



Hypophosphatemia in critically ill patients[☆]

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Abstract

Purpose: The aim of this study was to assess the association of phosphate concentration with key clinical outcomes in a heterogeneous cohort of critically ill patients.

Materials and Methods: This was a retrospective observational study at a general intensive care unit (ICU) of an Australian university teaching hospital enrolling 2730 adult critically ill patients.

Results: We studied 10 504 phosphate measurements with a mean value of 1.17 mmol/L (measurements every 28.8 hours on average). Hyperphosphatemia (inorganic phosphate [iP] concentration > 1.4 mmol/L) occurred in 45% and hypophosphatemia (iP ≤ 0.6 mmol/L) in 20%. Among patients without any episodes of hyperphosphatemia, patients with at least 1 episode of hypophosphatemia had a higher ICU mortality than those without hypophosphatemia ($P = .004$). In addition, ICU nonsurvivors had lower minimum phosphate concentrations than did survivors ($P = .009$). Similar results were seen for hospital mortality. However, on multivariable logistic regression analysis, hypophosphatemia was not independently associated with ICU mortality (adjusted odds ratio, 0.86 [95% confidence interval, 0.66–1.10]; $P = .24$) and hospital mortality (odds ratio, 0.89 [0.73–1.07]; $P = .21$). Even when different cutoff points were used for hypophosphatemia (iP ≤ 0.5, 0.4, 0.3, or 0.2 mmol/L), hypophosphatemia was not an independent risk factor for ICU and hospital mortality. In addition, timing of onset and duration of hypophosphatemia were not independent risk factor for ICU and hospital mortality.

Conclusions: Hypophosphatemia behaves like a general marker of illness severity and not as an independent predictor of ICU or in-hospital mortality in critically ill patients.

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1. Introduction

Inorganic phosphate (iP) is important to multiple key physiologic processes [1–8]. Accordingly, plasma iP levels are tightly regulated in humans. However, these regulatory processes are not reliably successful during acute illness,

and hypophosphatemia is, therefore, relatively common in critically ill patients [9-21].

Hypophosphatemia has been reported to be associated with increased morbidity [10-13] and mortality [13-16] in critically ill patients. However, this assessment of the relationship between hypophosphatemia and unfavorable clinical outcomes is derived from univariable analyses [11-15] or relatively small cohort studies [10,16]. The inability to adjust for major confounding and the impact of small study size markedly increase the risk of type I error. Thus, it remains uncertain whether hypophosphatemia does indeed have an independent association with mortality or whether it is simply another general marker of illness severity.

However, it is on the basis of such association that phosphate administration is recommended [6,22-29]. This is despite the lack of randomized controlled evidence of an impact on outcome and concerns about the adverse effects of intravenous phosphate therapy [5,7]. Thus, we sought to determine the epidemiology and outcome associations of hypophosphatemia in a large cohort of intensive care unit (ICU) patients.

2. Methods

The data collection for this study was part of an established quality assurance activity. The data collection and the data analysis for this study were approved by the local institutional ethics committee, which waived the need for informed consent. The Austin Hospital Ethics Committee approved investigations of the database used for this analysis and their submission for publication.

2.1. Study population and data sources

This study is a single-center, retrospective, and observational investigation of a prospectively gathered intensive care database. All patients admitted to an Australian university teaching hospital ICU over a 4-year period were included.

Age, sex, use of mechanical ventilation and renal replacement therapy, reason for ICU admission, and Acute Physiology and Chronic Health Evaluation II score [30] were obtained from the electronic data repositories of the ICU, using data that had been collected prospectively by trained data collectors.

Coding for admission diagnosis was by means of a modified Acute Physiology and Chronic Health Evaluation III system used by the Australian and New Zealand Intensive Care Society [31]. The Australian and New Zealand Intensive Care Society Centre for Outcome and Resources Evaluation independently collected information on clinical outcomes. The Australian and New Zealand Intensive Care Society Centre for Outcome and Resources Evaluation Adult Patient database is a high-quality database whose features have been previously described [32].

2.2. Phosphate monitoring and approach to hypophosphatemia

To measure iP concentration, arterial samples were drawn using a vacuum technique with lithium heparin tubes (Vacurette; Greiner Labortechnik, Kremsmunster, Austria). These samples were analyzed by staff at the hospital central laboratory (Hitachi 747; Roche Diagnostics, Sydney, NSW, Australia) using a phosphomolybdate complex colorimetric technique. Samples were not stored on ice. For each data set, a further sample was simultaneously collected in heparinized blood-gas syringes and analyzed immediately at 37°C in the ICU blood-gas analyzer (Rapilab; Bayer, Sydney, Australia) to collect data on blood pH, potassium, ionized calcium, and glucose concentrations. Trained nursing staff performed all blood analyses. All data were stored in computerized records. We retrieved all data for analysis from these records.

From the database, maximal (iP_{Max}) and minimal (iP_{Min}) iP concentrations were obtained for each patient, indicating the highest or lowest value recorded while in ICU. In addition, to avoid the potential effect of surveillance bias caused by increased monitoring in more severely ill patients, a time-weighted average of iP concentration during ICU stay (iP_{Tw}) was calculated. This method was modified from, and used in accordance with, an approach previously used by Finney et al [33] to describe time-weighted glycemia. The iP_{Adm} was defined as the first value measured after ICU admission. Finally, the SD of iP concentration during ICU stay (iP_{SD}) was calculated as arithmetical SD of the entire set of measurements during ICU stay in each patient. Because the reference range of phosphate for our hospital is between greater than 0.60 and 1.4 mmol/L, hypophosphatemia was defined as iP of 0.6 mmol/L or less. The duration of hypophosphatemia was calculated as the time from when an iP is 0.6 mmol/L or less was recorded until the time when a subsequent iP concentration first returned to a value greater than 0.6 mmol/L.

There was no strict protocol for how intravenous phosphate therapy should be given to correct hypophosphatemia in our ICU. However, the typical approach was to correct any degree of hypophosphatemia by the intravenous administration of 10 to 15 mmol of sodium dihydrogen phosphate given for 2 to 4 hours.

2.3. Statistical analysis

Continuous data are reported as means (SD) or medians (interquartile range), depending on the underlying data distribution. Categorical data are reported as proportions.

The primary end points for our analysis were ICU and hospital mortality. To determine the difference of patients' characteristics with and without hypophosphatemia, all variables were examined by univariable analysis using the χ^2 test for proportions, Student *t* test for normally distributed outcomes, and Wilcoxon rank sum test for nonparametric

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