Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2024, Volume 4, Page No: 194-206

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Galaxy Publication

Effect of Magnesium Infusion Rate on Serum Magnesium Levels Following Magnesium Replacement in Hospitalized Surgical Patients with Hypomagnesemia: An 11-Year Retrospective Cohort Analysis

Jan de Vries[1], Pieter L. Bakker[2]*

[1]Department of Clinical Pharmacy and Pharmacology, Faculty of Science, University of Groningen, Groningen, Netherlands.
[2]Department of Clinical Pharmacy, Faculty of Pharmacy, KU Leuven, Leuven, Belgium.

***E-mail** ✉ p.l.bakker_rug@outlook.com
Received: 27 April 2024; **Revised:** 16 August 2024; **Accepted:** 19 August 2024

ABSTRACT

Low serum magnesium levels are frequently observed in patients undergoing surgery and commonly necessitate intravenous (IV) magnesium supplementation. Given the kidneys' role in magnesium regulation, extending the infusion time of IV magnesium has been suggested to enhance retention by minimizing urinary loss. Nevertheless, supporting data for this approach remain scarce. To compare the rise in serum magnesium concentration from baseline following IV magnesium administration between extended infusions (rate < 0.5 g/h) and rapid infusions (rate ≥ 0.5 g/h) among hospitalized patients who have undergone surgery. We conducted a retrospective review of medical records from surgical patients admitted to a university hospital between 2012 and 2022 who had hypomagnesemia, received IV magnesium supplementation for three consecutive days. Patients were divided into two groups based on infusion rate: extended infusion and rapid infusion. The main outcome measure was the increase in serum magnesium level per gram of magnesium given relative to baseline. A secondary outcome was the proportion of patients reaching a target serum magnesium concentration following supplementation. A total of 114 patients were included. The rapid infusion group demonstrated a significantly larger increase in serum magnesium per gram administered (0.07 mg/dL/g) compared with the extended infusion group (0.05 mg/dL/g) ($p = 0.04$), with a between-group difference of 0.013 mg/dL/g. No significant difference was found in the proportion of patients achieving target serum magnesium levels (extended infusion: 66.7% vs. rapid infusion: 70.2%; $p = 0.84$). Factors influencing the change in serum magnesium included kidney function and the interval between completion of infusion and magnesium level assessment. In surgical inpatients, slowing the IV magnesium infusion to below 0.5 g/h offered no added advantage in elevating serum magnesium concentrations compared with faster infusion rates.

Keywords: Magnesium, Hypomagnesemia, Intravenous, Administration, Rate

How to Cite This Article: de Vries J, Bakker PL. Effect of Magnesium Infusion Rate on Serum Magnesium Levels Following Magnesium Replacement in Hospitalized Surgical Patients with Hypomagnesemia: An 11-Year Retrospective Cohort Analysis. 2024;4:194-206. https://doi.org/10.51847/HL5fn2NDeI

Introduction

Magnesium is essential for the activity of many enzymes and biochemical pathways, and it contributes to a wide range of physiological functions [1, 2]. Low serum magnesium concentrations (defined as <1.6 mg/dL) represent a frequent electrolyte disturbance in patients undergoing surgery, with reported rates varying from 12% to 71% in the postoperative period and reaching 61% among those who have undergone cardiovascular thoracic procedures [3-5]. Multiple factors contribute to this condition in surgical cases, including inadequate nutritional intake, enhanced urinary elimination, non-renal losses (such as through nasogastric suction or preoperative bowel cleansing), redistribution of magnesium from the extracellular compartment into cells, and the concurrent administration of medications that promote magnesium wastage [4, 6]. In post-operative patients, hypomagnesemia has been linked to prolonged mechanical ventilation and an elevated all-cause mortality rate.

Notably, in individuals undergoing cardiovascular or thoracic surgery, hypomagnesemia serves as an independent risk factor for postoperative atrial fibrillation and enhances atrial myocardial excitability [3, 5, 7-10]. Consequently, regular monitoring of serum magnesium is advised, and supplementation is frequently indicated to restore and sustain normal values [2].

Intravenous magnesium supplementation is commonly employed in surgical populations, largely due to perioperative fasting and postoperative emesis [11]. Renal excretion predominantly regulates serum magnesium homeostasis; therefore, rapid IV delivery can transiently elevate levels above the kidney's reabsorption threshold, prompting substantial urinary loss [6, 12]. In theory, extending the duration of magnesium infusion could enhance retention by lowering the peak load presented to the renal tubules, permitting greater intracellular uptake and reducing excretion [2]. For patients with mild, asymptomatic low magnesium, guidelines suggest infusion rates not exceeding 0.5 to 1 g/h [2, 11]. At our facility, the institutional guideline limits IV magnesium administration to a maximum rate of 0.5 g/h.

Despite widespread endorsement of slower infusion rates in routine care, a key drawback of extended IV magnesium delivery is potential incompatibility with other medications administered through the same intravenous line [12]. Moreover, contemporary investigations have not demonstrated clear advantages from slower infusions in general inpatient settings [13, 14]. These prior works, however, did not adequately account for confounders that influence serum magnesium, including kidney function, use of diuretic agents, and the interval between infusion completion and subsequent magnesium measurement, which restricts their conclusions. Accordingly, this investigation sought to evaluate the difference in serum magnesium elevation from baseline between extended and rapid IV magnesium infusions in hospitalized patients who had undergone surgery.

Materials and Methods

Study design

This retrospective cohort investigation was carried out at Songklanagarind Hospital, a tertiary university-affiliated facility under Prince of Songkla University in Thailand. Ethical approval was granted by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand (REC 65-428-19-6).

Participant selection

The study included adult patients aged ≥18 years admitted to surgical wards who had asymptomatic low serum magnesium (<1.6 mg/dL) and received intravenous (IV) magnesium supplementation daily for three consecutive days between December 2012 and November 2022. Patients were allocated into two equal-sized groups (1:1 ratio) according to the IV magnesium infusion rate: the extended infusion group received magnesium at <0.5 g/h, whereas the rapid infusion group received it at ≥0.5 g/h.

Exclusion criteria encompassed: 1) concurrent magnesium administration from alternative routes or sources (e.g., oral supplements, magnesium-containing intravenous fluids, total parenteral nutrition, or medications such as antacids and osmotic laxatives); 2) use of magnesium-wasting medications other than loop or thiazide diuretics (e.g., aminoglycosides, amphotericin B, cisplatin, cyclosporine, foscarnet, tacrolimus); 3) underlying disorders associated with altered magnesium homeostasis (e.g., acute kidney injury, end-stage kidney disease with eGFR <15 mL/min/1.73 m², kidney transplantation, polyuria, hyperthyroidism, primary hyperaldosteronism, Bartter syndrome, or Gitelman syndrome); and 4) acute conditions promoting extracellular-to-intracellular magnesium shifts (e.g., hungry bone syndrome, diabetic ketoacidosis, acute pancreatitis).

Since magnesium equilibrates between extracellular and intracellular spaces and excess is renally cleared, post-treatment serum magnesium concentrations measured 6–24 hours after the last dose were considered representative of steady-state distribution [2, 15]. Patients whose follow-up magnesium levels were drawn <6 hours or >24 hours after the final infusion were excluded.

Sample size calculation

Based on preliminary pilot data showing a between-group difference of 0.012 mg/dL per gram of IV magnesium administered, the required sample size was determined using Cohen's approach for multiple linear regression. A minimum of 57 patients per group was needed to achieve 80% statistical power [16].

Data acquisition

Information extracted from electronic health records included demographic details (sex, age, body weight, body mass index), kidney function, primary diagnosis, surgical procedure type, volume of IV fluids administered during magnesium therapy, and concurrent diuretic use. Total magnesium dose, infusion rates, baseline serum magnesium (measured within 24 hours before starting therapy), and post-treatment serum magnesium (6–24 hours after completion) were recorded.

For safety evaluation, any documented adverse effects during infusion—such as hypotension, flushing, neuromuscular abnormalities (muscle weakness, absent deep tendon reflexes, respiratory distress, Chvostek or Trousseau signs), nausea, or vomiting—potentially attributable to hypo- or hypermagnesemia were collected.

Endpoints

The primary endpoint was the increase in serum magnesium concentration per gram of total magnesium administered over the three-day course. To account for varying doses and potential confounders, adjustments were performed for baseline hypomagnesemia severity, renal function, diuretic co-administration, and timing of post-treatment magnesium measurement. The secondary endpoint was the proportion of patients achieving normal serum magnesium (1.6–2.6 mg/dL) after therapy completion. Safety was assessed by the occurrence of adverse events related to magnesium imbalance.

Statistical methods

Analyses were conducted using R software (version 2022.12). Normally distributed continuous variables were expressed as mean ± standard deviation and compared with independent t-tests; non-normal data were reported as median (interquartile range) and analyzed via Mann-Whitney U tests. Categorical data were presented as counts (%) and evaluated with chi-square or Fisher's exact tests.

Univariate linear regression identified variables potentially influencing magnesium change per gram ($p \leq 0.2$ threshold). These were then entered into multivariable linear regression to assess the relationship between infusion rate and magnesium increment while controlling for confounders. Statistical significance was defined as $p < 0.05$.

Results and Discussion

Baseline characteristics and enrollment

Of 1319 patients initially screened as eligible during the study interval, 1205 were excluded based on predefined criteria. Ultimately, 114 patients were included, with 57 assigned to each cohort. Patient flow is illustrated in **Figure 1**.

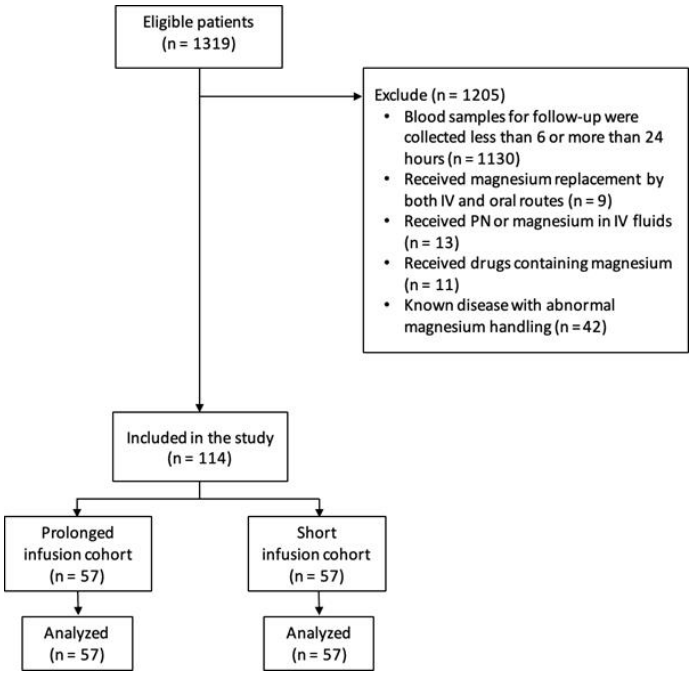


Figure 1. Study enrolment flow chart. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

The two groups exhibited comparable baseline characteristics **(Table 1)**. Overall mean age was 62.6 years (SD 13.1), with 59.6% of patients aged over 60 years. Mean estimated glomerular filtration rate (eGFR) was 89.1 mL/min/1.73 m² (SD 21). The average baseline serum magnesium concentration across all patients was 1.25 mg/dL (SD 0.23), and the majority presented with mild-to-moderate hypomagnesemia (serum magnesium ≥1.0 and <1.6 mg/dL).

Mean baseline serum potassium was 3.6 mEq/L (SD 0.57), with no significant differences between groups in either the mean baseline potassium value or the proportion of patients with hypokalemia. All individuals with low potassium received supplementation, and the total potassium dose administered did not differ significantly between the extended and rapid infusion groups (median 170 mEq [IQR 145–215] vs. 120 mEq [IQR 80–217.5]; p = 0.07). Post-treatment mean serum potassium levels were also similar between groups (extended infusion: 3.7 mEq/L [95% CI 3.59–3.81] vs. rapid infusion: 3.7 mEq/L [95% CI 3.62–3.78]; p = 0.629).

Table 1. Baseline Characteristics of the Study Participants

Characteristics	Rapid Infusion (n = 57)	Extended Infusion (n = 57)	p-value
Male gender, n (%)	37 (64.9)	28 (49.1)	0.130[a]
Age, years, mean (SD)	62.7 (13.6)	62.5 (12.8)	0.964[b]
Body weight, kg, mean (SD)	56.6 (13.7)	53.9 (12.1)	0.277[b]
Body mass index, kg/m², mean (SD)	21.6 (5.0)	21.5 (4.5)	0.919[b]
Estimated GFR, mL/min/1.73 m², mean (SD)	89.3 (20.9)	89.0 (21.4)	0.944[b]
Chronic kidney disease stage, n (%)			0.760[a]
Stage I or II	50 (87.7)	52 (91.2)	
Stage III	7 (12.3)	5 (8.8)	
Primary diagnosis, n (%)			0.003[a]
Gastrointestinal malignancy	13 (22.8)	25 (43.9)	
Other malignancies	19 (33.3)	8 (14.0)	
Intestinal disorders	5 (8.8)	13 (22.8)	
Infection	8 (14.0)	7 (12.3)	
Other conditions	12 (21.1)	4 (7.0)	
Underwent surgical procedure, n (%)	35 (61.4)	46 (80.7)	0.039[a]
Type of surgery performed, n (%)			0.072[a]
Gastrointestinal	18 (51.4)	35 (76.1)	
Urologic	8 (22.9)	5 (10.9)	
Cardiothoracic	4 (11.4)	2 (4.3)	
Plastic/reconstructive	4 (11.4)	1 (2.2)	
Other procedures	1 (2.9)	3 (6.5)	
Volume of intravenous fluids over 3 days of magnesium therapy, mL, median (IQR)	5010 (3410–5930)	4930 (3910–6115)	0.467[c]
Dietary magnesium intake over 3 days of magnesium therapy, mg, median (IQR)	150 (0–533.3)	150 (0–450)	0.795[c]
Use of loop diuretics, n (%)	13 (22.8)	15 (26.3)	0.828[a]
Presence of hypokalemia, n (%)	24 (42.1)	18 (31.6)	0.332[a]
Serum potassium, mEq/L, mean (SD)	3.6 (0.5)	3.7 (0.6)	0.595[b]
Serum calcium, mg/dL, mean (SD)	9.0 (0.8)	8.9 (0.6)	0.450[b]
Serum phosphate, mg/dL, mean (SD)	3.0 (0.9)	3.0 (0.7)	0.622[b]
Serum albumin, g/dL, mean (SD)	3.2 (0.7)	3.1 (0.7)	0.698[b]

$p < 0.05$ denotes statistical significance. [a]Chi-squared test or Fisher's exact test, [b]Independent t-test, [c]Mann-Whitney U test.
Abbreviations: BMI, body mass index; GFR, glomerular filtration rate.

Primary outcome

The median IV magnesium infusion rate was 0.3 g/h (range 0.17–0.33 g/h) in the extended infusion group and 0.5 g/h (range 0.5–1 g/h) in the rapid infusion group. Baseline serum magnesium concentrations and the interval between completion of therapy and post-treatment magnesium measurement were comparable between the two groups. Patients in the extended infusion group, however, received a significantly higher total dose of intravenous magnesium over the three-day period compared with the rapid infusion group **(Table 2)**.

Table 2. Primary and Secondary Outcomes

Outcome	Rapid Infusion (n = 57)	Extended Infusion (n = 57)	p-value
Total magnesium administered over 3 days, g, median (IQR)	6 (6–12)	12 (10–12)	<0.001[a]
Serum magnesium concentration			
Baseline, mg/dL, median (IQR)	1.34 (1.11–1.46)	1.23 (0.99–1.41)	0.138[a]
After completion of therapy, mg/dL, mean [95% CI]	1.79 [1.70–1.88]	1.78 [1.69–1.87]	0.829[b]
Absolute change from baseline, mg/dL, median (IQR)	0.48 (0.36–0.65)	0.50 (0.38–0.67)	0.616[a]
Time from therapy completion to post-treatment blood draw, hours, median (IQR)	10.2 (6.6–14.7)	11.7 (6.4–19.2)	0.982[a]
Primary outcome			
Change in serum magnesium per gram of magnesium administered, mg/dL/g, mean [95% CI]	0.07 [0.06–0.08]	0.05 [0.04–0.06]	0.004[b]
Secondary outcome			
Patients achieving target serum magnesium (1.6–2.6 mg/dL) after therapy, % [95% CI]	70.2 [57.3–80.5]	66.7 [53.7–77.5]	0.840[c]
Patients with persistent hypomagnesemia after therapy, % [95% CI]	29.8 [19.5–42.7]	33.3 [22.5–46.3]	0.739[c]

$p < 0.05$ denotes statistical significance. [a]Mann-Whitney U test, [b]Independent t-test, [c]Chi-squared test.

The short infusion cohort demonstrated a significantly larger mean increase in serum magnesium per gram of magnesium administered compared to the prolonged infusion cohort. Nevertheless, the serum magnesium levels at the completion of therapy showed no significant difference between the two groups **(Table 2)**.

In patients with mild to moderate hypomagnesemia, short intravenous magnesium infusion led to a significantly greater rise in serum magnesium levels than prolonged infusion. In contrast, among those with severe hypomagnesemia (serum magnesium <1.0 mg/dL), the increase in serum magnesium did not differ significantly between the short and prolonged infusion cohorts **(Table 3)**.

Table 3. Primary and Secondary Outcomes by Severity of Hypomagnesemia

Outcome	Short Infusion	Prolonged Infusion	p-value
Mild-to-Moderate Hypomagnesemia	n = 47	n = 42	
Baseline serum magnesium level (mg/dL), median (IQR)	1.41 (1.25–1.48)	1.32 (1.20–1.47)	0.232[a]
Change in serum magnesium per gram administered (mg/dL/g Mg), median (IQR)	0.07 (0.05–0.09)	0.05 (0.04–0.06)	0.011[a]
Participants achieving optimal serum magnesium target after treatment, % [95% CI]	85.1% [72.3–92.6]	76.2% [61.5–86.5]	0.425[b]
Severe Hypomagnesemia	n = 10	n = 15	
Baseline serum magnesium level (mg/dL), mean [95% CI]	0.88 [0.83–0.93]	0.92 [0.89–0.95]	0.178[c]
Change in serum magnesium per gram administered (mg/dL/g Mg), mean [95% CI]	0.07 [0.05–0.09]	0.05 [0.03–0.07]	0.225[c]
Participants achieving optimal serum magnesium target after treatment, % [95% CI]	0% [0–27.8]	40.0% [19.8–64.3]	0.051[d]

$p < 0.05$ indicates statistical significance. [a]Mann-Whitney U test; [b]Chi-squared test; [c]Student's t-test; [d]Fisher's exact test.

Results from the simple linear regression indicated that the intravenous magnesium infusion rate influenced the increase in serum magnesium levels per gram given, yielding a regression coefficient of 0.014 mg/dL per gram (95% confidence interval: 0.005 to 0.020), with a p-value of 0.004 for shorter infusion durations. Additionally, both the interval between completion of treatment and subsequent serum magnesium measurement, as well as kidney function, demonstrated significant correlations with the rise in serum magnesium concentration. In contrast, neither the initial degree of hypomagnesemia nor the concurrent administration of loop diuretics exhibited a statistically significant relationship with the observed change in serum magnesium **(Table 4)**.

Table 4. Linear Regression Analysis Examining Factors Affecting Change in Serum Magnesium Levels

Factors	Simple Linear Regression			Multiple Linear Regression		
	Regression Coefficient	p-value	95% CI	Regression Coefficient	p-value	95% CI
IV Magnesium Infusion Rate						
Prolonged infusion (< 0.5 g/h)	–	–	–	–	–	–
Short infusion (≥ 0.5 g/h)	0.014	0.004	0.005 – 0.024	0.013	0.007	0.004 – 0.022
Time from Therapy Completion to Serum Magnesium Sampling (per 1-hour increment)	-0.001	0.020	-0.002 – -0.0001	-0.001	0.011	-0.002 – -0.0002
Estimated Glomerular Filtration Rate (eGFR)						
≥ 60 mL/min/1.73 m²	–	–	–	–	–	–
30 to < 60 mL/min/1.73 m²	0.020	0.031	0.002 – 0.034	0.019	0.016	0.004 – 0.034
Severity of Hypomagnesemia						
Mild to moderate	–	–	–	–	–	–
Severe	-0.003	0.638	-0.015 – 0.009	–	–	–
Loop Diuretic Use						
No	–	–	–	–	–	–
Yes	-0.004	0.476	-0.016 – 0.007	–	–	–

Note: p-value < 0.05 indicates statistical significance.
Abbreviations: eGFR = estimated glomerular filtration rate.

A multivariable linear regression model was constructed incorporating all variables that demonstrated statistical significance in the univariable analyses **(Table 4)**. The underlying assumptions of linear regression were evaluated, confirming normality of residuals, homoscedasticity, and absence of multicollinearity (all variance inflation factors <10).

After controlling for the timing of serum magnesium assessment and renal function, short-duration intravenous magnesium replacement was associated with a significantly larger increase in serum magnesium concentration compared to prolonged infusion, yielding an adjusted regression coefficient of 0.013 mg/dL per gram [95% CI 0.004 to 0.022], p=0.007.

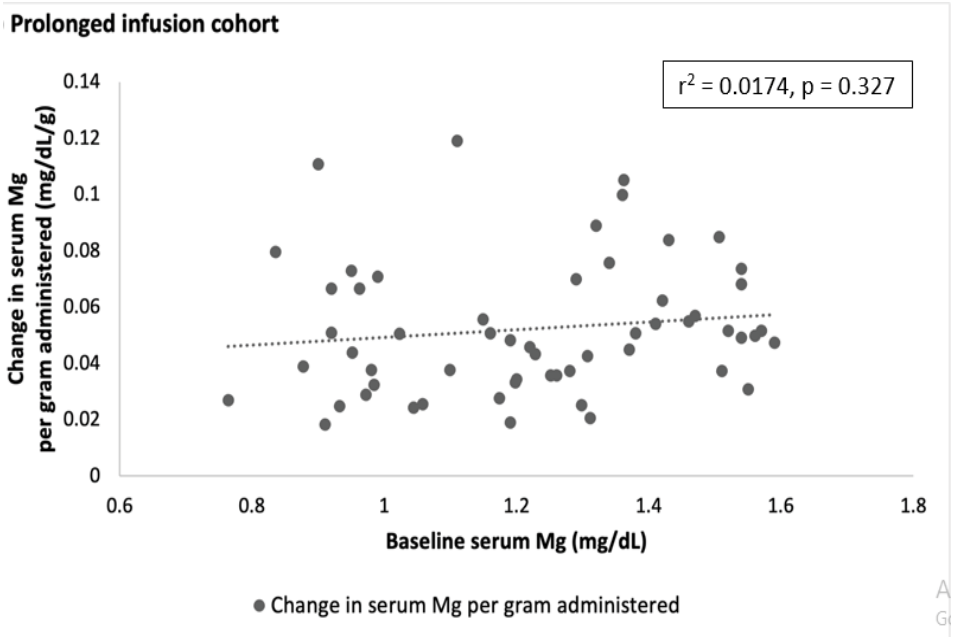
Secondary outcomes

The proportion of patients reaching target serum magnesium levels following treatment completion did not differ significantly between the two groups. Similarly, no significant difference was observed in the rates of persistent hypomagnesemia post-treatment, and no patient in either group developed hypermagnesemia (serum magnesium >2.6 mg/dL) after therapy **(Table 2)**.

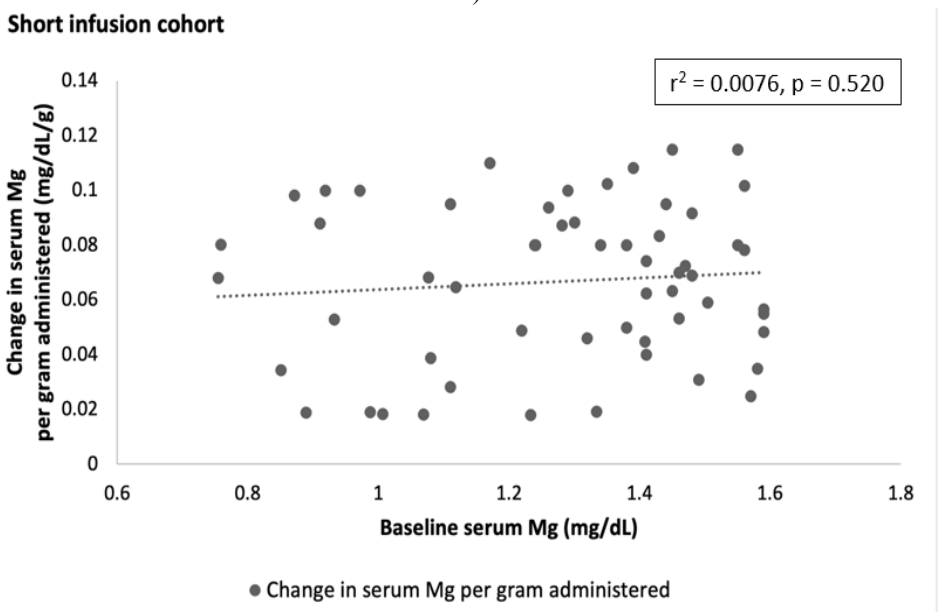
When stratified by baseline hypomagnesemia severity, the proportion of patients with mild-to-moderate hypomagnesemia who attained target levels after treatment was comparable between groups. In contrast, among those with severe hypomagnesemia, a greater proportion in the prolonged-infusion group achieved target serum magnesium levels, though this difference did not reach statistical significance **(Table 3)**.

Correlation analyses were performed to assess the relationships between the magnitude of serum magnesium change and both baseline serum magnesium concentration and estimated glomerular filtration rate (eGFR). Across the entire study population, the change in serum magnesium showed a weak positive trend with baseline levels,

but this was not statistically significant (r^2=0.0185, p=0.148). No significant association was observed within either treatment group individually **(Figure 2)**. The change in serum magnesium demonstrated a significant negative correlation with eGFR in the overall cohort (r^2=0.07, p=0.004), with similar negative trends noted in each group separately **(Figure 3)**.

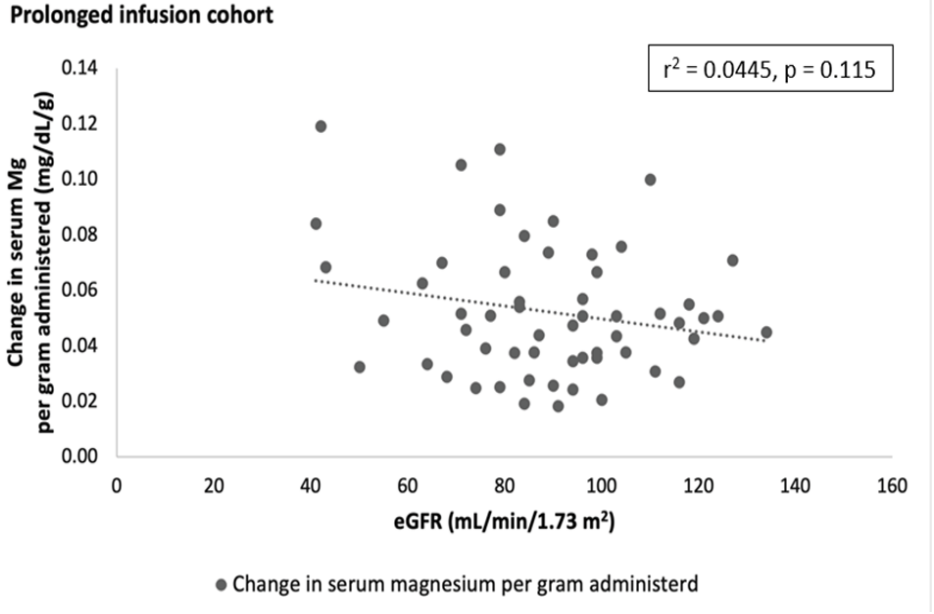


a)

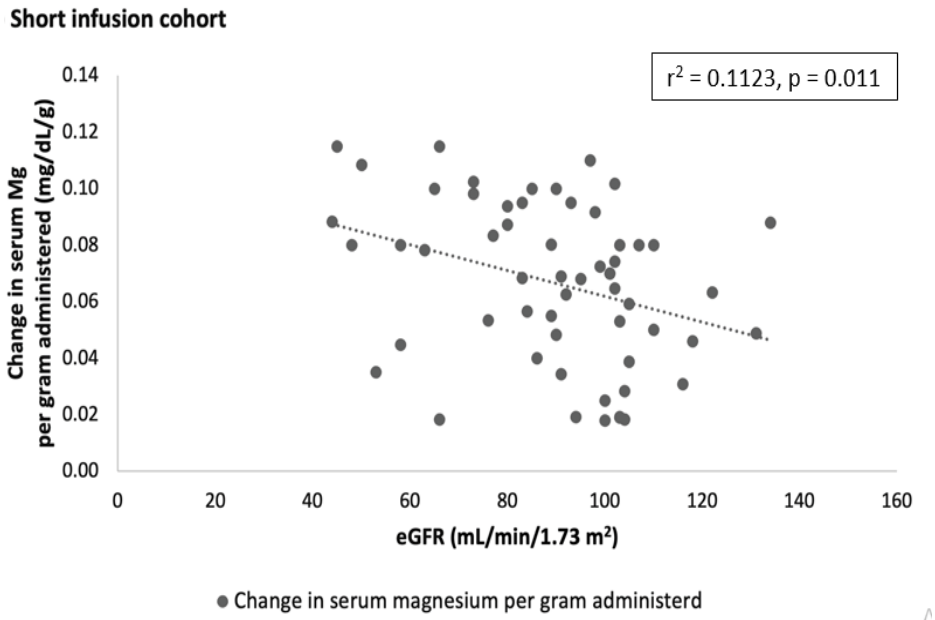


b)

Figure 2. Variation in serum magnesium levels per gram of magnesium administered in relation to the initial serum magnesium. The dashed line indicates the linear trend showing the correlation between the change in serum magnesium per gram and the baseline serum magnesium.



a)



b)

Figure 3. Variation in serum magnesium per gram administered based on eGFR. The dashed line illustrates the linear trend correlating the change in serum magnesium per gram with eGFR.

In participants who had normal baseline serum potassium, a short IV magnesium infusion resulted in a significantly larger increase in serum magnesium per gram compared to a prolonged infusion (0.07 mg/dL/g [95% CI 0.06–0.08] vs. 0.05 mg/dL/g [95% CI 0.04–0.06], $p < 0.001$). In contrast, among participants with hypokalemia, the increase in serum magnesium did not differ between the short and prolonged infusion groups **(Figure 4)**. Additionally, there was no relationship between the change in serum magnesium after treatment and baseline hypokalemia status (data not shown).

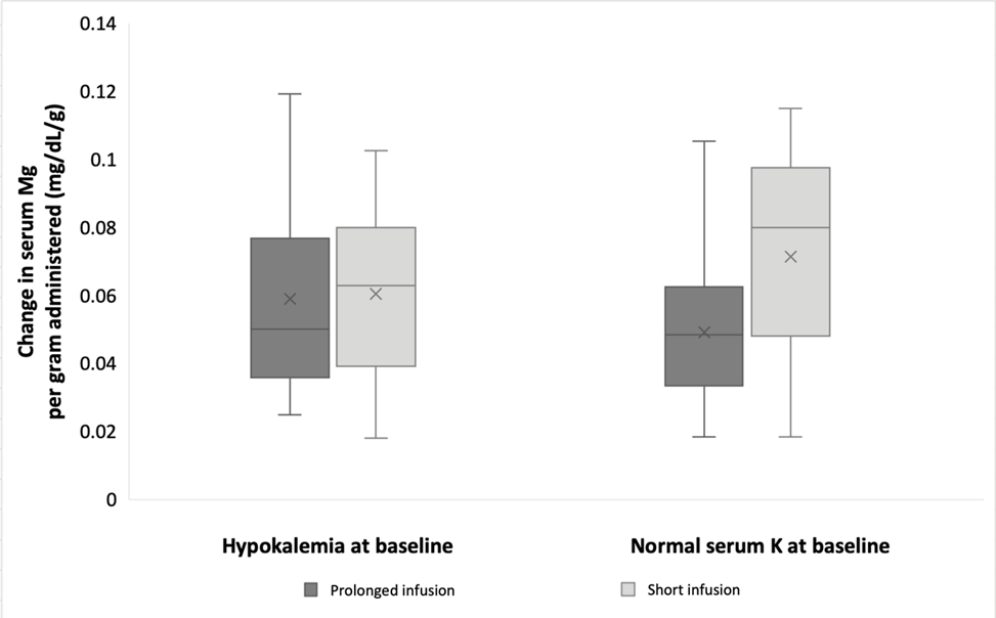


Figure 4. Variation in serum magnesium per gram administered among participants with baseline hypokalemia compared to those with normal serum potassium. In the boxplot, the mean is denoted by an X, the median by the horizontal line inside the box, the upper and lower edges of the box correspond to the 75th and 25th percentiles, and the whiskers show the minimum and maximum values

For the safety evaluation of symptoms associated with hypo- and hypermagnesemia, no occurrences of hypotension, flushing, abnormal neuromuscular signs, nausea, or vomiting were observed during intravenous magnesium replacement therapy.

The kidneys play a critical role in maintaining magnesium homeostasis by regulating serum magnesium levels primarily through urinary excretion. During magnesium deficiency, the kidneys conserve magnesium by decreasing its excretion, whereas they rapidly eliminate excess magnesium when intake is high or serum levels exceed the renal threshold. Moreover, due to the slow distribution of magnesium into other tissue compartments, extending the duration of magnesium infusions may enhance retention by allowing greater cellular uptake and reducing urinary loss [2, 6, 17].

Despite these theoretical benefits, the present study found no clinical advantage to prolonging magnesium infusions in hospitalized surgical patients. After adjusting for the timing of post-treatment serum magnesium measurement and renal function, shorter IV magnesium infusions resulted in a significantly greater rise in serum magnesium compared to prolonged infusions, with a difference of 0.013 mg/dL per gram administered. Furthermore, the proportion of participants achieving optimal serum magnesium levels after treatment completion was similar between the short and prolonged infusion groups. However, among those with severe hypomagnesemia, patients receiving prolonged infusions showed a trend toward normalizing magnesium levels more often than those receiving short infusions. This may reflect relatively depleted body magnesium stores in severe cases. In addition, the prolonged infusion group received higher total doses of magnesium replacement than the short infusion group, which likely contributed to the observed trend toward better normalization in severe hypomagnesemia.

These findings align with prior research. Snyder *et al*. observed no difference in the number of days requiring magnesium supplementation or in the duration of normal magnesium levels between prolonged (<0.5 g/h) and short (≥0.5 g/h) IV infusions in general medicine inpatients [13]. Similarly, Doshi *et al*. compared prolonged (<0.5 g/h) and short (1–2 g/h) infusion rates in hospitalized hematopoietic cell transplant patients and reported no differences in the duration of normal magnesium levels, days requiring IV magnesium, or total magnesium administered during hospitalization [14].

Magnesium homeostasis is mainly governed by renal threshold mechanisms, with a threshold of approximately 1.5–2.0 mg/dL [18]. Below this threshold, the kidneys reabsorb most filtered magnesium, while excretion rises sharply above it to preserve balance [1, 6]. Earlier studies have shown that urinary magnesium excretion increases rapidly and linearly once serum levels exceed 1.5–2.0 mg/dL in hypomagnesemic patients [17-19]. This likely accounts for the inverse relationship observed here between infusion duration and magnesium retention. Given

that post-treatment serum levels suggest concentrations during infusion exceeded the renal threshold, urinary excretion probably did not differ substantially between groups, and prolonging the infusion failed to improve retention through reduced loss. Although the prolonged infusion cohort had a higher median total magnesium dose than the short infusion cohort, the interquartile ranges overlapped considerably. Mean total doses were comparable between prolonged (10.7 ± 1.8 g) and short (8.7 ± 4.2 g) infusion groups.

Beyond the absence of benefit from prolonged infusions, shorter infusions produced a significantly larger increase in serum magnesium from baseline. This may stem from the pharmacokinetics of IV magnesium sulfate, yielding a higher peak concentration (Cmax) with rapid administration compared to slower delivery [20]. Consequently, post-infusion serum levels were lower in the prolonged group. Extended infusion times also permit greater distribution into tissues over a longer period, leaving less magnesium in the serum compartment.

In the linear regression model, both the timing of serum magnesium measurement and renal function were linked to the change in serum magnesium per gram administered. Later measurement timing was negatively associated with this change, likely due to ongoing distribution of parenterally administered magnesium into extracellular and intracellular compartments, coupled with renal elimination of excess [6, 21]. Thus, serum levels naturally decline over time following infusion.

Our linear regression analysis revealed that the change in serum magnesium per gram administered was influenced by renal function and the timing of post-treatment serum magnesium measurement. As anticipated, this change was negatively associated with renal function, since magnesium homeostasis relies on the kidneys' ability to adjust filtration and reabsorption. This adaptive capacity diminishes with declining renal function, leading to reduced urinary magnesium excretion in patients with impaired kidneys [6, 21]. Cunningham *et al*. observed a significant inverse relationship between serum magnesium levels and renal function in individuals with eGFR 30–115 mL/min/1.73 m². In stage III chronic kidney disease, magnesium excretion rises to offset reduced glomerular filtration rate, helping preserve normal serum levels, whereas excretion tends to fall in advanced stages (IV–V) [22]. These results highlight the need for lower magnesium replacement doses and frequent serum monitoring in patients with renal impairment to minimize hypermagnesemia risk [2, 11, 23].

The change in serum magnesium was also negatively associated with the timing of measurement, attributable to magnesium pharmacokinetics. Parenteral magnesium primarily distributes into intracellular compartments, with excess serum magnesium eliminated renally [6, 21]. Consequently, serum levels decline over time due to ongoing distribution and excretion.

Loop diuretics promote urinary magnesium loss and hypomagnesemia by indirectly impairing renal magnesium reabsorption [24-26]. Sheehan *et al*. noted hypomagnesemia in 19 of 40 congestive heart failure patients treated with furosemide for 12 months [27]. Sotorník *et al*. demonstrated increased urinary magnesium excretion in healthy volunteers after a single furosemide dose [28]. However, Leary *et al*. found that while loop diuretics markedly elevated urinary magnesium excretion in the first three hours post-dose, subsequent 24-hour collections revealed compensatory reduction [29]. Moreover, a large prospective cohort study of 9280 participants showed no elevated hypomagnesemia risk with loop diuretic use [30]. In our study, concomitant loop diuretic use was not associated with the change in serum magnesium. This may reflect renal adaptive mechanisms in filtration and reabsorption. Additionally, few participants received loop diuretics, and most had stage 1 or 2 chronic kidney disease, potentially explaining the absence of association.

Potassium, like magnesium, is predominantly intracellular. Potassium depletion can enhance renal magnesium excretion by inhibiting reabsorption in the thick ascending limb of the loop of Henle, while magnesium depletion can similarly provoke renal potassium loss and hypokalemia [1, 6]. Clinical studies indicate concurrent hypomagnesemia in 38–60% of hospitalized hypokalemic patients [31-33]. Conversely, some reports, including those by Deheinzelin *et al*. and Chernow *et al*. identified no link between serum magnesium and potassium in postoperative or critically ill patients [5, 34]. Consistent with this, our analysis showed no association between baseline hypokalemia and change in serum magnesium. Confounding factors—such as loop diuretic use, renal function, or conditions causing urinary potassium loss or intracellular shifts—may account for this [1]. Although hypokalemia can exacerbate renal magnesium wasting, the two often coexist. Thus, when treating hypomagnesemia, serum potassium should be assessed and corrected if low [2].

No participants exhibited clinical symptoms of hypo- or hypermagnesemia during or after IV magnesium replacement. However, such symptoms may be underreported due to their nonspecific nature, potentially leading to underestimation of adverse events in our study.

Although short infusions produced a greater increase in serum magnesium from baseline compared to prolonged infusions, the proportion achieving optimal post-treatment levels was similar between groups. Thus, the difference in magnesium rise may lack clinical significance. Nevertheless, shorter infusions could offer practical advantages, including lower risks of drug incompatibility, infusion interruptions, or delays in administering other incompatible IV medications.

This study was adequately powered to evaluate IV magnesium infusion rates in hospitalized surgical patients, with reliable data extracted from electronic medical records. Limitations include its retrospective design, which introduces potential residual confounding [35]. A key drawback is that serum magnesium poorly reflects total body stores, though it remains the standard clinical metric for assessing status and guiding therapy; we thus used it as the primary outcome. Infusion rates, particularly in the prolonged group, showed limited variability, which may restrict generalizability. Most participants had stage I or II chronic kidney disease, warranting caution in extrapolating to stage III or worse. Additionally, the cohort predominantly featured mild-to-moderate hypomagnesemia (mean baseline 1.25 mg/dL); further research is needed in severe cases, where depleted stores might necessitate prolonged replacement.

Conclusion

In hospitalized surgical patients, prolonging IV magnesium infusion to rates below 0.5 g/h offered no added benefit over shorter infusions in raising serum magnesium or attaining optimal levels. Absent clear advantages, prolonged infusions may still be appropriate for patients at risk of hypermagnesemia, such as those with renal impairment. However, shorter infusion protocols should be prioritized when aiming to reduce risks of drug incompatibility, interruptions, or delays with other IV medications.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Catharine RA, Benjamin C, Robert CJ, et al. Modern Nutrition in Health and Disease. 11th ed. Lippincott Williams & Wilkins; 2014.
2. Kraft MD, Btaiche IF, Sacks GS, et al. Treatment of electrolyte disorders in adult patients in the intensive care unit. Am J Health- Syst Pharm. 2005;62(16):1663-1682. https://doi.org/10.2146/ajhp040300
3. Aglio LS, Stanford GG, Maddi R, et al. Hypomagnesemia is common following cardiac surgery. J Cardiothorac Vasc Anesth. 1991;5:201-208. https://doi.org/10.1016/1053-0770(91)90274-w
4. Carrio ML, Lopez-Delgado JC, Javierre C, et al. Magnesium and Cardiac Surgery in the Critical Care Setting. Diet and Nutrition in Critical Care. 2016;459-472.
5. Chernow B, Bamberger S, Stoiko M, et al. Hypomagnesemia in Patients in Postoperative Intensive Care. Chest. 1989;95:391-397. https://doi.org/10.1378/chest.95.2.391
6. Dechent WJ, Ketteler M. Magnesium basics. Clin Kidney J. 2012;5:i3-i4. https://doi.org/10.31399/asm.tb.lmub.t53550141
7. Parotto M, Djaian G. Perioperative Hypomagnesemia and Increased Postoperative Morbidity and Mortality: Myth or Reality? J Cardiothorac Vasc Anesth. 2019;33:480-481. https://doi.org/10.1053/j.jvca.2018.07.026
8. Parra L, Fita G, Gomar C, et al. Plasma magnesium in patients submitted to cardiac surgery and its influence on perioperative morbidity. J Cardiovasc Surg (Torino). 2001;42:37-42.
9. Booth J v, Bute BP, McCants CB, et al. Low serum magnesium level predicts major adverse cardiac events after coronary artery bypass graft surgery. Am Heart J. 2003;145:1108-1113. https://doi.org/10.1016/s0002-8703(03)00077-2

10. Whittaker JD, Downes F, Becker H, et al. Influence of Perioperative Serum Magnesium for Cardiac and Noncardiac Morbidity and Mortality Following Emergency Peripheral Vascular Surgery. J Cardiothorac Vasc Anesth. 2019;33:474-479. https://doi. org/10.1053/j.jvca.2018.05.042
11. Kastrup EK. Drug facts and comparisons 2016. Facts & Comparisons; 2016.
12. Information TAHFSD. Handbook on injectable drugs. 19th Edition. American society of Health-System Pharmacist; 2017.
13. Snyder M, Shillingburg A, Newton M, et al. Impact of intravenous magnesium infusion rate during ambulatory replacements on serum magnesium concentrations after allogeneic stem cell transplant. Support Care Cancer. 2016;24(10):4237-4240. https://doi.org/10.1007/s00520-016-3252-9
14. Doshi S, Waller J, Clemmons A. Prolonged Versus Short Infusion Rates of IV Magnesium in Hospitalized General Medicine Patients with Hypomagnesemia. Hosp Pharm. 2020;55(1):64-68. https://doi.org/10.1177/0018578718817941
15. Barnes BA. Magnesium conservation: a study of surgical patients. Ann N Y Acad Sci. 1969 Aug 15;162(2):786-801. https://doi. org/10.1111/j.1749-6632.1969.tb13010.x
16. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, N.J: L. Erlbaum Associates; 1988.
17. Chesley LC, Tepper I. Some effects of magnesium loading upon renal excretion of magnesium and certain other electrolytes. J Clin Invest. 1958;37(10):1362-1372. https://doi.org/10.1172/jci103726
18. Heaton FW. The kidney and magnesium homeostasis. Ann N Y Acad Sci. 1969;162(2):775-85.
19. Heller BI, Hammarsten JF, Stutzman FL. Concerning the effects of magnesium sulfate on renal function, electrolyte excretion, and clearance of magnesium. J Clin Invest. 1953;32(9):858-61. https://doi.org/10.1172/jci102803
20. Shargel L, Yu ABC, editors. Applied biopharmaceutics & pharmacokinetics. Seventh edition. New York: McGraw-Hill Education; 2016.
21. Lu JF, Nightingale CH. Magnesium Sulfate in Eclampsia and Pre-Eclampsia, Pharmacokinetic Principles. Clin Pharmacokinet. 2000;38(4):305-314. https://doi.org/10.2165/00003088-200038040-00002
22. Cunningham J, Rodríguez M, Messa P. Magnesium in chronic kidney disease Stages 3 and 4 and in dialysis patients. Clin Kidney J. 2012;5:i39-i51. https://doi.org/10.1093/ndtplus/sfr166
23. McEvoy GK, Snow EK. AHFS Drug Information 2019. American Society of Health-System Pharmacists; 2019.
24. deBaaij JH, Hoenderop JG, Bindels RJ. Regulation of magnesium balance: lessons learned from human genetic disease. Clin Kidney J. 2012;5:i5-i24. https://doi.org/10.1093/ndtplus/sfr164
25. Glaudemans B, NVAM K, Hoenderop JG, et al. New molecular players facilitating Mg(2+) reabsorption in the distal convoluted tubule. Kidney Int. 2010;77(1):17-22. https://doi.org/10.1038/ki.2009.358
26. Atsmon J, Dolev E. Drug-Induced Hypomagnesaemia Scope and Management. Drug Saf. 2005;28(9):763-788. https://doi. org/10.2165/00002018-200528090-00003
27. Sheehan J, White A. Diuretic-associated hypomagnesaemia. Br Med J (Clin Res Ed). 1982;285(6349):1157-1159. https://doi. org/10.1136/bmj.285.6349.1157
28. Sotorník I, Schück O. Effect of single dose of diuretics on renal magnesium excretion in man, with special reference to their site of action. Physiol Bohemoslov. 1976;25(3):207-12.
29. Leary WP, Reyes AJ, Wynne RD, et al. Renal Excretory Actions of Furosemide, of Hydrochlorothiazide and of the Vasodilator Flosequinan in Healthy Subjects. J Int Med Res. 1990;18(2):120-141. https://doi.org/10.1177/030006059001800207
30. Kieboom BCT, Zietse R, Ikram MA, et al. Thiazide but not loop diuretics is associated with hypomagnesaemia in the general population. Pharmacoepidemiol Drug Saf. 2018;27(11):1166-1173. https://doi.org/10.1002/pds.4636
31. Whang R, Whang DD, Ryan MP. Refractory potassium repletion. A consequence of magnesium deficiency. Arch Intern Med. 1992;152(1):40-5. https://doi.org/10.1001/archinte.1992.00400130066006
32. Whang R, Oei TO, Aikawa JK, et al. Predictors of clinical hypomagnesemia. Hypokalemia, hypophosphatemia, hyponatremia, and hypocalcemia. Arch Intern Med. 1984;144(9):1794-6. https://doi.org/10.1001/archinte.144.9.1794
33. Boyd JC, Bruns DE, Wills MR. Frequency of hypomagnesemia in hypokalemic states. Clin Chem. 1983;29(1):178-9. https://doi. org/10.1093/clinchem/29.1.178

34. Deheinzelin D, Negri EM, Tucci MR, et al. Hypomagnesemia in critically ill cancer patients: a prospective study of predictive factors. Braz J Med Biol Res. 2000;33(12):1443-8. https://doi.org/10.1590/s0100-879x2000001200007
35. Boyko EJ. Observational research-opportunities and limitations. J Diabetes Complications. 27(6):642-8. https://doi. org/10.1016/j.jdiacomp.2013.07.007