



Towards Safer Phosphate Repletion: A 24-Hour Weight-Based Infusion Protocol for Hypophosphatemic ICU Patients

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Abstract

Background: Evidence on the safety and efficacy of phosphate (P) replacement in hypophosphatemic intensive care unit (ICU) patients remains limited.

Objectives: To evaluate the efficacy and safety of a 24-hour weight-based intravenous phosphate replacement protocol.

Methods: Adult ICU patients with hypophosphatemia received potassium acid phosphate (25 mL) diluted in 500 mL of saline or 5% glucose, administered via infusion pump. Dosing was 0.3 mmol/kg/24 h for mild hypophosphatemia (0.65 - 0.73 mmol/L) and 0.6 mmol/kg/24 h for moderate to severe cases (≤ 0.64 mmol/L). Phosphate levels were measured every 24 hours. Efficacy was defined as normalization of phosphate within 24 hours. Safety outcomes included hypocalcemia, hypotension, hyperphosphatemia, hyperkalemia, and acute kidney injury.

Results: Among 134 patients (aged 67.6 ± 14.6 years; 55% female; median APACHE II median 18), 197 hypophosphatemia episodes were treated. Phosphate normalized within 24 hours in 121 episodes (61%). Mild adverse events occurred in 28 patients (21%); no severe complications were reported.

Conclusions: This protocol is not a replacement for standard guidelines in symptomatic hypophosphatemia and unstable patients. It proved effective and generally safe in critically ill patients with mild to severe hypophosphatemia, offering a feasible approach in resource-limited ICU settings where oral formulations are unavailable and frequent laboratory monitoring is unfeasible.

Keywords: Hypophosphatemia, Intensive Care Units, Repletion

1. Background

Hypophosphatemia frequently occurs during intensive care unit (ICU) stays and is associated with various conditions (e.g., sepsis, alcohol withdrawal, malnutrition, refeeding syndrome, renal replacement therapy) and medications (e.g., diuretics, catecholamines, insulin) (1). While oral phosphate is preferred for mild cases and intravenous replacement is reserved for moderate to severe or symptomatic

hypophosphatemia (1, 2), oral formulations are often unavailable in Brazil. Most published protocols for intravenous phosphate focus on rapid correction (using doses up to 45 mmol and infusion rates up to 20 mmol/h) with monitoring every 6 hours (2), making them unsuitable for settings with limited resources.

2. Objectives

This study assesses the feasibility, efficacy, and safety of a low-intensity, 24-hour phosphate infusion protocol

using potassium-acid-phosphate, the only available IV phosphate formulation in the study setting.

3. Methods

This study complied with the Declaration of Helsinki and was approved by the Institutional Ethics Committee (CAAE: 5095315.0000.5149). Written informed consent was obtained from all patients or their legal representatives. This was a secondary analysis of a prospective observational cohort (3), involving patients admitted to three ICUs (clinical, surgical, and coronary) in a tertiary hospital in Brazil, between August 2016 and February 2017.

Inclusion criteria were age ≥ 18 years, ICU stay ≥ 24 hours, and hypophosphatemia either on admission or during the ICU stay. Exclusion criteria were pre-existing phosphate supplementation or dialytic chronic kidney disease, and contraindications to potassium-acid-phosphate infusion (e.g., hyperkalemia, uncontrolled shock, severe lactic acidosis).

Demographic and clinical data included age, sex, ICU admission diagnosis, SOFA scores (4) (days 1, 3, and 7), APACHE II score (5) at admission, mechanical ventilation use and duration, ICU and hospital length of stay, and mortality. Phosphate levels were measured on admission (within 1 hour) and every 24 hours using arterial or venous blood samples analyzed via a phosphomolybdate method (Abbot, USA). According to cut-off values suggested by the manufacturer, hypophosphatemia was defined as serum phosphate < 0.74 mmol/L and categorized as mild ($0.65 - 0.73$ mmol/L), moderate ($0.32 - 0.64$ mmol/L), or severe (< 0.32 mmol/L).

Replacement used 25 mL of potassium-acid-phosphate (1 mmol/mL phosphate and 2 mEq/mL potassium) diluted in 500 mL saline or 5% glucose and administered via infusion pump through a dedicated line, ensuring potassium concentration ≤ 10 mEq/100 mL. Dilution in lactated Ringer's was avoided due to precipitation risk. Replacement dosing was 0.3 mmol/kg/24 h for mild hypophosphatemia and 0.6 mmol/kg/24 h for moderate to severe cases, based on pilot observations at our institution indicating good tolerance and low rates of adverse events.

Phosphate levels were reassessed after each 24-hour infusion, and replacement was repeated, stopped, or adjusted based on serum phosphate levels and adverse events. Infusions were stopped if phosphate levels normalized or adverse events occurred. Efficacy was defined as normalization of serum phosphate within 24 hours post-infusion. Recurrent hypophosphatemia was

defined as a new episode at least 24 hours after phosphate normalization.

Adverse events included hypocalcemia (ionized calcium < 1.15 mmol/L), hyperkalemia (potassium > 5.0 mmol/L), hyperphosphatemia, hypotension (MAP < 65 mmHg) (3), and acute kidney injury ($\geq 50\%$ rise in creatinine or dialysis requirement) [3]. Ionized calcium, potassium, phosphate, and creatinine were measured daily. Events occurring during or within 24 hours after infusion, without other identifiable causes, were attributed to phosphate replacement.

Data were analyzed using SPSS version 19.0. Descriptive statistics were presented as mean $\pm$ SD, median (range), or count (percentage), as appropriate. Non-parametric tests were used for comparisons. The significance was set at $P < 0.05$.

4. Results

A total of 134 patients were included. Patient characteristics are summarized in Table 1.

They experienced 197 hypophosphatemia episodes: Eighty-five (43%) mild, 107 (54%) moderate, and 5 (3%) severe. Moderate to severe cases were grouped given the rare occurrence of severe episodes. Twenty-seven patients (20%) had only mild episodes. The median number of hypophosphatemia episodes per patient was 2 (range 1 - 25). Recurrent hypophosphatemia occurred in 52/121 patients whose phosphate levels normalized (43%), particularly in those with moderate/severe cases, compared to those with mild hypophosphatemia (median episodes (range): Two (1 - 25) vs. 1 (1 - 3); $P < 0.0001$).

Phosphate levels normalized within 24 hours in 121 episodes (61%), partially improved in 38 (19%), and did not improve in 38 (20%). In non-responders or partial responders, replacement was recalculated and repeated daily until phosphate normalization. Mild adverse events occurred in 28 patients (21%), all of whom had moderate/severe hypophosphatemia. These included hyperkalemia in 15 (11%), hyperphosphatemia in 8 (6%), and hypocalcemia in 6 (4.5%). No cases of hypotension or AKI were linked to phosphate replacement. Adverse events of hyperkalemia and hyperphosphatemia were managed by stopping phosphate replacement, and hypocalcemia was managed through intravenous replacement.

5. Discussion

This study demonstrates that a slower, 24-hour infusion approach for hypophosphatemia in the ICU may offer a safer and effective alternative to more

Table 1. Population of the Study ^a

Variables	Population (N = 134)
Age (y)	67.6 ± 14.6
Female gender	74 (55)
Whites	51 (38)
Admission for clinical (non-surgical) disease	67 (50)
APACHE II	18 (6 - 36)
SOFA 1 (n = 128)	5 (0 - 17)
SOFA 3 (n = 118)	4 (0 - 15)
SOFA 7 (n = 73)	5 (0 - 13)
MV	78 (58)
MV duration (d)	6 (1 - 50)
ICU mortality	31 (23)
In-hospital mortality	44 (33)
ICU LOS (d)	8 (1 - 66)
In-hospital LOS (d)	20 (4 - 346)

Abbreviation: MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay.

^a Values are expressed as mean ± standard deviation, No. (%), or median (minimum-maximum).

aggressive regimens, particularly in settings where oral formulations are unavailable and frequent laboratory testing and rapid infusion monitoring are not feasible. Although the phosphate normalization rate was slightly lower than that reported in 6-hour protocols (61% vs. 72%), the safety profile was favorable, with no severe complications observed (2). No patients with mild hypophosphatemia developed complications, suggesting a better safety and efficacy profile of the lower replacement dose. For moderate/severe hypophosphatemia, this dose warrants evaluation in future studies. The study also highlights the need for daily phosphate monitoring, especially among patients with moderate/severe deficiencies.

This study has limitations. It was conducted in a single center, and the findings may not be generalizable. This protocol has not been tested and must not replace the current guidelines in symptomatic hypophosphatemia or unstable patients, in which frequent monitoring may be warranted. The absence of a comparator group limits the ability to assess relative efficacy. Patients with chronic kidney disease, shock, or hyperkalemia — those most vulnerable to phosphate-related complications — were excluded, so the protocol's safety in these groups remains unknown. The 24-hour monitoring frequency may miss acute complications, and the cost-effectiveness of this approach was not evaluated. Finally, while adverse events were uncommon and mild, further studies should determine whether modified dosing could improve efficacy in moderate/severe cases without compromising safety.

5.1. Conclusions

A 24-hour weight-based intravenous phosphate replacement protocol using potassium-acid-phosphate appears safe and effective for ICU patients with mild to moderate/severe hypophosphatemia. This protocol appears particularly suitable in resource-limited settings, where oral and other intravenous phosphate formulations are unavailable, and frequent laboratory monitoring is unfeasible. Future randomized studies are needed to validate its broader use and compare it to more intensive or rapid infusion protocols.

Footnotes

Authors' Contribution: Conceptualization, data curation, methodology, and project administration: W. L., D. C. C., R. P., M. O. M., and G. A. F.; Formal analysis: W. L., D. C. C., and G. A. F.; Funding acquisition: Not applicable; Investigation: W. L., R. P., M. C., J. A. L., and M. O. M.; Software: Not applicable; Resources, supervision, validation, visualization, writing-original draft, writing-review, and editing: W. L., D. C. C., R. P., M. C., J. A. L., M. O. M., and G. A. F. Final approval of the version to be submitted: All authors.

Conflict of Interests Statement: The authors declare no conflict of interests.

Data Availability: The dataset presented in the study is available on request from the corresponding author.

The data are not publicly available due to restrictions imposed by the institutional ethics review board.

Ethical Approval: This study complied with the Declaration of Helsinki and was approved by the Institutional Ethics Committee (CAAE: 5095315.0000.5149).

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References

1. Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE, Schultz MJ. Treatment of hypophosphatemia in the intensive care unit: a review. *Crit Care*. 2010;**14**(4):R147. [PubMed ID: [20682049](#)]. [PubMed Central ID: [PMC2945130](#)]. <https://doi.org/10.1186/cc9215>.
2. Engwerda E, van den Berg M, Blans M, Bech A, de Boer H. Efficacy and safety of a phosphate replacement strategy for severe hypophosphatemia in the ICU. *Neth J Med*. 2018;**76**(10):437-41. [PubMed ID: [30569887](#)].
3. Lima W, Calderaro DC, Passos R, Corte M, Leal JA, Mayrink MO, et al. Lower mean phosphate independently predicts mortality in critically ill patients: Results from a prospective cohort study. *J Crit Care*. 2023;**75**:154273. [PubMed ID: [36739201](#)]. <https://doi.org/10.1016/j.jcrc.2023.154273>.
4. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;**22**(7):707-10. [PubMed ID: [8844239](#)]. <https://doi.org/10.1007/BF01709751>.
5. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;**13**(10):818-29. [PubMed ID: [3928249](#)].