 % CI: 0.93 to 1.77, respectively; Figures 3 and 4, Supple-

mentary Tables S7 and S8). On multivariable analysis, the association between PCA and 180-day mortality reached near-significance (aHR=1.63, 95 % CI: 0.99 to 2.69) in patients with sepsis; however, no significant association was observed in those without sepsis (aHR=1.06, 95 % CI: 0.74 to 1.51).

The patient groups with and without sepsis were categorized as having mild or moderate hypocalcemia. In patients having sepsis with mild hypocalcemia, multivariable analyses revealed an association between PCA and increased 180- and 90-day mortality (aHR=1.79, 95 % CI: 1.07 to 3.00 and aHR=1.88, 95 % CI: 1.02 to 3.47, respectively; Supplementary Tables S9 and S10). However, no difference was observed in terms of 28-day mortality (aHR=1.19, 95 % CI: 0.64 to 2.23; Supplementary Ta-

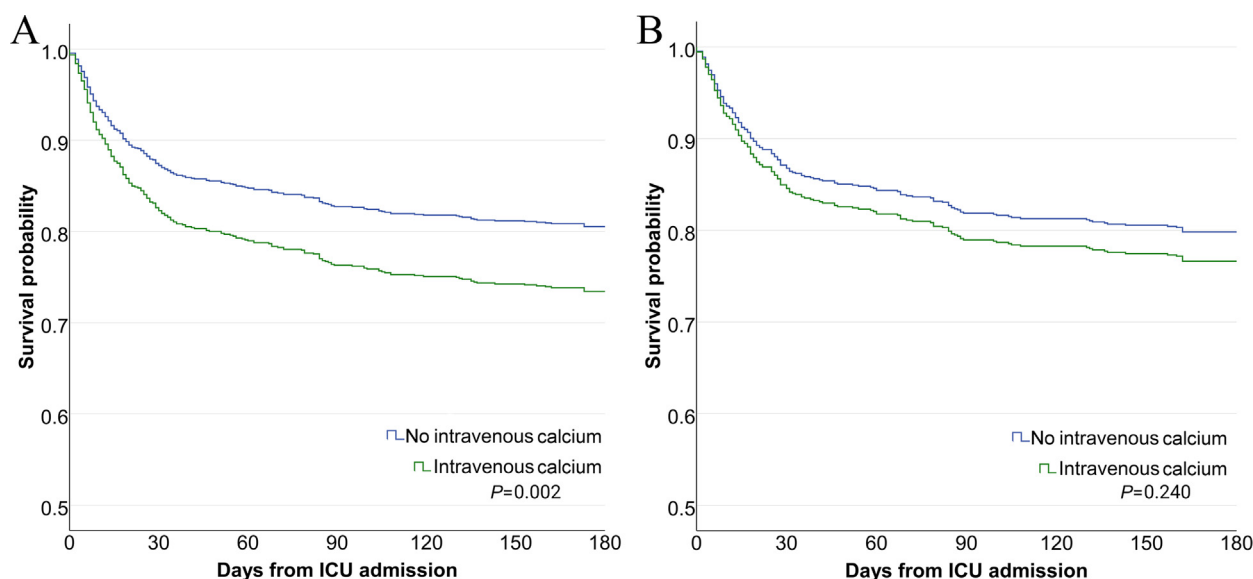


Figure 2. Survival curves of included patients with hypocalcemia who received and did not receive intravenous calcium. A: Univariate Cox regression analysis curve. B: Multivariable Cox regression analysis curve after correction for covariates age, APACHE IV score, BMI, Barthel index, COPD, serum albumin, arterial pH, serum creatinine, and duration of vasopressor therapy.

APACHE IV: Acute physiological and chronic health evaluation IV; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit.

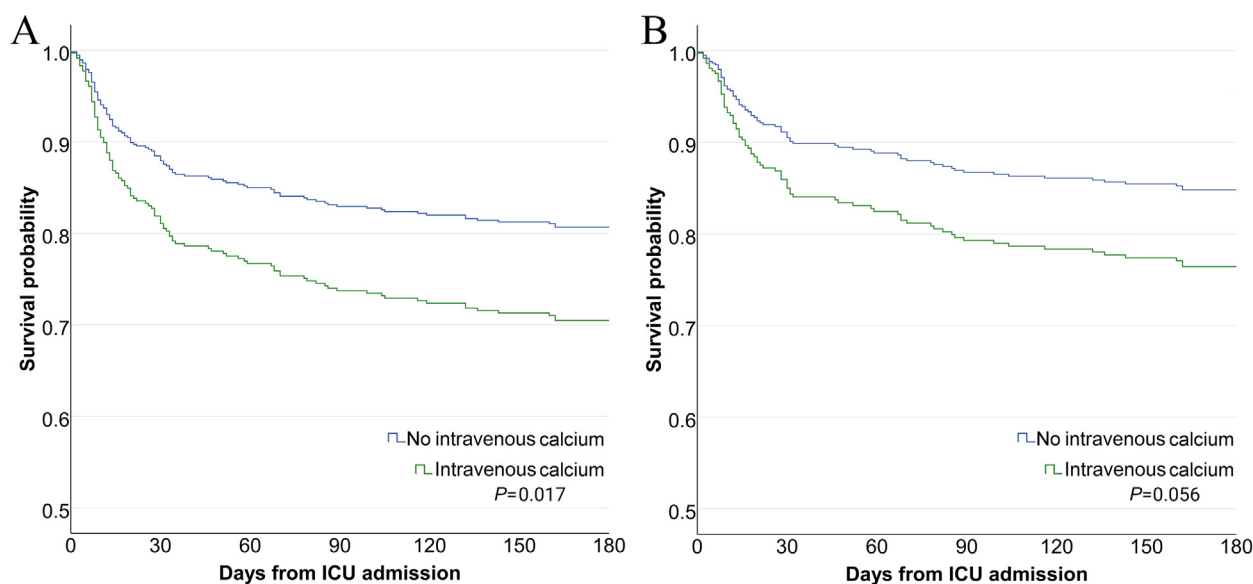


Figure 3. Survival curves of patients with sepsis and hypocalcemia who received and did not receive intravenous calcium. A: Univariate Cox regression analysis curve. B: Multivariable Cox regression analysis curve after correction for covariates age, APACHE IV score, BMI, Barthel index, DM, and vasopressor duration.

APACHE IV: Acute physiological and chronic health evaluation IV; BMI: Body mass index; DM: Diabetes mellitus; ICU: Intensive care unit.

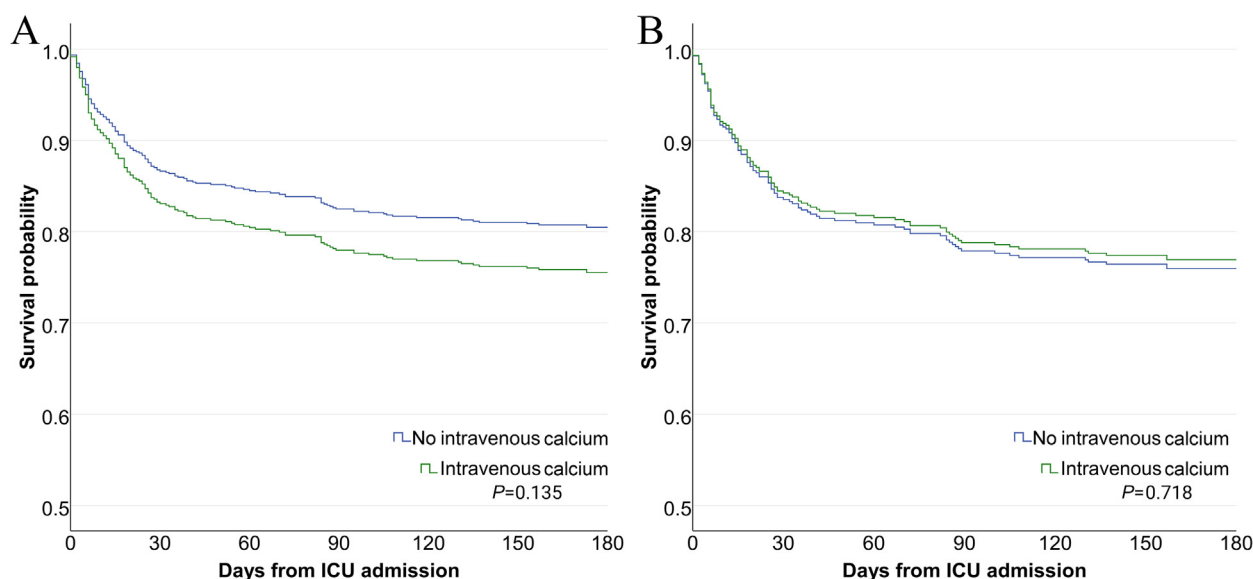


Figure 4. Survival curves of non-sepsis patients with hypocalcemia who received and did not receive intravenous calcium. A: Univariate Cox regression analysis curve. B: Multivariable Cox regression analysis curve after correction for the covariates age, APACHE IV score, Barthel index, COPD, serum albumin, and vasopressor duration.

APACHE IV: Acute physiological and chronic health evaluation IV; COPD: Chronic pulmonary obstructive disease; ICU: Intensive care unit.

ble S11). In the remaining subgroups, multivariable analyses demonstrated no significant association between PCA and 180-day mortality (Supplementary Tables S12–S14).

Time to shock resolution

Patients who received PCA required a longer duration of vasopressor therapy (median=4, [IQR: 3–7] days vs. median=3, [IQR: 2–5] days, $P = 0.001$). On multivariable regression analysis, the group that received PCA showed a lower likelihood of experiencing a shorter time to shock resolution (adjusted odds ratio [aOR]=0.81, 95 % CI: 0.70 to 0.94; Supplementary Table S15); this was particularly relevant in patients without sepsis (aOR= 0.76, 95 % CI: 0.63 to 0.94; Supplementary Table S16) but not in sepsis patients (Supplementary Table S17). In addition, subgroup analyses showed that PCA in patients with mild hypocalcemia, both with and without sepsis, reduced the probability of a faster shock resolution (aOR=0.74, 95 % CI: 0.56 to 0.97 and aOR=0.71, 95 % CI: 0.54 to 0.92, respectively; Supplementary Tables S18 and S19), while this was not in patients with moderate hypocalcemia (Supplementary tables S20 and S21).

Additional analyses

The findings from univariate analysis of additional outcome parameters, in both PCA and control groups, are presented in Supplementary Tables S22–S28. The parameters included the HLOS, duration of mechanical ventilation; and ICU-, 28-day, and 90-day mortality in the subgroups. Multivariable analysis showed a non-significant association between ICULOS and PCA (aOR=0.89, 95 % CI: 0.88 to 1.01; Supplementary Table S29). In patients with hemorrhage or hyperkalemia, PCA was not associated with either 180-day mortality (HR=1.05, 95 % CI: 0.29 to 3.75 and HR=2.23, 95 % CI: 0.66 to 7.52, respectively; Supplementary Table S30) or shorter time to shock resolution

(aOR=0.66, 95 % CI: 0.17 to 2.54 and aOR=1.34, 95 % CI: 0.61 to 2.95, respectively; Supplementary Tables S31 and S32).

Discussion

The findings from this retrospective cohort study, which included ICU patients with serum hypocalcemia, showed that intravenous calcium administration offered no benefits in terms of long-term mortality and time-to-shock resolution. Conversely, patients with hypocalcemia who were administered intravenous calcium demonstrated longer durations of ICULOS, mechanical ventilation, and vasopressor therapy; they also showed lower survival rates on univariate analysis. After adjusting for covariates, intravenous calcium administration was found to be independently associated with a reduced likelihood of shorter time to shock resolution. In addition, subgroup analyses showed that PCA was independently associated with increased all-cause 90- and 180-day mortality in patients with sepsis who had mild hypocalcemia (iCa 1.06 - 1.14 mmol/L).

Hypocalcemia is common in critically ill patients, and is especially seen in cases of excessive inflammation and catecholamine release.^[3,5,13,14,21,22] Although the pathophysiological mechanisms are poorly understood, they may result from side effects of drugs and critical illness; both of these affect calcium homeostasis, leading to high levels of intracellular calcium and low levels of extracellular iCa.^[1,3–6] The reported prevalence rates of hypocalcemia are found to vary among patients admitted to the ICU; this is most likely to be caused by differences among study populations and cutoff values used.^[2] In our study, 83 % of patients admitted to the ICU had developed hypocalcemia (defined by iCa levels of <1.15 mmol/L) during the first 7 days of admission; this finding is consistent with those of previous studies.^[5,6]

Retrospective studies that evaluated the association between hypocalcemia and mortality in ICU patients, have reported mixed results.^[7–14,31] Severe and persistent hypocalcemia dur-

ing critical illness has shown the strongest association with mortality.^[5,15,29,36] However, the causality between iCa levels and adverse outcomes remains unclear; in this context, hypocalcemia could represent an adaptive response to critical illness, and reflect disease severity.^[2] Notably, iCa levels have often been found to spontaneously normalize during the course of a critical illness.^[15,16,36] Nevertheless, patients admitted to the ICU are commonly administered intravenous calcium in an attempt to correct hypocalcemia;^[2,16,36] this practice was also followed in more than half of the cases in our study cohort.

Current guidelines recommend calcium supplementation in patients with major bleeding and hypocalcemia, as calcium plays a vital role in coagulation;^[19] studies show that low iCa levels may be predictive of poor clinical outcomes in these patients.^[37] However, there is no available data to suggest that the achievement of normocalcemia offers any benefits in these patients.^[38] In this context, it is common practice to administer calcium in cases of hyperkalemia-induced ECG abnormalities in order to stabilize the myocellular membrane; however, its effectiveness has not been demonstrated in any randomized controlled trials (RCTs).^[20] In the current study, PCA was neither associated with rapid shock reversal nor improved survival in the subsets of patients with hyperkalemia and hemorrhage.

A recent RCT on patients with out-of-hospital cardiac arrest found calcium administration to offer no benefits in terms of return of spontaneous circulation; the trial was terminated prematurely, as fewer patients in the treatment arm reported favorable neurological outcomes and quality of life at 90 days.^[32] The investigators hypothesized that calcium administration may result in cytosolic and mitochondrial calcium overload; this could stimulate oxidative stress and activate calcium-dependent proteolytic pathways. This hypothesis is similar to the proposed mechanism for calcium-induced toxicity in critical illness, particularly sepsis.^[3] Several studies on animal models of sepsis have demonstrated increased morbidity and mortality following PCA; this may be attributed to activation of destructive enzymes and consequent mitochondrial dysfunction and cell injury.^[21,23,25,26,39]

Previous studies have suggested that calcium supplementation may improve hemodynamics by increasing vascular resistance and left ventricular function owing to its positive inotropic effect.^[17,18,40] However, a long-lasting clinically relevant benefit (in terms of hemodynamic parameters) has never been described in the critically ill.^[3] In their study, Dotson et al.^[24] found PCA to be associated with in-hospital mortality, acute respiratory failure, and new-onset shock in ICU patients who received parenteral nutrition. In the current study, patients receiving PCA showed a longer time to shock resolution, even after adjusting for confounders relevant to the hemodynamic status (such as duration of mechanical ventilation, albumin, and disease severity). Although causal inferences cannot be made from our data, it can be hypothesized that calcium administration may have increased vascular leak (as observed in animal models), and thereby extended the duration of vasopressor dependency.^[21,24]

Only one study has shown calcium supplementation to offer potential benefits in ICU patients, indicating an independent association with lower mortality rates.^[30] A sub-analysis of patients with sepsis, derived from the same database, demonstrated 28-day mortality after calcium supplementation to be

higher in cases where iCa levels at admission were 1.01–1.20 mmol/L; however, those with iCa levels of <1.01 mmol/L possibly benefited from supplementation.^[31] In the present cohort, PCA showed a trend toward a significant increase in 180-day mortality among patients with sepsis who had hypocalcemia. In those with mild hypocalcemia, PCA was associated with decreased 90- and 180-day survival; this concurs with the findings of He et al.^[31] Nevertheless, the association between PCA and 28-day mortality was not significant. This observation is similar to the findings from the RCT performed by Vallentin et al.^[32] that included patients with cardiac arrest; it may be explained by the long-term toxic effects of calcium overload, such as mitochondrial damage.^[22] Notably, the duration of vasopressor therapy is known to contribute to ICULOS and ICU-acquired muscle weakness, which is associated with morbidity and poor long-term outcomes.^[41–43] It is unclear whether this led to poor long-term outcomes in the present cohort; further investigation is needed via prospective trials that need to include follow-up evaluation after ICU and hospital discharge.

Certain limitations need to be considered while interpreting the results of this study. The findings from our single-center retrospective study may have limited generalizability due to specific ICU practices and patient demographics at our center. As in most ICUs, calcium was administered at the discretion of the attending ICU physician; this introduced potential selection bias, as patients receiving calcium were likely to be in a more serious condition. In addition, center-specific patterns may have hampered the applicability of our findings to other settings. Finally, the data were not sufficient to adjust for other potential covariates of vasopressor dependency, such as fluid balance and left ventricular function. Although it was possible to adjust for several strong predictors of mortality (including age, disease severity, and clinical frailty upon ICU admission^[44–46]), residual confounding could have remained. Additionally, some factors may have acted as mediators rather than confounders, potentially obscuring the true effects of calcium administration.

Although our study provides valuable insights, its conclusions are not definitive and should be corroborated by further research. Multi-center prospective studies and comprehensive data collection should ideally be employed for further evaluation.

Conclusions

Hypocalcemia and consequent PCA were common in our large cohort of critically ill patients. However, PCA was not associated with improved outcomes. On the contrary, it was associated with prolongation of the time to shock resolution and reduced long-term survival in patients with sepsis. These findings underscore the need for caution during routine calcium administration in critically ill patients with hypocalcemia. An RCT is warranted to confirm our findings, elucidate the underlying mechanisms, and establish evidence-based treatment guidelines.

CRedit Authorship Contribution Statement

Max Melchers: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hanneke Pierre Franciscus Xavierius**

Moonen: Writing – review & editing, Methodology, Data curation, Conceptualization. **Tessa Maria Breeman:** Writing – review & editing, Methodology, Data curation. **Sjoerd Hendrika Willem van Bree:** Writing – review & editing, Methodology. **Arthur Raymond Hubert van Zanten:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization.

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Ethics Statement

The study titled “Hypophosphatemia and hypocalcemia: course, supplementations and associations with outcome in the general intensive care population” was approved by the Institutional Review Board (approval number: 2101–012) of Gelderse Vallei Hospital, Ede, on February 4, 2021.

Conflict of Interest

Prof. Dr. Arthur Raymond Hubert van Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Abbott, AOP Pharma, Baxter, Danone-Nutricia, Dutch Medical Food, GE Healthcare, Medcaptain, Nestlé, PAION, and Rousselot. The other authors have nothing to declare. The author Arthur Raymond Hubert van Zanten is an Editorial Board Member for this journal and was not involved in the editorial review or the decision to publish this article.

Data Availability

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request. The author Arthur Raymond Hubert van Zanten is an Editorial Board Member for this journal and was not involved in the editorial review or the decision to publish this article.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jointm.2024.08.003](https://doi.org/10.1016/j.jointm.2024.08.003).

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