Original Article

A prospective observational study to identify the effectiveness of intravenous magnesium replacement in an intensive care setting

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Abstract

Background and Aims: To estimate the incidence of hypomagnesemia and identify the effectiveness of a calculated dose of intravenous magnesium sulfate ($MgSO_4$) in correction of hypomagnesemia and its relationship with renal function in critically ill patients.
Material and Methods: All patients admitted in the adult intensive care unit were enrolled in the study and magnesium levels were monitored. Patients with serum magnesium levels <1.7 mg/dL received calculated doses of Intravenous $MgSO_4$. The average rise in serum magnesium levels per gram of $MgSO_4$ administered was calculated and relationship with estimated glomerular filtration rate (eGFR) was identified.
Results: In total, 27.27% of patients admitted in our intensive care unit had an incidence of hypomagnesemia. The average rise of serum magnesium levels in patients with hypomagnesemia was 0.13 (±0.05) mg/dl. The average rise of serum magnesium levels was 0.10 (±0.04) mg/dL in patients with eGFR ≥ 90 mL/min/1.73 m^2 and 0.15 (± 0.05) mg/dL in patients with eGFR < 90 mL/min/1.73 m^2. This difference between the two groups (*P*-value = 0.002) and the trend of increasing average rise in serum magnesium levels with declining eGFR values (*P*-value = 0.013) were both statistically significant.
Conclusion: Incidence of hypomagnesemia in the critically ill population is around 27.27%. Intravenous administration of 1 g of $MgSO_4$ results in a rise of serum magnesium levels by 0.1 mg/dL in patients with normal eGFR and around 0.15 mg/dL in patients with eGFR values between 30 and 89 mL/min/1.73 m^2.

Keywords: Critical care, hypomagnesemia, magnesium sulfate

Introduction

Magnesium is an essential element in maintaining critical functions like cardiac membrane potential, intracellular signaling, and it also serves as a cofactor for several enzymes involved in protein and DNA synthesis.[1] Magnesium is majorly an intracellular ion, and pharmacokinetics of magnesium replacement in critically ill has not been extensively studied.[2]

Hypomagnesemia is an entity of interest in critically ill patients due to its high prevalence, around 25% and its multisystem effects on human body.[2,3] Hypomagnesemia is also found to be associated with mortality and prolonged intensive care unit (ICU) stay.[3] The causes of hypomagnesemia include poor dietary intake, diarrhea, excessive loss of gastrointestinal secretions, and renal losses.[4]

Intravenous magnesium replacement has been used in critically ill patients with hypomagnesemia, but the calculation of dose

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is based on several nonvalidated assumptions. The general rule of thumb that is used for the intravenous correction of magnesium assumes a rise of 0.18 mg/dL (0.15 mEq/L) per gram of magnesium sulfate ($MgSO_4$) administered and Hammond *et al*. concluded that using this formula leads to undercorrection in over 40% of patients.[5] Routine correction of hypomagnesemia has been found to improve outcomes in critically ill patients.[6] A small study conducted in patients with underlying malignancy found that magnesium levels increased by 0.11 mmol/L after administration of 1 g of $MgSO_4$ infusion.[7] A systematic review investigating the biochemical outcomes following magnesium administration could not reveal a consistent finding.[8]

The aim of our study was to estimate the incidence of hypomagnesemia, investigate the average rise of serum magnesium levels per gram of intravenous $MgSO_4$, and identify its relationship with renal function in critically ill patients.

Material and Methods

After Institute research committee and ethics committee approval (IEC Ref No: 78/19/IEC/JMMC&RI), the study was initiated in a multidisciplinary critical care unit in a tertiary hospital in India that admitted adult critically ill patients.

All consecutive adult patients admitted in our ICU were enrolled in the study. Serum magnesium was measured daily for all patients admitted in the ICU where the study was conducted. Normal serum magnesium levels are 0.7 to 1.0 mmol/L or 1.4–2.0 mEq/L (1.7 – 2.4 mg/dl).[1] Patients greater than 18 years of age having serum magnesium levels less than 1.7 mg/dL were considered to have hypomagnesemia. Those patients who were oliguric (<400 mL urine/day) or receiving renal replacement therapy or diuretics were excluded from our study. The primary outcome of the study was to identify the incidence of hypomagnesemia in critically ill patients. Secondary outcome was to estimate the average increase in serum concentration of magnesium per 1 g of intravenous MgSO4 administered.

Patients with hypomagnesemia were administered intravenous $MgSO_4$ infusions to target a serum magnesium concentration of 2 mg/dL. The dose was calculated based on anticipated rise of 0.1 mg/dL (0.0833 mEq/L) for every gram of MgSO4 infused. This hypothesis was generated based on a previous pilot study conducted in our ICU. The required dose is diluted in 100 mL of 0.9% normal saline and was administered within 4 h. A maximum dose of 9 g was given in a single administration. The patient's heart rate, blood pressure, ECG, and oxygen saturation were monitored throughout the period of administration.

Glomerular filtration rate (eGFR) on the day of hypomagnesemia was measured using chronic kidney disease-epidemiology collaboration (CKD-EPI) creatinine equation. Age, gender, simplified acute physiology score II (SAPS II) and serum potassium levels were recorded for each patient. Repeat serum magnesium levels were measured after 24 h of infusion. The average rise of serum magnesium levels per gram of intravenous $MgSO_4$ administered was calculated by dividing the total rise of serum magnesium levels by the total dose of $MgSO_4$ administered.

Serum magnesium levels were measured daily throughout the period of ICU stay. Subsequent episodes of hypomagnesemia after normalization of magnesium levels were considered as a fresh episode and correction was undertaken as per study protocol. Patients were monitored for arrhythmia, ileus, abdominal distension, feed intolerance, diarrhea, sedation, and apnea.

Statistical analysis was performed using IBM SPSS Statistics Version 23, IBM, Armonk, New York, United States of America. All normally distributed quantitative variables have been expressed in terms of mean and standard deviation and analyzed using two-tailed Student's *t*-test or one-way ANOVA method, wherever applicable. All qualitative data have been expressed in terms of frequency and percentage and analyzed using Chi-square test.

Results

Out of 231 patients admitted in our ICU during the study period (November 2019–March 2020), 63 patients experienced episodes of hypomagnesemia (27.27%). There were a total of 72 episodes of hypomagnesemia.

The mean age of patients with hypomagnesemia was 55.68 (±17.2) years and mean SAPS II score was 26.46 (±15.8). The incidence of hypomagnesemia was equally distributed between the two genders (males 55.6% and females 44.4%). Only 22.2% of these patients had coexisting hypokalemia, whereas 77.7% of patients had isolated hypomagnesemia.

In total, 22.22% patients experienced severe hypomagnesemia (magnesium levels < or = 1.2 mg/dL). There was no significant difference between the distribution of age, SAPS II scores, and gender among patients who experienced severe hypomagnesemia. The details of patients who experienced severe hypomagnesemia are mentioned in Table 1.

After excluding patients with incomplete data, patients who were on renal replacement therapy, oliguric, or received diuretics, there were 48 episodes of hypomagnesemia that were included in the analysis of dose response study. The CONSORT diagram is shown in Figure 1.

The mean rise in magnesium levels per gram of intravenous $MgSO_4$ administered was found to be 0.13 mg/dL per gram in these patients.

The magnitude of rise in magnesium levels was found to be significantly increased in patients with impaired renal function. Among patients with normal renal function (eGFR > or = 90), mean rise in magnesium levels per gram of MgSO4 administered was 0.10 mg/dL, whereas the mean rise in serum magnesium levels among patients with eGFR <90 was 0.15 mg/dL. This difference in rise was significant between the two (*P*-value = 0.002). The results are summarized in Table 2.

The degree of rise was found to be maximum in patients with eGFR <30, where the magnitude of rise was 0.195 mg/dL per gram of MgSO4 administered. The trend of increasing levels of rise among patients with increasing severity of renal impairment was found to be significant by one-way ANOVA method (*P*-value = 0.013). The results of analysis of average rise between different categories of eGFR are mentioned in Table 3 and Figure 2.

All treated cases of hypomagnesemia were found to have normal magnesium levels the next day. The mean dose of magnesium administered was 6 g. Subsequent episodes of hypomagnesemia were observed in six patients during their ICU stay (15.38%).

None of the patients experienced arrhythmia, ileus, feed intolerance, abdominal distension, diarrhea, sedation, or apnea.

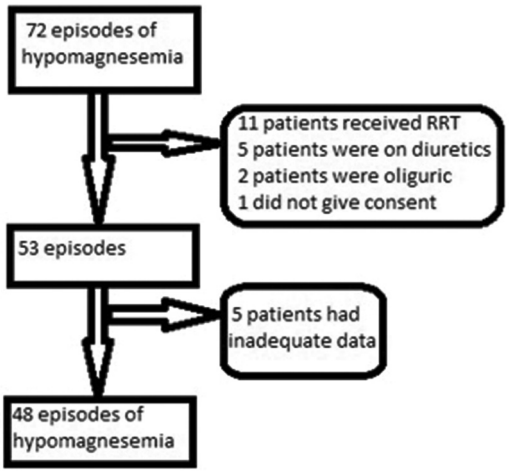

Figure 1: CONSORT diagram. Source: Original

Discussion

During the study period, 231 patients were admitted in the ICU and were enrolled in our study. Sixty-three patients (27.27%) experienced episodes of hypomagnesemia during ICU stay. Other studies in critically ill population have also reported similar findings with incidence rates between 23 and 30%.[3,9,10] Our study did not identify a significant gender predilection in patients who experienced hypomagnesemia.

In this study, severe hypomagnesemia was defined as serum magnesium levels less than or equal to 1.2 mg/dL (0.5 mmol/L). The mean age of patients who experienced severe hypomagnesemia (62.14) was higher than that of patients who experienced mild to moderate degrees of hypomagnesemia (53.84). The mean SAPS II score was also higher in patients with severe hypomagnesemia (31.43) as compared to patients with mild to moderate severity of hypomagnesemia (25.04). This substantiates the findings of previous investigators that severity of hypomagnesemia is directly correlated with adverse outcomes in patients admitted in ICU. Research in critically ill patients have identified increased length of stay, morbidity, and mortality in patients with hypomagnesemia.[11] A recent meta-analysis has suggested increased length of ICU stay with higher risk

Table 1: Distribution of age and SAPS II score among patients who experienced hypomagnesemia

Parameter	Expressed as mean (±standard deviation)		*P*
	Severe hypomagnesemia (*n*=14)	Mild to moderate hypomagnesemia (*n*=49)	
Age (in years)	62.14 (± 14.43)	53.84 (± 17.69)	0.113
SAPS II score	31.43 (± 18.94)	25.04 (± 14.77)	0.186

Table 2: Average rise in serum magnesium levels in patients with normal and abnormal eGFR

eGFR (mL/min/1.73 m²)	Mean (±Standard deviation)	*P*
≥90 (*n*=26)	0.10 (± 0.04)	0.002*
≤89 (*n*=22)	0.15 (± 0.05)	

**P<0.05 is considered significant*

Table 3: Average rise in serum magnesium levels at different eGFR values

eGFR (mL/min/1.73m²)	Mean (±standard deviation)	*P*
<30 (*n*=2)	0.19 (± 0.06)	0.013*
30-59 (*n*=10)	0.15 (± 0.05)	
60-89 (*n*=10)	0.14 (± 0.05)	
≥90 (*n*=26)	0.10 (± 0.04)	
Total (*n*=48)	0.13 (± 0.05)	

**P<0.05 is considered significant (by one-way ANOVA method)*

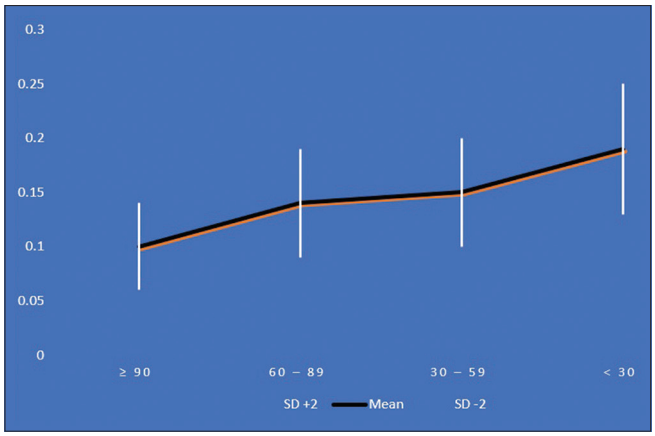

Figure 2: Graph showing the relationship of average rise in serum magnesium levels at different eGFR values. *x*-axis: eGFR (in mL/min/1.73 m^2), *y*-axis: Average rise in serum magnesium levels (in mg/dL). SD: Standard deviation. Source: Original

of invasive ventilation and mortality in critically ill patients with hypomagnesemia.[12]

The "rule of thumb" that has been traditionally used for magnesium replacement is an estimation that administration of 1 g of $MgSO_4$ increases the serum magnesium concentration by 0.15 mEq/L (0.18 mg/dL). A study conducted in medical intensive care patients had previously observed that the use of this rule results in under correction of hypomagnesemia in 40.2% of patients.[5] Correction of hypomagnesemia with a revised formula revealed better correction in a pilot study conducted by us. Hence, we decided to test the hypothesis that 1-g administration of parenteral $MgSO_4$ leads to an estimated increase of 0.10 mg/dL. We found that the average rate of increase of magnesium levels was 0.10 mg/dL in patients with eGFR >89.

Since the role of normal renal function in the excretion of magnesium has been previously understood, our findings of increased rise of serum magnesium in patients with impaired eGFR are as expected. However, one must also keep in mind that hypomagnesemia is observed in the diuretic phase of acute kidney injury, in post obstructive diuresis, in post renal transplant patients, and occasionally in chronic kidney disease patients due to increased renal losses.[6] In our study, the average rise of serum magnesium levels with intravenous MgSO4 administration was significantly higher in patients with lower eGFR. Our findings suggest that an average rise of around 0.15 mg/dL should be anticipated with 1 g administration of intravenous $MgSO_4$ in patients with eGFR between 30 and 89 mL/min/1.73 m^2. In patients with eGFR <30 mL/min/1.73 m^2, the average rise was around 0.19 mg/dL and, hence, caution should be exercised while using intravenous magnesium correction in this group of patients.

Hypomagnesemia less than 1.2 mg/dL (less than 1 mEq/L) can result in symptoms like muscular spasms, seizures, weakness, depression, cardiac dysrhythmias, arterial vasospasm, hypertension, and eclamptic fits. Low magnesium levels may lead to renal potassium wasting, impaired parathyroid hormone secretion, and vitamin D resistance that can subsequently lead to low levels of potassium and calcium.[2] Magnesium homeostasis may also be essential for management of patients with diabetes mellitus and those in sepsis.[13,14]

Hypomagnesemia can be corrected by either oral or parenteral routes. Oral magnesium supplements are available in different formulations like magnesium oxide, magnesium chloride, or magnesium aspartate. They are also available as syrup formulations like magnesium hydroxide or citrate. These formulations may be considered in asymptomatic clinically stable patients. They are associated with gastrointestinal side effects in majority of patients and even at maximum doses; correction of hypomagnesemia is slow due to poor intestinal absorption of magnesium.[15] These reasons make parenteral formulations favorable in critically ill patients who require magnesium correction.

The parenteral correction of serum magnesium levels is usually done with intravenous administration of $MgSO_4$. A 10 mL vial of a 10% $MgSO_4$ solution contains 1g of $MgSO_4 \cdot 7H_2O$ with an available magnesium fraction of approximately 4 mmol or 97 mg. Magnesium distributes to both intracellular and extracellular spaces and is also excreted by renal clearance.[1]

The influence of infusion rate on target levels of magnesium achieved has also been studied previously with mixed results. A renal threshold for excretion of intravenous magnesium has been postulated, and hence, slow infusions have been traditionally advised for the parenteral correction of magnesium.[16] Study by Hammond *et al*. suggested that the administration time was not a significant predictor influencing the rate of rise of serum magnesium levels.[5] Our study found repeat episodes of hypomagnesemia only in six patients (15.38%). All our patients had normal magnesium levels following intravenous correction over 4 h. Intravenous $MgSO_4$ administration may be associated with flushing, hypotension or cardiac arrhythmias.[15] None of our patients experienced hypermagnesemia or side effects following intravenous magnesium correction. Considering the inconvenience of prolonged infusions, low rate of rebound hypomagnesemia, and safety of infusion speed studies in our protocol, we are of the opinion that intravenous $MgSO_4$ infusions over 4 h are ideal.

The study has several limitations like single center nature of the study and nonfeasibility of blinding. More research is

needed to ascertain the effect of correcting hypomagnesemia on clinical outcomes. Dosage requirements for maintenance of normal magnesium levels in critically ill population are also outside the scope of this study.

Conclusions

The incidence of hypomagnesemia in critically ill population is around 27.27%. Intravenous administration of 1 g of $MgSO_4$ results in a rise of serum magnesium levels by 0.1 mg/dL in patients with normal eGFR and around 0.15 mg/dL in patients with eGFR values between 30 and 89 mL/min/1.73 m^2.

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Conflicts of interest

There are no conflicts of interest.

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