ORIGINAL ARTICLE

Correlation of Serum Magnesium Levels with Clinical Outcome: A Prospective Observational Study in Critically Ill Patients Admitted to a Tertiary Care ICU in India

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Received on: 07 March 2023; *Accepted on:* 04 April 2023; *Published on:* 29 April 2023

Abstract

Background: We studied the incidence of magnesium (Mg) disturbances in patients admitted to a multidisciplinary intensive care unit (ICU) and correlated serum magnesium levels with clinical outcomes.

Materials and methods: The study was conducted on 280 critically ill patients aged above 18 years and admitted to the ICU. Serum magnesium levels at admission were correlated with mortality, need for and duration of mechanical ventilation, duration of ICU stay, presence of comorbid conditions, and electrolyte disturbances.

Result: There was a high incidence of Mg disturbances at admission among patients admitted to the ICU. The incidence of hypomagnesemia and hypermagnesemia was 40.9 and 13.9% respectively. The mean Mg level among patients who expired was 1.55 ± 0.68 mg/dL, and the association with outcome was found to be statistically significant ($p = 0.001$).

Hypomagnesemia (HypoMg) was associated with significantly higher mortality (51.3%) as compared to normomagnesemia (NormoMg) (29.3%) and hypermagnesemia (HyperMg) (23.1%) (HypoMg vs NormoMg, HypoMg vs HyperMg, $p = 0.001$, 0.002 respectively). The need for mechanical ventilation was significantly higher in hypomagnesemic as compared to hypermagnesemia patients ($p = 0.012$). The association of baseline APACHE II and SOFA scores with serum Mg levels was statistically significant ($p = 0.001$ and 0.002 respectively).

The incidence of gastrointestinal disorders was significantly higher among hypomagnesemia patients (HypoMg vs NormoMg, $p = 0.023$), while chronic kidney disease was significantly higher in hypermagnesemic patients (HypoMg vs HyperMg, $p = 0.0009$, NormoMg vs HyperMg, $p = 0.0004$). On comparing the incidence of electrolyte disorders between HypoMg, NormoMg, and HyperMg groups, it was found that hypokalemia and hypocalcemia ($p = 0.0003$ and 0.039 respectively) were associated with hypomagnesemia and hyperkalemia and hypercalcemia ($p = 0.001$ and 0.005 respectively) were associated with hypermagnesemia.

Conclusion: Our study highlights the role of Mg monitoring in critically ill patients admitted to the ICU and its value for a favorable outcome. We found that hypomagnesemia was significantly associated with adverse outcomes and higher mortality in critically ill patients. Intensivists should maintain a high index of suspicion for Mg disturbances and evaluate patients appropriately.

Keywords: Clinical outcome, Critical care, Dyselectrolytemia, Electrolytes, Hypermagnesemia, Hypomagnesemia, ICU, Magnesium, Mechanical ventilation, Mortality, Sepsis, Tertiary care.

Indian Journal of Critical Care Medicine (2023): 10.5005/jp-journals-10071-24451

Introduction

Electrolyte disturbances are extremely prevalent amongst patients who are critically ill and admitted to intensive care units (ICU) and are correlated with more mortality and morbidity.[1] Magnesium (Mg) has the second highest intracellular cation concentration after potassium and has an important role in various physiological and biochemical processes. It acts as a co-factor for enzyme and transport systems (for ions like potassium and calcium), regulation of cardiac and smooth muscle tone, and modulation of immune function.[2–5] It is neither exchanged across cell membranes nor is it under hormonal regulation, therefore, the main determinant of magnesium balance is serum magnesium itself.[6]

Magnesium is often known as the "forgotten electrolyte". This is because, even though alterations in level are common, the diagnosis, clinical implications, and treatment are often overlooked.[2] The incidence of abnormalities of Magnesium occurring in critically ill patients in ICU is 65%.[7]

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How to cite this article: Gonuguntla V, Talwar V, Krishna B, Srinivasan G. Correlation of Serum Magnesium Levels with Clinical Outcome: A Prospective Observational Study in Critically Ill Patients Admitted to a Tertiary Care ICU in India. Indian J Crit Care Med 2023;27(5):342–347.

Source of support: Nil

Conflict of interest: None

Hypomagnesemia is caused by conditions like inadequate dietary magnesium intake and gastrointestinal and renal disorders[8] and correlates with increased morbidity and mortality in hospitalized patients and correlates with prolonged duration of ICU stay, increased need and time of requirement of mechanical ventilation (MV), increased incidence of sepsis and other electrolyte disturbances (hypocalcemia and hypokalemia).[7] On the other hand, hypermagnesemia occurs less frequently and is seen in 5% of hospitalized patients.[7] It occurs as a result of impaired renal magnesium excretion, iatrogenic administration of magnesium in antacids, enemas, or parenteral nutrition, diabetic ketoacidosis etc., and may have serious implications.[6]

The primary objective of the present study was to estimate the incidence of hypomagnesemia and hypermagnesemia in critically ill patients admitted to a multidisciplinary ICU and to correlate serum magnesium levels at admission with mortality. The secondary objective was to correlate serum magnesium levels with the length of ICU stay, need for and duration of mechanical ventilation, other electrolyte abnormalities, and comorbid conditions in critically ill patients.

Materials and Methods

After Institutional ethical clearance (IEC/VMMC/SJH/Thesis/October/2018-121), this single center, prospective, observational study was conducted on 280 patients admitted to the ICU who were 18 years or above. Patients with documented hypomagnesemia/hypermagnesemia before admission, previous magnesium supplementation, mortality within 24 hours of admission to ICU, and those in whom serum magnesium testing was missed on day one, were excluded from the study.

Patients were treated as per ICU protocol, and on day 1 of admission, samples were sent for routine investigations, serum magnesium levels, and any investigations which were specific to patient diagnosis. Acute physiology and chronic health evaluation score II (APACHE II) and sequential organ failure assessment (SOFA) scores were calculated with the collected values of physiological and biochemical data.[9,10]

Correlation of serum magnesium levels with mortality need for and duration of MV, duration of ICU stay, APACHE II and SOFA score, comorbidities, and other electrolyte abnormalities (serum phosphate, calcium, potassium, and sodium) was done. Usage of magnesium-lowering drugs (aminoglycosides, mannitol, diuretics), sepsis, and biochemical parameters (creatinine and albumin) were noted.

Patients were considered normomagnesemic (NormoMg) if levels of serum magnesium were between 1.6 and 2.6 mg/dL, hypomagnesemic (HypoMg) if Mg was <1.6 mg/dL, and hypermagnesemia (HyperMg) if Mg >2.6 mg/dL.[11] Standard correction of hypomagnesemia and hypermagnesemia was done as per institutional protocol.

Statistical Analysis

Minhua Chen et al. research demonstrated that serum magnesium has an odds ratio (OR) of 2.163 and is an independent mortality risk factor. Using this value as a reference, our study needed a minimum sample size of 280 patients with 80% statistical power and a significance level of 5%.

The data was recorded on a Microsoft Excel spreadsheet and analyzed using SPSS version 16.0. The mean and standard deviation were used to compare continuous parametric data while meaning and interquartile range was used for continuous non-parametric data and percentages for categorical data. The comparison of categorical data was conducted using Chi-square test, while that of continuous data was done using an independent *t*-test. One-way ANOVA was used to compare data between the groups. Pearson correlation coefficient was applied to evaluate correlation between two continuous variables and Spearman rank the correlation was used to analyze the correlation between categorical variables. A *p*-value of less than 0.05 was deemed significant for statistical significance.

Results

Out of the 280 patients analyzed, most (58.9%) were aged 50 years or older, and the mean age was 50.05 years (±16.09). About 55.7% of patients were males and 44.3% were females. 40.9% (115/280) of patients were hypomagnesemia, 13.9% (39/280) were hypermagnesemia and 44.8% (126/280) were normomagnesemia. There was no notable correlation observed between age and gender with serum magnesium levels (p = 0.999 and 0.740 respectively) (Table 1).

Table 1: Correlation of age, gender and comorbidities with serum magnesium levels

Total no. of patients = 280	*HypoMg (115)*	*NormoMg (126)*	*HyperMg (39)*	*p-value*
Age (years)	50.03 ± 17.01	50.04 ± 15.50	50.15 ± 15.52	0.999
Gender				
Male	63 (40.4%)	73 (46.8%)	20 (12.8%)	0.740
Female	52 (41.9%)	53 (42.7%)	19 (15.3%)	
Comorbidities				
Diabetes mellitus (n = 115)	50 (43.8%)	54 (42.8%)	11 (28.2%)	0.211
Gastrointestinal disorders (n = 95)	49 (42.6%)	36 (28.5%)	10 (25.6%)	0.036*
Alcoholism (n = 85)	40 (34.7%)	41 (32.5%)	4 (10.2%)	0.012*
Hypertension (n = 45)	16 (13.9%)	20 (15.8%)	9 (23%)	0.403
Coronary heart disease (n = 32)	14 (12.1%)	14 (11.1%)	4 (10.2%)	0.938
Chronic kidney disease (n = 7)	1 (0.008%)	1 (0.007%)	5 (12.8%)	0.001*
Hypothyroidism (n = 19)	8 (0.06%)	7 (0.05%)	4 (10.2%)	0.592

*Statistically significant

Table 2: Correlation of serum Magnesium levels with mortality

	Expired patients (37.5%)	*Patients transferred to Ward (62.5%)*	*p-value*
Mean Magnesium levels (mg/dL)	1.55 ± 0.68	1.90 ± 0.72	0.001*
Outcome	Hypomagnesemia	Normomagnesemia	Hypermagnesemia
Mortality (105/280)	59 (51.3%)	37 (29.3%)	9 (23.1%)
	Hypomagnesemia vs Normomagnesemia: *p*-value = 0.001* Hypomagnesemia vs Hypermagnesemia: *p*-value = 0.002* Normomagnesemia vs Hypermagnesemia: *p*-value = 0.444		

*Statistically significant

Our study population included patients with various co-morbidities as shown in Table 1. On correlating serum magnesium levels with various comorbidities, we found a significantly higher incidence of gastrointestinal disorders in the hypomagnesemia group (HypoMg vs NormoMg, HypoMg vs HyperMg, and NormoMg vs HyperMg *p*-value = 0.023*, 0.060 and 0.899). The incidence of alcoholism was higher with statistical significance amongst patients with hypomagnesemia and normomagnesemia. (HypoMg vs NormoMg, HypoMg vs HyperMg, and NormoMg vs HyperMg *p*-value = 0.713, 0.003* and 0.006*). The hypermagnesemic group was associated with a higher incidence of chronic kidney disease (CKD). (HypoMg vs NormoMg, HypoMg vs HyperMg and NormoMg vs HyperMg *p*-value = 0.948, 0.0009* and 0.0004* respectively). We did not find any significant correlation of serum magnesium with diabetes, hypertension, coronary artery disease and hypothyroidism.

The mean magnesium levels at admission were 1.77 + 0.73 mg/dL, with the minimum value being 1 mg/dL and the maximum being 4 mg/dL. The mean level of magnesium in the deceased patients was significantly lower (1.55 + 0.68 mg/dL), as compared to those, who were transferred out from the ICU (1.9 + 0.72 mg/dL), ($p = 0.001$*). Overall, 62.5% of patients were treated and transferred out, while 37.5% of patients expired during their stay in the ICU. The hypomagnesemia group (51.3%) had a significantly higher mortality rate as compared to the normomagnesemic (29.3%) and hypermagnesemic groups (23.1%) (HypoMg vs NormoMg, HypoMg vs HyperMg and NormoMg vs HyperMg p = 0.001*, 0.002* and 0.444) (Table 2).

Of the total number of study subjects, 86.4% required mechanical ventilation, with a mean duration of 9.04 ± 5.41 days. There was a statistically significant association of the need for mechanical ventilation with serum magnesium levels (p = 0.016*) with hypomagnesemia and normomagnesemic groups having more need, as compared to the hypermagnesemic group (HypoMg vs NormoMg, HypoMg vs HyperMg, and NormoMg vs HyperMg *p*-value = 0.962, 0.012* and 0.009* respectively). The duration of ICU stay ($p = 0.748$) and duration of mechanical ventilation ($p = 0.308$) did not show any association with serum magnesium levels. The duration of ICU stay was 9.65 ± 5.72 days (mean).

There was a statistically significant correlation between baseline APACHE II and SOFA scores with serum magnesium levels (p = 0.001* and 0.002* respectively). The hypomagnesemia group had a significantly higher baseline APACHE II score when compared to the normomagnesemic and hypermagnesemia groups, and the normomagnesemic group had a significantly higher APACHE II score as compared to the hypermagnesemic group (HypoMg vs NormoMg, HypoMg vs HyperMg, and NormoMg vs HyperMg p = 0.019*, 0.0006* and 0.048* respectively). Baseline SOFA scores in patients with hypomagnesemia significantly more (HypoMg vs NormoMg, HypoMg vs HyperMg and NormoMg vs HyperMg, *p*-value = 0.008*, 0.0025*, and 0.193 respectively) (Fig. 1).

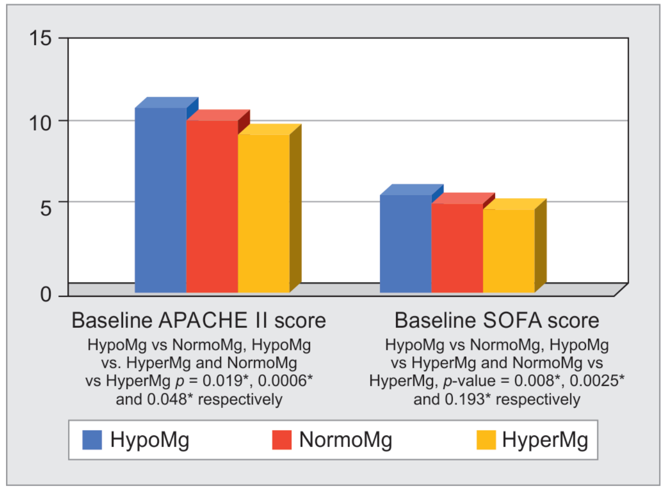

Fig. 1: Correlation of serum magnesium with APACHE II and SOFA Scores

We studied the relationship of magnesium disturbances with other electrolyte disorders and found a correlation that was statistically significant with hypokalemia ($p = 0.0003$*), hyperkalemia ($p = 0.001$*), hypocalcemia ($p = 0.039$*), and hypercalcemia ($p = 0.005$*). The incidence of hypokalemia was significantly higher in the presence of hypomagnesemia (HypoMg vs NormoMg, HypoMg vs HyperMg, and NormoMg vs HyperMg *p*-value = 0.002*, 0.0006* and 0.151 respectively), as also the incidence of hypocalcemia (HypoMg vs NormoMg, HypoMg vs HyperMg and NormoMg vs HyperMg *p*-value = 0.021*, 0.079 and 0.821 respectively).

The group with hypermagnesemia had a significantly higher number of patients with hyperkalemia compared to groups with normomagnesemia and hypomagnesemia (HypoMg vs NormoMg, HypoMg vs HyperMg, and NormoMg vs HyperMg *p*-value = 0.042*, 0.0001*, and 0.044* respectively). Hypercalcemia was significantly higher in the hypermagnesemic and normomagnesemic groups as compared to the hypomagnesemia group (HypoMg vs NormoMg, HypoMg vs HyperMg and NormoMg vs HyperMg, *p*-value = 0.002*, 0.0005*, and 0.679 respectively).

We did not find any statistically significant association between serum magnesium and the use of magnesium-lowering drugs (loop diuretics, thiazide diuretics, mannitol, and aminoglycosides)

($p = 0.684$), serum creatinine ($p = 0.522$) and serum albumin levels ($p = 0.112$) and the presence of sepsis ($p = 0.078$).

Discussion

Magnesium disturbances are common in the ICU, with hypomagnesemia occurring more frequently than hypermagnesemia.[7,12] Despite this, their clinical implications and treatment are often overlooked.[13] There is a paucity of studies on the effect of magnesium disruptions on the morbidity and mortality of patients in a multidisciplinary ICU in the Indian context who are critically ill. A study was conducted by us on 280 patients who were critically ill and admitted to the ICU and were 18 years or above. Serum magnesium levels at admission were correlated with mortality, need for and duration of mechanical ventilation and ICU stay, presence of comorbid conditions, and electrolyte disturbances.

The incidence of hypomagnesemia and hypermagnesemia at admission was found to be 40.9 and 13.9% respectively, in our study. Kumar et al. showed a 25% incidence of hypomagnesemia in a medical ICU in rural central India.[14] Similar to our study, Escuela et al. reported an incidence of 52.5, 34, and 13.5% of hypomagnesemia, normomagnesemia, and hypermagnesemia respectively in 144 patients, in a Spanish multidisciplinary ICU.[15] The high incidence of hypomagnesemia amongst ICU patients may be attributed to various factors like impaired magnesium absorption secondary to decreased gastrointestinal activity, malnutrition, presence of comorbidities like diabetes mellitus, gastrointestinal disorders, alcoholism, and frequent occurrence of other electrolyte imbalances along with the concurrent use of magnesium lowering medications.[3]

We found that the mean APACHE II and SOFA scores were significantly higher in patients with hypomagnesemia followed by those with normomagnesemia and hypermagnesemia ($p = 0.001$, $p = 0.002$ respectively). Our results differed from Kumar et al. and Safavi et al., who did not find any statistically significant correlation between magnesium levels and the severity scores.[14,16] El Said et al. found a significantly higher SOFA score in patients with hypermagnesemia, followed by normomagnesemia and hypomagnesemia.[17]

There was significantly higher mortality in hypomagnesemia patients (51.3%) as compared to normomagnesemic (29.3%) and hypermagnesemia patients (23.1%) ($p = 0.001$ and 0.002 respectively) in our study. Likewise, higher mortality in hypomagnesemic patients as compared to normomagnesemic patients was reported by Safavi et al. (55% vs 35%), Chernow et al. (41% vs 13%), Rubeiz et al. (46% vs 25%) and Solanki et al.[12,16,18,19] A higher mortality in this group of patients can be ascribed to concomitant electrolyte abnormalities, the presence of multiple comorbidities, and higher APACHE II and SOFA scores at admission.[3,7,12] The mean magnesium level was 1.55 + 0.68 mg/dL among the patients who expired, while it was 1.9 + 0.72 mg/dL among the survivors. The association of mean magnesium levels with outcome was found to be statistically significant in our study ($p = 0.001$).

Hypomagnesemia can lead to muscle weakness and respiratory failure, while hypermagnesemia is associated with neuromuscular blockade and consequent muscle paralysis. Thus, magnesium disturbances may be associated with increased requirement and duration of mechanical ventilation in critically ill patients.[13,14] In our study, the need for mechanical ventilation was significantly higher in hypomagnesemia and normomagnesemic patients as compared to hypermagnesemic patients ($p = 0.012$ and 0.009 respectively). This was comparable to other studies.[13,20,21] We did not observe any differences in the duration of ICU stay and duration of mechanical ventilation based on serum magnesium levels. This was similar to the study of Kumar et al., although Limaye et al., and Mousavi et al. found that patients with hypomagnesemia required a significantly longer duration of mechanical ventilation.[14,20,22]

We found that the incidence of gastrointestinal disorders was significantly higher in hypomagnesemia as compared to normomagnesemic patients ($p = 0.023$). This is comparable to the results obtained by Chernow et al. and Deheinzelin et al.[18,23] Magnesium deficiency is common in patients with gastrointestinal disorders, due to loss of magnesium via continuous nasogastric drainage, abdominal drains, and secretions, altered magnesium absorption from the gut, and use of total parenteral nutrition.[7] Magnesium depletion in chronic alcoholism may be attributed to malnutrition, chronic diarrhea, pancreatitis, and renal tubular dysfunction caused by alcohol leading to wasting of magnesium by the kidney.[7] We found a significantly increased incidence of alcoholism in patients with decreased and normal magnesium levels as compared with higher magnesium levels. Soliman et al. observed an increasing trend of hypomagnesemia in persons consuming alcohol.[13] However, they could not prove statistical significance.

Chronic kidney disease is associated with high magnesium levels due to inefficient renal excretion. A number of patients with CKD were found to be significantly higher in the hypermagnesemic group as compared to the hypomagnesemia and normomagnesemic groups. ($p = 0.0009$ and 0.0004 respectively). Magnesium deficiency is common in diabetic patients and occurs secondary to insulin resistance and increased renal loss of magnesium accompanying glycosuria. Though we found a high incidence of hypomagnesemia in diabetic patients (43.8%), there was no significant association with magnesium levels. However, Safavi et al. and Limaye et al. found a statistically significant correlation between low serum magnesium and diabetes mellitus.[16,20]

Magnesium disturbances are often associated with other electrolyte disorders. We found the incidence of hypokalemia to be significantly higher in the hypomagnesemia group as compared to the normomagnesemic and hypermagnesemic groups ($p = 0.002$ and 0.0006 respectively). This is corroborated by many other studies.[19,24,25] Hypokalemia is common in patients with hypomagnesemia and is refractory to isolated potassium supplementation unless the magnesium deficiency is treated. Magnesium deficiency increases potassium wasting by increasing distal potassium secretion.[26] The incidence of hyperkalemia was significantly higher in patients with hypermagnesemia (HyperMg vs HypoMg and HyperMg vs NormoMg, 0.0001 and 0.044 respectively) and was attributed to the increased association of chronic kidney disease with hypermagnesemia and hyperkalemia.[7]

Hypocalcemia is also caused by hypomagnesemia as defects in release, synthesis, and end-organ resistance of parathyroid hormone can occur.[11] In our study, there were substantially more patients with hypocalcemia in the hypomagnesemia group than in the normomagnesemic group. Limaye et al., Soliman et al., Saleem et al., and Pannem et al. all came to similar conclusions.[20,24,27,28] In comparison to the normomagnesemic and hypomagnesemia groups, the number of patients with hypercalcemia was considerably higher in the hypermagnesemic group. This results from people with the chronic renal disease having hypermagnesemia and hypercalcemia simultaneously.[29]

By observing that individuals with hypomagnesemia had sepsis twice as frequently as those with normomagnesemia, Kumar and Limaye et al. established a statistically significant association between the two.[14,20] The difference in the incidence of sepsis between the various magnesium groups in our study although, was not significant. Magnesium depletion is brought on by drugs that impede magnesium reabsorption at the renal tubules, including loop and thiazide diuretics, mannitol, and aminoglycosides. In contrast to our investigation, Zafar et al. found no statistically significant association between the usage of magnesium-lowering medications and hypomagnesemia.[30]

Our study has some limitations. We correlated all the parameters with magnesium levels on the day of admission and changes in magnesium levels during the course of the ICU stay were not evaluated. Patients were followed up until their stay in the ICU, which may have affected the overall outcome parameters. Ionized magnesium, which is the metabolically active form, was not evaluated.[31]

Conclusion

Our study revealed that hypermagnesemia and hypomagnesemia are commonly encountered in ICU patients. Hypomagnesemia is associated with a higher ICU mortality and requirement for mechanical ventilation and higher APACHE II and SOFA scores at admission. The incidence is increased in the presence of gastrointestinal disorders and alcoholism, and electrolyte disorders like hypokalemia and hypocalcemia are commonly associated. The incidence of hypermagnesemia is higher in patients with chronic kidney disease and hyperkalemia and hypercalcemia are often associated.

We recommend, for all patients admitted to the ICU, evaluation of Mg, especially in patients susceptible to Mg disturbances like gastrointestinal disorders, alcoholism, and chronic kidney disease. Vigilant monitoring of other electrolytes like potassium and calcium in patients with Mg disturbances is also warranted. It may be considered prudent to identify and correct Mg disturbances, though further studies are recommended to evaluate if correction of Mg disturbances at admission decreases ICU mortality.

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