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Original Research

Impact of magnesium infusion rate on serum magnesium level after magnesium replacement in hospitalized surgical patients with hypomagnesemia: A 11-year retrospective cohort study

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Abstract

Background: Hypomagnesemia is common for surgical patients and often requires intravenous (IV) magnesium replacement. Due to the renal handling mechanism of magnesium, prolonging the duration of an IV magnesium infusion has been postulated to improve magnesium retention by reducing the renal excretion of magnesium. However, the evidence supporting this hypothesis is limited. **Objective:** To determine the change in serum magnesium level after IV magnesium replacement from baseline compared between prolonged (infusion rate < 0.5 g/h) and short infusions (infusion rate < 0.5 g/h) in hospitalized surgical patients. **Methods:** Medical records of surgical patients with hypomagnesemia who received IV magnesium replacement for three consecutive days and admitted to a university hospital between 2012 and 2022 were reviewed. Patients were separated by the replacement rate into two cohorts: prolonged infusion and short infusion. The primary outcome was a change in serum magnesium per gram administered from the baseline. The secondary outcome was the percentage of patients who achieved an optimal serum magnesium level after IV magnesium replacement. **Results:** 114 participants were enrolled in the study. The short infusion cohort showed a significantly greater increase in serum magnesium change per gram administered from baseline (0.07 mg/dL/g) compared to the prolonged infusion cohort (0.05 mg/dL/g) (p = 0.04). The difference of serum magnesium level between the two cohorts was 0.013 mg/dL/g of Mg. The percentage of patients who achieved the optimal serum magnesium level after IV magnesium replacement was not different between the two cohorts (prolonged infusion 66.7% vs. short infusion 70.2%; p = 0.84). The change in serum magnesium levels was influenced by renal function and the timing of serum magnesium level measurement after IV magnesium replacement. Conclusion: In hospitalized surgical patients, prolonging the IV magnesium infusion rate to less than 0.5 g/h did not provide additional benefits to increase serum magnesium levels compared to a short infusion rate.

Keywords: magnesium; hypomagnesemia; intravenous; administration; rate

INTRODUCTION

Magnesium plays an important role in facilitating the proper functioning of numerous enzymes and biochemical reactions, as well as being involved in various physiological processes.[1,2] Hypomagnesemia (serum magnesium level < 1.6 mg/dL) is a common electrolyte imbalance observed in surgical patients, with a prevalence ranging from 12% to 71% in post-operative patients and 61% in cardiovascular thoracic patients.[3-5] There are many causes of hypomagnesemia in surgical patients, such as insufficient intake, increased renal losses, and extrarenal losses (e.g., gastric aspirate, received bowel preparation before surgery), increased extracellular magnesium shifts from plasma into cells, and concurrent used of magnesium wasting drugs.[4,6] Hypomagnesemia in post-operative patients was associated with longer mechanical ventilation support, and higher all-cause mortality rate. Especially in patients with cardiovascular thoracic surgery, hypomagnesemia is an independent risk factor for postoperative atrial fibrillation and increases atrial myocardial excitability.[3,5,7–10] For these reasons, the serum magnesium levels should be monitored, and magnesium replacement is often recommended to maintain a normal physiological level.[2]

IV magnesium replacement is often used in surgical patients, mainly as a result of preoperative and postoperative fasting and postoperative nausea and vomiting.[11] However, the serum magnesium level is primarily controlled by its excretion in urine. Thus, IV administration of magnesium may rapidly increase in serum magnesium level over the renal threshold, resulting in rapid excretion of magnesium into the urine.[6,12] Theoretically, prolonging the infusion rate of IV magnesium administration has been postulated to improve magnesium retention by reducing magnesium load delivered to the kidneys, allowing for a longer period for cellular distribution and decreasing urinary magnesium excretion.[2] In patients with asymptomatic hypomagnesemia, the recommended administration of magnesium was administered at a prolonged

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rate not exceeding 0.5 to 1 g/h.[2,11] The standard protocol at our institution was to administer magnesium intravenously at no more than 0.5 g/h.

Although the concept of prolonging IV magnesium infusion has been recommended in clinical practice, the primary concern with prolonged IV magnesium administration is the incompatibility of magnesium with other IV drugs given via Y-site connector.[12] In addition, recent studies have failed to reveal the clinical benefit of prolonging magnesium infusions in hospitalized patients.[13,14] However, they did not control the variables that may affect the serum magnesium levels, such as renal function, concomitant used of diuretics, and the timing of measurement of serum magnesium level following completion of IV magnesium replacement that limits the interpretation of the results. Thus, the aim of this study was to determine the change in serum magnesium level from baseline compared between prolonged and short infusion of IV magnesium replacement in hospitalized surgical patients.

METHODS

Study description

This was a retrospective cohort study conducted at Songklanagarind Hospital, a university hospital, Prince of Songkla University, Thailand. The study was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand (REC number 65-428-19-6).

Study population

Adults aged 18 years or more with asymptomatic hypomagnesemia (serum magnesium <1.6 mg/dL) admitted to the surgical units who received IV magnesium replacement for 3 consecutive days between December 2012 and November 2022 were included. Eligible participants were separated into two cohorts with a 1:1 ratio based on an infusion rate of IV magnesium replacement. Participants in the prolonged infusion cohort received IV magnesium replacement at an infusion rate of <0.5 g/h, while participants in the short infusion cohort received IV magnesium replacement at an infusion rate of ≥0.5 g/h. Participants in each cohort were excluded if any exclusion criteria were met: 1) received magnesium from other sources i.e., oral magnesium replacement, fluid replacement containing magnesium, parenteral nutrition, or drugs containing magnesium (i.e., antacids and osmotic laxatives), 2) received magnesium wasting drugs except loop and thiazide diuretics i.e., aminoglycosides, amphotericin B, cisplatin, cyclosporin, foscarnet, tacrolimus, 3) known medical conditions with abnormal magnesium handling i.e., acute kidney injury, end stage renal disease (eGFR <15 mL/min/1.73 m^2), renal transplant, polyuria, hyperthyroidism, hyperaldosteronism, and Bartter and Gitelman's syndromes and 4) participants who presented to the hospital with medical conditions with extracellular magnesium shifts i.e. hungry bone syndrome, diabetic ketoacidosis, and acute pancreatitis.

Magnesium is distributed in the extracellular and intracellular compartments, and excess magnesium given parenterally is eliminated by the kidneys. The serum magnesium levels obtained between 6 and 24 hours after the final dose were analyzed because we expected these values to reflect the magnesium equilibrium distribution.[2,15] Participants who had serum magnesium levels were obtained within 6 hours or more than 24 hours after the final dose of magnesium were excluded.

Sample size

The sample size was estimated from the pilot study. The difference in the change in serum magnesium per gram administered from baseline between the two cohorts was 0.012 mg/dL/g of total IV magnesium replacement. Calculated from Cohen's formula for multiple linear regression analysis, the study required at least 57 participants in each cohort to provide 80% power of analysis.[16]

Data collection

The following demographic data were gathered from electronic medical records: sex, age, body weight, body mass index (BMI), renal function, primary diagnosis, types of surgery, amount of IV fluids during magnesium IV replacement therapy, and concomitant use of diuretics. The total amount of magnesium replacement and the rate of infusion were collected. In addition, baseline serum magnesium levels (obtained within 24 hours prior to magnesium IV replacement) and serum magnesium levels obtained within 6 to 24 hours after the completion of magnesium IV replacement were collected.

Documented adverse events during IV magnesium replacement, including symptoms related to hypo- and hypermagnesemia such as hypotension, flushing, abnormal neuromuscular function (e.g., muscle weakness, loss of deep tendon reflex, dyspnea, Chvostek's and Trousseau's signs), nausea, and vomiting, were also collected from electronic medical records for safety analysis.

Outcomes

The primary outcome of the study was the change in serum magnesium after the replacement between the two cohorts. As participants may receive varying doses of magnesium replacement over three consecutive days, we therefore evaluated the change in serum magnesium per a total amount of magnesium administered during the treatment period. Adjustments were made to control for confounding variables that may influence the change in serum magnesium, including the severity of hypomagnesemia, renal function, concomitant use of diuretics, and timing of serum magnesium level measurement after completing therapy. The secondary outcome was the percentage of participants with normal serum magnesium levels (serum magnesium level of 1.6-2.6 mg/dL) after completion of therapy. The incidence of adverse events, including symptoms related to hypo- and hypermagnesemia symptoms during IV magnesium replacement, was assessed for safety analysis

Data analysis

Statistical analysis was performed using the R program version 2022.12. Continuous data were presented as mean (standard

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deviation; SD) or as median (interquartile range; IQR), depending on data distribution, and were analyzed using an independent t-test or Mann-Whitney U test. Categorical variables were presented as numbers (%) and were compared using the Chi-square test or Fisher's exact test. Simple linear regression analysis was used to identify potential confounding variables that may affect the change in serum magnesium per gram administered. Variables with p values ≤ 0.2 were considered as potential confounders and were further examined in a multiple linear regression analysis to estimate the association between IV magnesium replacement infusion rate and the change in serum magnesium per gram administered, while adjusting for these potential confounding variables. A p-value of less than 0.05 was regarded as being statistically significant.

RESULTS

Patient characteristics

A total of 1319 participants met the inclusion criteria during the study period. However, 1205 participants were excluded. Hence, 114 participants were enrolled in the study. Each cohort consisted of 57 participants. The study enrollment is shown in Figure 1.

Baseline characteristics data were similar between the two cohorts (Table 1). The mean age of the participants was 62.6 (SD=13.1) years, and 59.6% of them were > 60 years. The mean eGFR was 89.1 (SD=21) mL/min/1.73 m^2. The mean baseline serum magnesium level of all participants was 1.25 (SD=0.23) mg/dL, and most participants had mild-moderate hypomagnesemia (serum magnesium level ≥1.0 and <1.6 mg/dL). The mean baseline potassium level of all participants was 3.6 (SD=0.57) mEq/L, and there was no significant difference in the mean baseline potassium level and the percentage of participants with hypokalemia between the two cohorts. All participants with hypokalemia received potassium replacement, and the total amount of potassium replacement was not significantly different between the prolonged and short infusion cohorts (170 mEq (IQR 145,215) vs 120 mEq (IQR 80,217.5), p = 0.07). The mean serum potassium level after completing magnesium replacement was not different, prolonged 3.7 mEq/L [95%CI 3.59:3.81] vs short 3.7 mEq/L [95%CI 3.62:3.78] (p= 0.629).

Primary outcome

The median infusion rate of IV magnesium was 0.3 g/h (range 0.17-0.33 g/h) in the prolonged infusion cohort and 0.5 g/h (range 0.5-1 g/h) in the short infusion cohort. Baseline serum magnesium level and the timing of serum magnesium level measurement after completing therapy was not different between the two cohorts. However, participants in the prolonged infusion cohort received more total amount of IV magnesium than the short infusion cohort (Table 2).

Compared with the prolonged infusion cohort, the short infusion cohort had a significantly greater mean change in serum magnesium per gram administered. However, serum magnesium level after completing therapy was not significantly

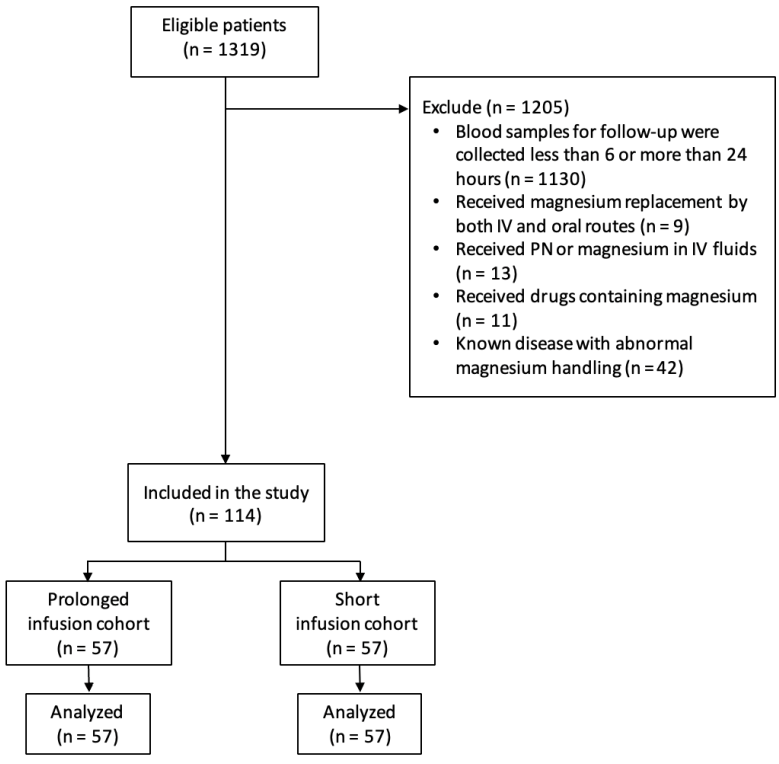

Figure 1. Study enrolment flow chart. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

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Table 1. Characteristics of the study population

Characteristics	Prolonged infusion (n = 57)	Short infusion (n = 57)	p-value
Male Sex, n (%)	28 (49.1)	37 (64.9)	0.130[a]
Age, years, mean (SD)	62.5 (SD=12.8)	62.7 (SD=13.6)	0.964[b]
Body weight, kg, mean (SD)	53.9 (SD=12.1)	56.6 (SD=13.7)	0.277[b]
BMI, kg/m^2, mean (SD)	21.5 (SD=4.5)	21.6 (SD=5)	0.919[b]
eGFR, mL/min/1.73 m^2, mean (SD)	89 (SD=21.4)	89.3 (SD=20.9)	0.944[b]
Stage of chronic kidney disease, n (%)			0.760[a]
Stage I or II	52 (91.2)	50 (87.7)	
Stage III	5 (8.8)	7 (12.3)	
Primary diagnosis, n (%)			0.003[a]
Gastrointestinal cancer	25 (43.9)	13 (22.8)	
Others cancer	8 (14)	19 (33.3)	
Intestinal problem	13 (22.8)	5 (8.8)	
Infection	7 (12.3)	8 (14)	
Others	4 (7)	12 (21.1)	
Undergoing surgery, n (%)	46 (80.7)	35 (61.4)	0.039[a]
Type of surgical procedure, n (%)			0.072[a]
Gastrointestinal surgery	35 (76.1)	18 (51.4)	
Urology surgery	5 (10.9)	8 (22.9)	
Cardiothoracic surgery	2 (4.3)	4 (11.4)	
Plastic surgery	1 (2.2)	4 (11.4)	
Others surgery	3 (6.5)	1 (2.9)	
Amount of IV fluid (mL) received in 3-days of IV magnesium replacement, median (IQR)	4930 (3910,6115)	5010 (3410,5930)	0.467[c]
Amount of magnesium in diet (mg) in 3-days of IV magnesium replacement, median (IQR)	150 (0,450)	150 (0,533.3)	0.795[c]
Received loop diuretics, n (%)	15 (26.3)	13 (22.8)	0.828[a]
Hypokalemia, n (%)	18 (31.6)	24 (42.1)	0.332[a]
Serum potassium, mEq/L, mean (SD)	3.7 (SD=0.6)	3.6 (SD=0.5)	0.595[b]
Serum calcium, mg/dL, mean (SD)	8.9 (SD=0.6)	9 (SD=0.8)	0.450[b]
Serum phosphate, mg/dL, mean (SD)	3 (SD=0.7)	3 (SD=0.9)	0.622[b]
Serum albumin, g/dL, mean (SD)	3.1 (SD=0.7)	3.2 (SD=0.7)	0.698[b]

p-value<0.05 indicates statistical significance
[a]Chi-squared test, [b]Student's t-test, [c]Mann-Whitney *U*-test
Abbreviations: BMI, body mass index; BW, body weight; eGFR, estimated glomerular filtration rate

different between the two cohorts (Table 2). In participants with mild to moderate hypomagnesemia, the short IV infusion of magnesium resulted in a significantly greater increase in the change in serum magnesium than prolonged infusion. However, the change in serum magnesium was not significantly different between the two cohorts of participants with severe hypomagnesemia (serum magnesium level < 1.0 mg/dL), as shown in (Table 3).

Data from the simple linear regression analysis showed that the infusion rate of IV magnesium was associated with the change in serum magnesium per gram administered with the regression coefficient 0.014 mg/dL/g [95%CI 0.005:0.020], p =

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Table 2. Primary and secondary outcomes

	Prolonged infusion (n = 57)	Short infusion (n = 57)	p-value
Total amount of magnesium replacement, g, median (IQR)	12 (10,12)	6 (6,12)	<0.001[a]
Serum magnesium level			
Baseline, mg/dL, median (IQR)	1.23 (0.99,1.41)	1.34 (1.11,1.46)	0.138[a]
After the completion of therapy, mg/dL, mean [95% CI]	1.78 [1.69:1.87]	1.79 [1.70:1.88]	0.829[b]
Change in serum magnesium level from baseline, mg/dL, median (IQR)	0.5 (0.38,0.67)	0.48 (0.36,0.65)	0.616[a]
Time between completing therapy and blood sampling for serum magnesium level, hour, median (IQR)	11.7 (6.4,19.2)	10.2 (6.6,14.7)	0.982[a]
Primary outcome			
Change in serum magnesium per gram administered, mg/dL/g of Mg, mean [95% CI]	0.05 [0.04:0.06]	0.07 [0.06:0.08]	0.004[b]
Secondary outcome			
Percentage of participants achieved the optimal serum magnesium target after therapy, [95% CI]	66.7 [53.7:77.5]	70.2 [57.3:80.5]	0.840[c]
Percentage of participants had hypomagnesemia after therapy, [95% CI]	33.3 [22.5:46.3]	29.8 [18.1:40.1]	0.739[c]

p-value<0.05 indicates statistical significance
[a]Mann-Whitney *U*-test, [b]Student's t-test, [c]Chi-squared test

Table 3. Primary and secondary outcomes according to severity of hypomagnesemia

	Prolonged infusion	Short infusion	p-value
Mild-moderate hypomagnesemia	n = 42	n = 47	
Baseline serum magnesium level, mg/dL, median (IQR)	1.32 (1.2,1.47)	1.41 (1.25,1.48)	0.232[a]
Change in serum magnesium per gram administered, mg/dL/g of Mg, median (IQR)	0.05 (0.04,0.06)	0.07 (0.05,0.09)	0.011[a]
Percentage of participants achieved the optimal serum magnesium target after therapy, [95% CI]	76.2 [61.5:86.5]	85.1 [72.3:92.6]	0.425[b]
Severe hypomagnesemia	n = 15	n = 10	
Baseline serum magnesium level, mg/dL, mean [95% CI]	0.92 [0.89:0.95]	0.88 [0.83:0.93]	0.178[c]
Change in serum magnesium per gram administered, mg/dL/g of Mg, mean [95% CI]	0.05 [0.03:0.07]	0.07 [0.05:0.09]	0.225[c]
Percentage of participants achieved the optimal serum magnesium target after therapy, [95% CI]	40 [19.8:64.3]	0 [0:27.8]	0.051[d]

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

0.004 for short infusion rate. The timing of serum magnesium level measurement after completing therapy and renal function were also significantly associated with the change in serum magnesium. However, the severity of hypomagnesemia and the concomitant use of loop diuretics did not show a significant association with the change in serum magnesium (Table 4).

Multiple linear regression analysis was performed by including all significant variables from the simple linear regression analysis (Table 4). Assumptions of linear regression were test and found that the regression was normality, homoscedasticity, and no multicollinearity (VIF <10). After adjusting for the timing of serum magnesium level measurement and renal function, the short infusion of IV magnesium replacement was found to have a significantly greater change in serum magnesium than the prolonged infusion of IV magnesium, with a regression coefficient of 0.013 mg/dL/g [95%CI 0.004:0.022], p = 0.007.

Secondary outcome

The percentage of participants who achieved optimal serum magnesium level after completing therapy was not different between the two cohorts. Additionally, there was no significant difference in the percentage of participants who had hypomagnesemia after completing therapy between the two cohorts and no participants in either cohort had hypermagnesemia (serum magnesium level > 2.6 mg/dL) after completing therapy. (Table 2).

When considering the severity of hypomagnesemia, the percentage of participants with mild to moderate hypomagnesemia who achieved the optimal serum magnesium level after completing therapy was not different between the two cohorts. However, in participants with severe hypomagnesemia, a higher percentage of those in the prolonged infusion cohorts achieved the optimal serum magnesium level after completing therapy, although the difference was not statistically significant (Table 3).

Association analyses were conducted to examine the relationship between the change in serum magnesium and the baseline serum magnesium level, as well as eGFR. The result showed that the change in serum magnesium tended to be positively associated with the baseline serum magnesium level in all participants, but it was not statistically significant (r^2 = 0.0185, p = 0.148). Furthermore, the change in serum

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Table 4. Linear regression analysis for the change in serum magnesium level

	Simple linear regression analysis			Multiple linear regression analysis		
Factors	**Regression Coefficient**	**95% CI**	**p-value**	**Regression Coefficient**	**95% CI**	**p-value**
Infusion rate of IV magnesium						
Prolonged infusion (< 0.5 g/h)	-	-	-	-	-	-
Short infusion (≥ 0.5 g/h)	0.014	0.005:0.024	0.004	0.013	0.004:0.022	0.007
Time between completing therapy and blood sampling for serum magnesium level [a]	-0.001	-0.002:-0.0001	0.020	-0.001	-0.002:-0.0002	0.011
eGFR						
≥ 60 mL/min/1.73 m^2	-	-	-	-	-	-
30 to < 60 mL/min/1.73 m^2	0.02	0.002:0.034	0.031	0.019	0.004:0.034	0.016
Severity of hypomagnesemia						
Mild-moderate hypomagnesemia	-	-	-			
Severe hypomagnesemia	-0.003	-0.015:0.009	0.638			
Received loop diuretics						
No	-	-	-			
Yes	-0.004	-0.016:0.007	0.476			

p-value<0.05 indicates statistical significance
[a] Per increment of 1 hour
Abbreviations: eGFR, estimated glomerular filtration rate

magnesium was not associated with the baseline serum magnesium level in both cohorts (Figure 2). The change in serum magnesium and eGFR was negatively associated in all participants (r^2 = 0.07, p = 0.004). Additionally, the change in serum magnesium and eGFR tended to be negatively associated with eGFR in both cohorts. These associations are shown in (Figure 3).

In participants with normal serum potassium at baseline, the short infusion of IV magnesium led to a significantly greater increase in serum magnesium change than the prolonged infusion (0.07 mg/dL/g [95%CI 0.06:0.08] vs 0.05 [95%CI 0.04:0.06], p <0.001). However, the change in serum magnesium was not different between the two cohorts of participants with hypokalemia (Figure 4). There was no association between serum magnesium change after therapy and the presence of hypokalemia at baseline (data not shown).

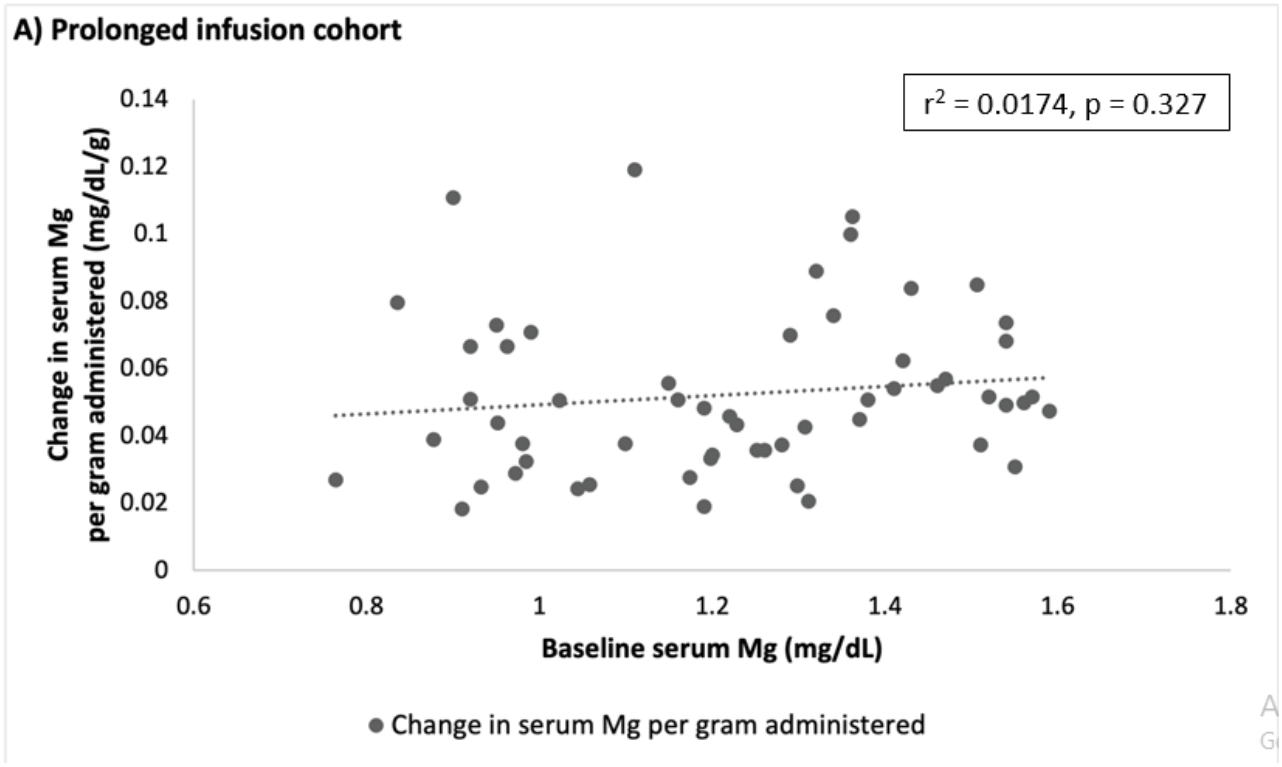
For the safety analysis assessing symptoms related to hypo- and hypermagnesemia. No hypotension, flushing, abnormal neuromuscular function, nausea, and vomiting were reported during IV magnesium replacement therapy.

DISCUSSION

The kidneys play a vital role in the magnesium balance in the body and maintain normal serum magnesium level, as serum magnesium level is primarily controlled by its excretion in urine. The kidneys can conserve magnesium during magnesium deprivation by reducing its excretion. However, magnesium can be rapidly excreted in cases of excess intake or when the serum magnesium level exceeds the renal threshold. In addition to the slow distribution of magnesium in the other tissue compartment; therefore, magnesium retention could be improved by prolonging magnesium infusions, which can extend the cellular distribution of magnesium and reduce urinary magnesium excretion.[2,6,17]

Despite the theoretical advantage, our study did not find a clinical benefit in prolonging magnesium infusions in hospitalized surgical patients. After adjustment for the timing of serum magnesium level measurement and renal function, shorter infusion of IV magnesium replacement had a significantly greater increase in the change in serum magnesium than the prolonged infusion, with the difference of change in serum magnesium 0.013 mg/dL/g. In addition, the percentage of participants who achieved optimal levels of serum magnesium after completion of treatment was no different between the short and prolonged IV infusion. However, following the completion of magnesium replacement therapy, participants with severe hypomagnesemia who received magnesium via prolonged IV infusion method tended to reach normal magnesium levels more than those who received via a short IV infusion method. This may be because participants with severe hypomagnesemia may have relatively low levels of stored magnesium in their body. Additionally, it was observed that the prolonged infusion cohort received a higher dosage of magnesium replacement compared to the short infusion cohort. As a result, participants with severe hypomagnesemia in the prolonged infusion cohort tended to reach optimal serum magnesium levels more than the short infusion cohort.

Our results were consistent with the previously published studies. Snyder et al. reported no difference in the number of days requiring magnesium replacement. In addition, the



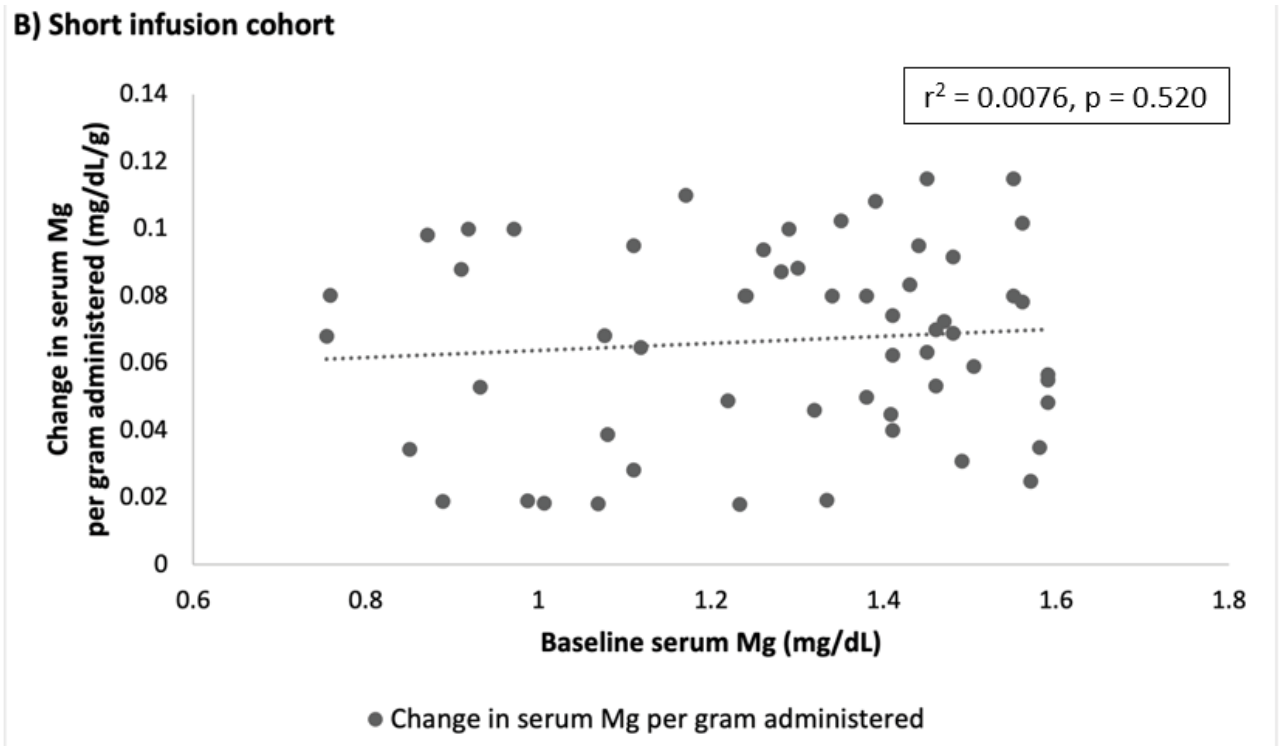


Figure 2. Change in serum magnesium per gram administered according to baseline serum magnesium. The dotted line represents the trend in a linear correlation between change in serum magnesium per gram administered and baseline serum magnesium

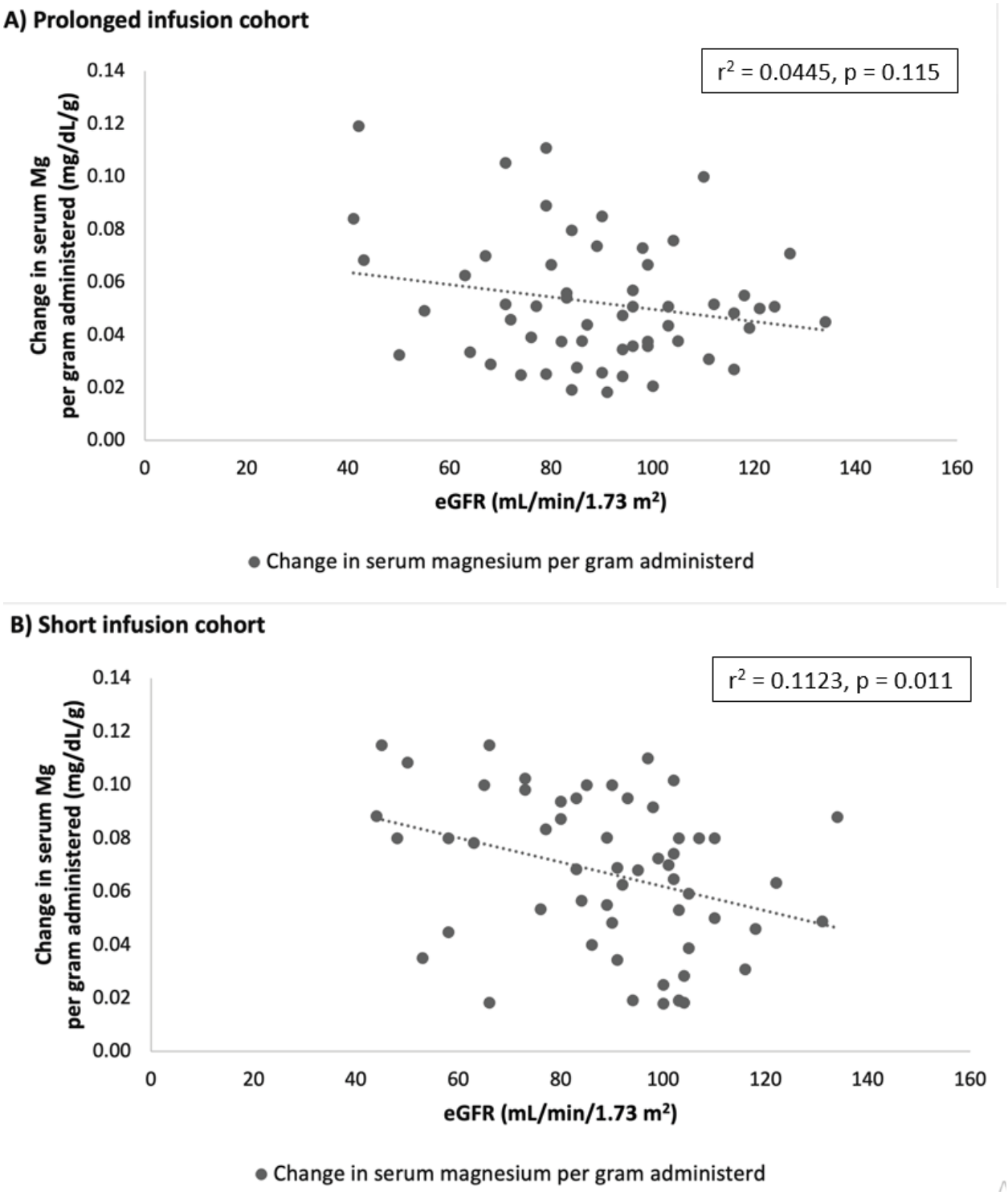


Figure 3. Change in serum magnesium per gram administered according to eGFR. The dotted line represents the trend in a linear correlation between change in serum magnesium per gram administered and Egfr

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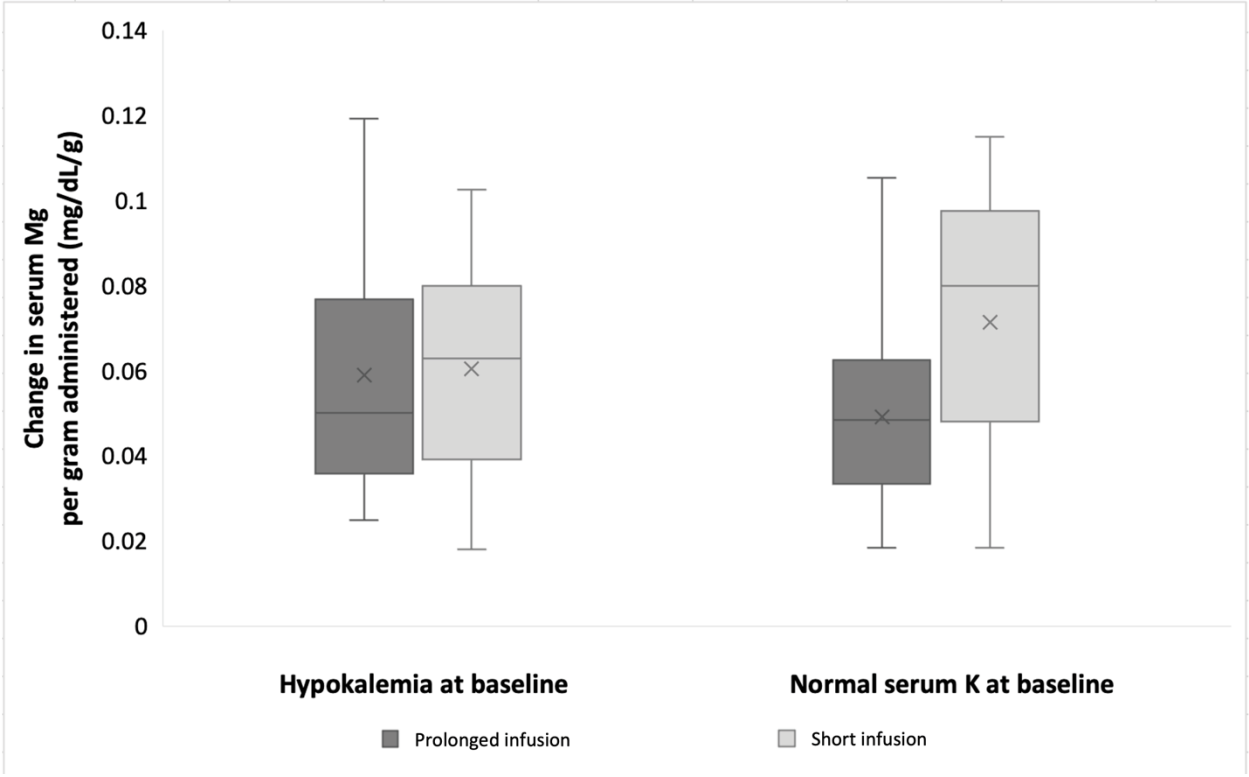

Figure 4. Change in serum magnesium per gram administered in participants with hypokalemia and normal serum potassium at baseline. Within the boxplot, the mean value is represented by the X, the median by the horizontal dividing line, and the top and bottom of the box represent the 75th and 25th percentile, with the whiskers indicating the maximum and minimum points

duration of magnesium levels in normal ranges was similar between prolonged (< 0.5 g/h) and short infusion (≥0.5 g/h) IV magnesium infusion in patients admitted to general medicine.[13] Doshi et al. compared the two IV infusion rates of magnesium replacement, prolonged (< 0.5 g/h) and short (1-2 g/h), in hospitalized hematopoietic cell transplant patients.[14] They found no difference in the duration of magnesium levels in the normal ranges, the number of days requiring IV magnesium therapy, and the total amount of IV magnesium replaced during hospitalization between the two groups.

Magnesium homeostasis is primarily regulated by the kidneys through the renal threshold mechanisms. The renal threshold of magnesium is 1.5-2.0 mg/dL.[18] Below the renal threshold, magnesium is mostly reabsorbed by the kidneys, while above this threshold, magnesium excretion increases to maintain optimum magnesium levels.[1,6] Previously published studies have demonstrated the effect of magnesium infusion on urinary magnesium excretion in hypomagnesemia patients. Urine excretion of magnesium was reported to increase rapidly and linearly when serum magnesium exceeded 1.5-2.0 mg/dL.[17–19] This may explain the negative association observed in our study between prolonging the infusion rate and enhanced magnesium retention. Based on serum magnesium levels obtained after completion of treatment, it can be presumed that the serum magnesium level during IV magnesium administration was above the renal magnesium threshold. Therefore, urinary magnesium excretion may not differ between the prolonged and short infusion cohorts, and prolongation of infusion may not improve serum magnesium levels by reducing urinary magnesium excretion. Moreover, in consideration of the total amount of magnesium replacement, we found that the prolonged infusion cohort received a higher median amount of magnesium replacement compared to the short infusion cohort. However, the quartile range of the total amount of magnesium replacement was similar between the two cohorts. Thus, the mean total magnesium replacement was analyzed and found to be similar in both the prolonged and short infusion cohorts, at 10.7 (SD=1.8) and 8.7 (SD=4.2) grams, respectively.

In addition to the finding of no apparent benefit of prolonging magnesium infusions, we also found that the prolonged infusion had a significantly smaller increase in the serum magnesium from baseline than the short infusion. The probable reason for the lower magnesium levels in the prolonged infusion cohort may be due to the pharmacokinetics of IV magnesium sulfate, which led to a lower maximum level of magnesium (C_{max}) compared to the short infusion cohort. Consequently, serum magnesium level after the end of infusion was also lower in the prolonged infusion cohort.[20] Additionally, prolonging the infusion time allows distribution of magnesium to other tissues for a longer period, resulting in less magnesium remaining in the serum.

In our linear regression analysis, the timing of serum magnesium level measurement and renal function were associated with the change in serum magnesium per gram administered. The change in serum magnesium per gram administered was negatively associated with the timing of serum magnesium level measurement. This relationship may be explained by the pharmacokinetics of magnesium. When administered parenterally, it is distributed in the extracellular and intracellular compartments, and excess magnesium is eliminated by the kidneys.[6,21] As a result, the serum magnesium level may decline over time according to the distribution and elimination of magnesium.

Our linear regression analysis showed that the change in serum magnesium was associated with the renal function and the timing of serum magnesium level measurement. As expected, the change in serum magnesium was negatively associated with renal function. Because the magnesium balance depends on the adaptability of the filtration and reabsorption of magnesium in the kidneys. However, this capacity deteriorates as renal function declines, resulting in decreased urinary magnesium excretion in patients with renal impairment.[6,21] Cunningham et al. reported a significant inverse association between serum magnesium level and renal function in participants with eGFR 30-115 mL/min/1.73 m^2. In stage III chronic kidney disease, magnesium excretion increases to compensate for the reduction in glomerular filtration rate, which helps maintain normal serum magnesium levels. However, magnesium excretion tends to decrease in patients with advanced chronic kidney disease (stage IV-V chronic kidney disease).[22] Our findings emphasize the importance of lower doses of magnesium replacement and monitoring serum magnesium levels frequently in patients with renal impairment to reduce the risk of hypermagnesemia.[2,11,23] The change in serum magnesium was a negatively associated with the timing of serum magnesium level measurement, which can be explained by the pharmacokinetics of magnesium. When magnesium is administered parenterally, it is mainly distributed in the intracellular compartments, and excess magnesium present in the serum is eliminated by the kidneys.[6,21] As a result, the serum magnesium level may decline over time depending on the distribution and elimination of magnesium.

Loop diuretics can increase urinary magnesium excretion and cause a decrease in serum magnesium levels by indirectly inhibiting magnesium reabsorption by the kidneys.[24–26] Sheehan et al. reported that 19 out of 40 congestive heart failure patients who received furosemide for 12 months developed hypomagnesemia.[27] Sotorník et al. found that urinary magnesium excretion increased in healthy volunteers who received a single dose of furosemide.[28] However, Leary et al. reported that loop diuretics significantly increased urinary magnesium excretion three hours after a single dose of furosemide in healthy volunteers. But subsequent collections for the remaining 24 hours showed an overall compensatory response, with a decrease in urinary magnesium excretion.[29] In addition, a prospective population-based cohort study involving 9280 subjects found that the use of loop diuretics did not increase the risk of hypomagnesemia.[30] Our study did not find an association between the concomitant use of loop diuretics and the change in serum magnesium. The possible explanations may be related to the adaptability of the filtration and reabsorption of magnesium in the kidneys. In addition, our study had a small number of participants who received loop diuretics, and most of the participants had stage 1 or 2 chronic kidney disease, which may have resulted in the lack of association between receiving loop diuretics and the change of serum magnesium.

Potassium is an intracellular electrolyte, just like magnesium. Potassium depletion can increase renal magnesium loss by inhibiting magnesium reabsorption at the thick ascending limb of the loop of Henle. Additionally, magnesium depletion can also cause renal potassium loss, resulting in hypokalemia.[1,6] Studies have shown that 38-60% of hospitalized patients with hypokalemia also have hypomagnesemia.[31–33] However, some studies, including those by Deheinzelin et al. and Chernow et al., have found no association between serum magnesium and serum potassium levels in post-operative and critically ill patients.[5,34] Our study also found that the change in serum magnesium was not associated with the presence of hypokalemia at baseline. This lack of association may be due to confounding factors such as the use of loop diuretics, renal function, and the presence of conditions that cause the loss of potassium through urine or shift of potassium into cells.[1] Although low serum potassium levels can increase renal magnesium loss, patients with hypokalemia often have hypomagnesemia. Therefore, in the treatment of hypomagnesemia, serum potassium levels should also be evaluated and treated if the patient has low serum potassium levels.[2]

No participants developed clinical symptoms of hypo- or hypermagnesemia during or after receiving IV magnesium replacement. However, clinical symptoms may be overlooked and underdiagnosed due to the nonspecific clinical features of hypo- and hypermagnesemia. Thus, the incidence of adverse events during IV magnesium replacement therapy in our study, may be underestimated.

Although an increase in the change in serum magnesium level from baseline was greater with the short infusion than the prolonged infusion, the percentage of participants achieved optimal serum magnesium level after completing therapy was not different between the two cohorts. Therefore, the short infusion may not be clinically significant in the change of serum magnesium level compared to the prolonged infusion. However, the short infusion of IV magnesium may have clinical benefits to the patient's care, such as reducing the risk of drug incompatibility, interruptions, or delays in receiving the other incompatible IV drug.

Our study is adequately powered to compare the infusion rate of IV magnesium in hospitalized surgical patients. We collected the data from the electronic medical record, which provided accurate and reliable data. However, there are limitations to this study. This study was a retrospective study design. So, there are residual confounders in the nature of the study design.[35] The most important limitation in our study was that

the serum magnesium level is a poor surrogate for total body magnesium storage. However, serum magnesium level is the most common standard method for assessment of magnesium status and is used to guide therapeutic decisions in clinical practice. We therefore considered using the serum magnesium level as the primary variable for analysis. Another limitation is that the administration rate of magnesium in this study does not vary, especially in the prolonged infusion cohort, which may affect the generalizability of the results. Most participants in our study had stage I or II CKD; therefore, it should be caution when expand our results to CKD patients with stage III or lower. In addition, the majority of participants in our study had mild to moderate hypomagnesemia (mean serum magnesium level of 1.25 mg/dL at baseline). Further studies would be needed in severe hypomagnesemia participants who have lower total body magnesium storage and may require long-term magnesium replacement.

CONCLUSION

In hospitalized surgical patients, prolonging the IV magnesium infusion rate below 0.5 g/h did not provide additional benefits over the shorter infusion rate in increasing serum magnesium levels and achieving optimal serum magnesium levels. Given the lack of clinical benefits, prolonged infusion of magnesium may be used in patients who are at risk of developing high blood magnesium levels, such as those with renal impairment. However, the shorter IV magnesium infusion rate protocol should be considered, particularly for patients who need to minimize the risk of drug incompatibility, interruptions, or delays in receiving other incompatible IV drugs.

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ETHICS APPROVAL

The study was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkhla University, Songkhla, Thailand (REC number 65-428-19-6)

CONFLICTS OF INTEREST STATEMENT

All authors have declared no conflicts of interest.

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AUTHORS CONTRIBUTIONS

Nichakarn Apiromruck: Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft, Visualization; Somkiat Sunpaweravong: Conceptualization, Methodology, Writing - Review & Editing; Sasiwimon Iwsakul**:** Methodology, Formal analysis, Writing - Review & Editing; Thitima Doungngern: Conceptualization, Methodology, Validation, Formal analysis, Writing - Review & Editing.

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