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Study of Serum Magnesium Levels in Patients Admitted with Sepsis in Intensive Care Unit

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ABSTRACT

Background

Magnesium plays an important role in sepsis, and this could be attributed to its effects on the immune system, which are important in the pathogenesis of sepsis. Magnesium deficiency, one of the underrated electrolyte abnormalities, is observed in critically ill patients admitted to intensive care unit (ICU).

Objective

To find the association of serum magnesium with the outcome, duration, and need for ventilation.

Method

The hospital-based prospective observational study included patients > 18 years (N=150) with sepsis admitted to intensive care unit. Patients were divided into normomagnesemia (n=75) and hypomagnesemia (n=75) groups. Sequential Organ Failure Assessment Score (SOFA) score, length of intensive care unit stay, need and duration of mechanical ventilatory requirement, and outcomes were compared between the two groups.

Result

The mean Sequential Organ Failure Assessment score (5.87 ± 2.31 vs. 3.85 ± 1.75), mean duration of intensive care unit stay (in days) (7.21 ± 1.74 vs. 5.24 ± 1.38), the mean duration of mechanical ventilatory requirement (in days) (4.05 ± 3.47 vs. 1.13 ± 1.98), and mortality rate were (33% vs. 4%) were higher in the hypomagnesemia group when compared to the normomagnesemia group ($p < 0.001$ for all).

Conclusion

The study concludes that hypomagnesaemia is a significant electrolyte abnormality in critically ill sepsis patients. Hypomagnesaemia, Sequential Organ Failure Assessment Score, and mechanical ventilation are the factors that independently predicted mortality in intensive care unit patients. Hence, clinicians should regularly monitor the occurrence of hypomagnesemia in intensive care unit patients to reduce its poor clinical outcomes.

KEY WORDS

Artificial, Critical care, Magnesium, Mortality, Organ dysfunction scores, Respiration, Sepsis

INTRODUCTION

Magnesium, second most prevalent intracellular cation, plays an essential physiological role in many functions of the human body.[1,2] It acts as a cofactor in various enzymatic reactions and has a key role in immunological processes.[2,3] Normal serum magnesium levels range between 1.46 and 2.68 mg/dL. Hypomagnesemia is caused when there is a low level (< 1.46 mg/dL) of serum magnesium in the blood.[4] The incidence of hypomagnesemia in general population is 2%, 10% to 20% in hospitalized patients, and 50% to 60% in intensive care unit (ICU) patients.[4]

Hypomagnesemia, one of the underrated electrolyte disorders, has been implicated in the pathophysiology of several diseases in critically ill patients in ICU.[1] Magnesium ions play a critical role in the immune system in fighting against infection via inflammatory response and nitric oxide production.[5] Hence, measurement of magnesium levels in patients with infections is useful for diagnosis and treatment.[5,6] Furthermore, sepsis is also considered as an independent risk factor for the development of hypomagnesemia in elderly patients.[7] Hence, detection of serum magnesium levels in sepsis patients may be vital as this could be connected with severity of illness and increases the rate of mortality and morbidity.[8]

Several studies have determined the implication of serum magnesium levels in critically ill patients and its influence on the outcome.[1,2,6,9] However, Indian literature addressing the influence of this under-diagnosed electrolyte deficiency in ICU-admitted sepsis patients is scarce.[10,11] Hence, the present study was planned against this milieu at a tertiary care hospital to study the serum magnesium levels in patients admitted with sepsis to ICU and its association with the outcome, duration and need for mechanical ventilation.

METHODS

The hospital-based prospective observational study was conducted in a tertiary care hospital for two years from October 2018 to September 2020 after obtaining approval from the Institutional Ethical committee. Patients aged > 18 years admitted with sepsis (according to new consensus definitions SEPSIS 3) to ICU and Sequential Organ Failure Assessment (SOFA) Score > 2 were enrolled after taking prior informed consent.[12,13] Patients were exempted from the study if they have received blood products, magnesium, or calcium infusions before specimen collection.

Kumar et al. observed that normal magnesium levels was 3.93% ± 3.88 mg/dl, whereas with hypomagnesemia was 5.46% ± 5.75 mg/dl among critically ill patients in ICU.[2] Expecting similar results with 80% power, 95% confidence level, and effect size 0.470, we required 142 subjects with 71 in each group.

Enrolled subjects were grouped into patients with sepsis with normal magnesium levels (Group -1 = 75) or with hypomagnesemia (Group -2 = 75). The normal reference value of serum total magnesium is between 1.7 mg/dL and 2.7 mg/dl and the patients with serum magnesium levels of < 1.7 mg/dL were considered to have hypomagnesemia.

Demographic data and detailed history of the patients were taken, and routine clinical examinations were performed. SOFA (Sequential Organ Failure Assessment) score was calculated for each patient on the day of admission to ICU. A venous sample of 3mL collected from every patient within the first 24 hours of admission into the ICU was estimated to evaluate the serum magnesium levels by xylidyl blue colorimetric method on Cobas- 2000 autoanalyzer (Roche, Switzerland).[14]

Data were analyzed using R software version 4.1.0. Continuous variables are given in Mean ± SD/ Median (Min, Max) form. Frequency tables were used to represent categorical variables. Continuous variables were represented by Mean ± SD/Median (Min, Max) form. Chi-Square test was performed to check the association between attributes and two sample t-test/ Mann Whitney U-test to compare the means/distributions between the groups. Stepwise multiple logistic regression model was applied for the determination of factors associated with hypomagnesemia. $P \leq 0.05$ indicates statistical significance.

RESULTS

Table 1 presents comparisons of study variables between hypomagnesemia and normomagnesemia groups. Of 150 patients studied, the majority i.e., 76 (50.66%) were in the age group of 61-75 years with female preponderance in normomagnesemia group and male preponderance in the hypomagnesemia group, though it did not reach statistical significance (p=0.0715). The most common cause for sepsis was pneumonia (34%) followed by urosepsis (22%) in either group. Type 2 Diabetes mellitus (42%) and hypertension (32%) were the most common comorbid conditions among patients in both groups.

Mean pulse rate, total bilirubin levels, and international normalized ratio in the hypomagnesemia group were significantly higher than in normomagnesemia group. The hypomagnesemia group had a PaO2/Fio2 ratio, mean systolic and diastolic blood pressure, oxygen saturation, Glasgow Coma scale (GCS) score, serum magnesium levels, platelet count, significantly lower than the normomagnesemia group. The mean respiratory rate and serum creatinine levels were higher in the hypomagnesemia group than the normomagnesemia group, though insignificant ($p < 0.05$ for all). Body temperature in both hypomagnesemia and normomagnesemia groups were comparable, though the mean temperature was higher among the normomagnesemia group (p=0.67).

Table 1. Comparison of variables between the groups

Variables	Hypomagnesemia	Normomagnesemia	P-value
Age (years)			
≤ 45	6 (8%)	7 (9.33%)	0.2984[C]
46-60	19 (25.33%)	15 (20%)	
61-75	33 (44%)	43 (57.33%)	
> 75	17 (22.67%)	10 (13.33%)	
Mean ± SD (years)	65.45 ± 12.47	63.68 ±12.68	0.5097[MW]
Gender			
Female	29 (38.67%)	40 (53.33%)	0.0715[C]
Male	46 (61.33%)	35 (46.67%)	
Cause of sepsis			
Pneumonia	28 (37.33%)	23 (30.66%)	-
Urosepsis	18 (30.66%)	15 (20%)	
GI sepsis	11 (14.66%)	16 (21.33%)	
Cellulitis	6 (8%)	7 (9.33%)	
Pyelonephritis	5 (6.66%)	8 (10.66%)	
Miscellaneous causes	7 (9.33%)	6 (8%)	
Comorbidities			
Diabetes	35(46.66%)	28 (37.33%)	0.11
Hypertension	20(26.66%)	28 (37.33%)	0.88
Ischemic heart disease	9(12%)	8 (10.66%)	0.93
Chronic obstructive pulmonary disorder	8 (10.66 %)	6 (8%)	0.24
Cerebrovascular accident	3(4%)	5 (6.66%)	0.21
PaO2/Fio2 ratio	302.67 ±59.21	353.33 55.34	**<0.001[MW*]**
Pulse rate (bpm)	98.45 ± 15.84	97.37 ±15.92	0.6777[t]
Diastolic blood pressure (mmHg)	109.36 ± 24.97	117.33 ±19.89	**0.0322[t*]**
Systolic blood pressure (mmHg)	69.2 ± 9.12	73.33 ± 8.75	**0.0032[MW*]**
Respiratory rate (cpm)	23.73 ± 4.16	23.27 ± 4.34	0.5025[t]
Oxygen saturation (%)	83.85 ± 7.24	89.32 ± 8.12	**<0.001[MW*]**
Temperature (°F)	98.49 ± 1.12	98.44 ± 1.13	0.7372[MW]
Mean arterial pressure (mmHg)	82.52 ± 13.66	87.49 ±11.19	**0.0159[*]**
Glasgow Coma Scale score	9.99 ± 2	11.84 ± 1.4	**< 0.001[t*]**
Serum Magnesium (mg/dl)	1.52 ± 0.08	2.06 ± 0.24	**<0.001[MW*]**
Platelets count (cells/cu mm3)	146314.7 ± 138803.9	199531.9 ± 140149	**0.0208[t*]**
Serum creatinine (mg/dl)	2.29 ± 1.56	2.1 ± 1.8	0.0633[MW]
Total bilirubin (mg/dl)	1.75 ± 2.52	1.22 ± 2.58	**0.0079MW***
International normalized ratio	1.53 ± 0.88	1.28 ± 0.3	**0.0306MW***

C-Chi square test, t – Two-sample t-test, MW-Mann Whitney U test, * indicates statistical significance. Data are presented as n (%), unless otherwise indicated. PaO2/Fio2, Partial pressure of oxygen in arterial blood/ fraction of inspired oxygen

Hypomagnesemia group had higher mean SOFA score, duration of ICU stays (in days), ventilatory requirement, duration (days) of mechanical ventilatory requirement, and mortality rate when compared with the normomagnesemia group ($p < 0.001$; Table 2).

Table 2. Comparison of outcomes between hypomagnesemia and normomagnesemia groups

Variables	Hypomagnesemia	Normomagnesemia	p-value
SOFA score	5.87 ± 2.31	3.85 ± 1.75	< 0.001MW*
ICU days	7.21 ± 1.74	5.24 ± 1.38	< 0.001MW*
Ventilator requirement (days)	4.05 ± 3.47	1.13 ± 1.98	< 0.001MW*
Ventilator requirement			
No	28 (37.33%)	55 (73.33%)	< 0.001C*
Yes	47 (62.67%)	20 (26.67%)	
Mortality			
No	50 (66.67%)	72 (96%)	< 0.001C*
Yes	25 (33.33%)	3 (4%)	

C-Chi square test, t – Two-sample t-test, MW-Mann Whitney U test, * indicates statistical significance. Data are presented as n (%), unless otherwise indicated; SOFA, Sequential Organ Failure Assessment Score; ICU, Intensive care unit

Systolic blood pressure (SBP), GCS, platelets, SOFA score, and ventilator requirement were the factors that had an independent association with hypomagnesemia (Table 3). Odds of having hypomagnesemia increase by 0.93 times with unit increase in SBP, 0.52 times with unit increase in GCS, 0.999997 times with unit increase in platelets. Odds of having hypomagnesemia increase by 1.31 times with a unit increase in SOFA score, 3.48 times more for the patients who required mechanical ventilation compared to the one who didn't require mechanical ventilation (Table 3).

Table 3. Stepwise multiple logistic regression to determine factors associated with hypomagnesemia

	Estimate	P-value	Odds Ratio
(Intercept)	11.1	**0.0002***	-
SBP	-0.0741	**0.0056***	0.93(0.88 - 0.98)
GCS	-0.6547	**< 0.001***	0.52(0.37 - 0.7)
Platelets	-0.000003	**0.0377***	0.999997 (0.9999932 - 0.9999998)
SOFA score	0.2713	**0.0128***	1.31(1.07 - 1.64)
Ventilator Requirement (ref: No)			
Yes	1.247	**0.0069***	3.48(1.43 - 8.83)

GCS, Glasgow Coma Scale, SOFA, Sequential Organ Failure Assessment Score; SBP, Systolic blood pressure

Low total bilirubin levels, low serum magnesium, high SOFA score, and ventilator requirement were the factors that had an independent association with mortality in ICU (Table 4). Odds of death increase by 0.79 times with unit increase in total bilirubin, 0.09 times with unit increase in serum

Mg, 2.37 times with unit increase in SOFA score. Odds of death increases by 38.13 times in patients who required a ventilator support compared to those who didn't (Table 4).

Table 4. Stepwise Multiple Logistic regression to determine factors associated with mortality

	Estimate	P-value	Odds Ratio
(Intercept)	-4.6823	**0.0419***	-
Total Bilirubin	-0.2308	**0.1610**	0.79(0.54 - 1.03)
Serum magnesium	-2.433	**< 0.001***	0.09(0.01 - 0.7)
SOFA score	0.8647	**< 0.001***	2.37(1.67 - 3.74)
Ventilator Requirement (ref: No)			
Yes	3.641	< 0.001*	38.13(7.01 - 393.69)

SOFA, Sequential Organ Failure Assessment Score

DISCUSSION

Fluid and electrolyte abnormalities are the most common abnormalities seen in ICU patients.[15] Low serum magnesium levels encountered frequently in critically ill patients are involved in the development of systemic inflammatory response syndrome and also organ dysfunction.[15] Therefore, magnesium deficit in critically ill sepsis patients results in poor outcome. Proper diagnosis and magnesium supplementation might be useful to ease the sepsis mortality or morbidity.[15] Therefore, in our study, we studied the serum magnesium levels in critically-ill sepsis patients when compared to normal patients. The occurrence of magnesium deficiency in our study was associated with higher disease severity, increased ICU or ventilator stay, greater ventilator requirement, and higher mortality in critically ill sepsis patients.

Of 150 critically ill sepsis patients, half of the patients (50%) had hypomagnesaemia suggesting the notable incidence of hypomagnesaemia in ICU patients. A study by Kumar et al. reported low magnesium levels in 59.30% of critically ill elderly patients suggesting the frequent occurrence of low magnesium in them.[16] Mean serum magnesium level in hypomagnesaemia group (1.52 ± 0.0768 mg/dl) and in the normomagnesemia group (2.038 ± 0.23 mg/dl) was comparable to studies by Safavi et al. (1.08 ± 0.02 mg/dl vs. 1.98 ± 0.06 mg/dl) and Subhraprakashpramanik et.al (1.23 ± 0.18 mg/dl vs. 1.89 ± 0.12 mg/dl).[13,17] Therefore, serum magnesium levels need to be monitored for prompt therapeutic and prognostic implications.

In a prospective study by Assarian et al. hypomagnesemic septic patients have shown higher acute physiology and chronic health evaluation (APACHE) II score (11.67 ± 3.83, vs. 9.44 ± 4.33), SOFA score [4 (3.75-6.25) vs. 3 (3.00-5.00)]. Also, the hypomagnesemic septic patients had 28-day mortality due to sepsis (50%), greater duration of ventilator support [12.00 (4.00-14.25) days] and ICU stay [14.00 (12.75-17.25) days].[10] Safavi et al. has also shown higher APACHE and SOFA scores on admission, maximum SOFA score, greater ventilator support, and higher mortality in hypomagnesemia patients during ICU stay.[13] Limaye et al. also found that need for ventilation (73% vs. 53%), duration of mechanical ventilation (4.27 vs. 2.15 days), sepsis cases (38% vs. 19%), and mortality rates (57.7% vs. 31.7%) were higher in hypomagnesemic patients than those with normomagnesemia.[7] Mushtaq et al. also reported that hypomagnesemia is associated with higher mortality rate without impacting the duration of ICU stay.[18] Similarly, we found hypomagnesaemic patients had longer ICU stay, higher SOFA scores, and higher mortality, longer ventilator days, and higher ventilator requirement. Longer duration and frequency of ventilator support in hypomagnesemic patients in our study might be because of muscle weakness which causes respiratory distress and consequent weaning of patient from ventilator support. In our study, sepsis might be the probable reason for higher mortality rate in hypomagnesemic patients, which is a common cause of death in ICU patients.[2,13]

In our study, low SBP, low GCS, low platelets, higher SOFA score, and ventilator requirement were the few significant independent predicators affecting the serum magnesium levels in critically ill sepsis patients. In a study conducted by Kumar et al. study variables did not associate with serum magnesium levels.[16] While Subhraprakashpramanik found sepsis ($\beta = -0.561$; $p < 0.001$) and the highest SOFA ($\beta = -1.043$; $p < 0.001$) score were the factors that showed significant correlation with low magnesium levels.[17] Logistic regression analysis revealed hypomagnesaemia, highest SOFA score, and mechanical ventilation were the risk factors that independently predicted for mortality in the critically ill sepsis patients and therefore should be cautiously evaluated in these patients. In a study conducted by Chen et al. APACHE II score [OR = 1.129, 95% CI = 1.064-1.197, p = 0.000] and serum magnesium level (OR = 2.163, 95% CI = 1.015-4.610, p = 0.046) were independent risk factors for death in critically ill patients.[3]

Overall, hypomagnesaemia is common in ICU-admitted sepsis patients. Hence, ICU clinicians should be well oriented about the fluid and electrolyte pathophysiology to recommend optimal care. Furthermore, as hypomagnesaemia significantly associated with high mortality rate in critically ill sepsis patients, physicians should keep a high index of suspicion for hypomagnesaemia to identify and correct the deficiency with proper treatment to decrease the mortality rate.

The study has few potential limitations that need to be acknowledged. Major limitation is the restricted sample size. This is a single-centre observational study; hence, further large multicentre interventional studies are required to validate the current outcome. Another limit is presence of many confounding variables that were not adjusted for.

CONCLUSION

The study concludes that hypomagnesaemia is a significant electrolyte abnormality in critically ill sepsis patients. Hypomagnesaemia, SOFA score, and mechanical ventilation are the risk factors that independently predicted mortality in ICU patients. Hence, clinicians should regularly monitor the occurrence of hypomagnesaemia in the critically ill patients to reduce poor clinical outcomes.

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