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The predictive role of serum magnesium in prognosis of critically ill medical patients

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Abstract: *Introduction:* Magnesium deficiency is a common disorder, but easily ignored as compared to other electrolyte abnormalities. Other studies are showing varied prevalence and increased association with morbidity and mortality. *Aims & Objectives:* The aim of our study is to find out the prevalence of hypomagnesemia among the critically ill medical patients and to correlate the serum magnesium levels with the mortality and morbidity outcome considering the length of ICU stay, duration of ventilatory support, APACHE 2 score, SOFA score, primary medical conditions in critically ill patients in medical ICU. *Methodology:* This prospective observational study was conducted in Medical intensive care unit of a tertiary care hospital. After the approval from Institutional ethical committee patients admitted to the medical intensive care unit with age more than 12 years and admitted for more than 2 days were included in the study after obtaining written informed consent. Laboratory tests and radiological investigations were done. APACHE 2(acute physiology and chronic health evaluation) score, SOFA score, total ICU stay, hospital stay, need of mechanical ventilation, duration of ventilatory assistance and associated medical conditions like diabetes, sepsis and electrolyte abnormalities were followed up to assess the relation with mortality and morbidity. *Results:* Among total of 170 critically ill medical patients were included in the study, prevalence of hypomagnesemia was 56.8 %. The morbidity was higher in hypomagnesaemic patients (48.5% vs 23.4%), longer ICU stay (6.96 ± 3.85 vs 5.12 ± 1.31) and need of mechanical ventilation was also more (68.9% vs 40.4 % p value < 0.003). Sepsis and maximum SOFA score indicate being the predominant underlying factor for hypomagnesemia. Even though association was there between mortality and hypomagnesemia, mortality has not correlated significantly [beta -0.041, t -0.473, 95 % CI -0.219 and 0.138]. *Conclusion:* Hypomagnesemia is more prevalent among the critically ill medical patients. Hypomagnesemia was also associated with increased mortality, longer ICU stay, higher APACHE 2 score, SOFA score, frequent ventilatory support and significant electrolyte abnormalities also.

Keywords: Hypomagnesemia, Mortality, Criticallyill patients, Sepsis, APACHE Score.

Introduction

In critically ill hospitalised patients, the most common under diagnosed electrolyte disturbance is hypomagnesemia. Disorders of magnesium are among the most common electrolyte abnormalities in hospitalised patients, especially in critically ill patients. Considerable controversy is present regarding the effect of hypomagnesemia on mortality and morbidity and the prevalence of hypomagnesemia has a wide prevalence (11-61%)[1-2]. The incidence of hypomagnesemia is 2 % in general population, 10-20% in hospitalised patients, 50-60% in ICU patients, 30-80 % in persons with alcoholism and 25 % in outpatients with diabetes [3].

Magnesium plays an important role in maintaining body homeostasis, acting as cofactor for most of the ATP ase by forming ATP- magnesium complex. The clinical

manifestations of magnesium deficiency are arrythmias, cardiac insufficiency, coronary vasospasm, sudden death, skeletal and respiratory muscle weakness, bronchospasm, tetany and neuromuscular abnormalities and electrolyte abnormalities including hypokalemia, hypocalcemia, hyponatremia and hypophosphatemia [4-5]. But hypomagnesemia is often underdiagnosed and overlooked in current clinical practice [6]. For its prognostic significance hypomagnesemia should be searched systematically [7]. Varied prevalence and increased mortality and morbidity were observed in many studies. The aim of our study to find out the prevalence of hypomagnesemia among the critically ill medical patients and to correlate the serum magnesium level with mortality and morbidity.

Material and Methods

This prospective observational study was conducted in the Trichy SRM medical college hospital and research institute, intensive care unit from January 2022 to July 2022. The study was approved by the Institutional ethical committee. Patients admitted to the intensive care unit with age more than 12 years and for more than 2 days of admission were included in the study after obtaining written informed consent. Patients on magnesium supplementation prior to transfer to ICU were excluded from the study. On the day of admission to ICU a blood sample was collected for the estimation of serum magnesium. A detailed clinical examination and thorough history collection were done for all the patients. Other laboratory tests and radiological investigations were done as per routine ICU protocol as indicated for each patients. According to the standard scoring system, APACHE 2 (acute physiology and chronic health evaluation) score was calculated on the day of admission.

SOFA score was calculated every day and mean and maximum values were calculated and documented. Total ICU stay, hospital stay, need of mechanical ventilation, duration of ventilatory assistance and associated medical conditions like diabetes, sepsis and electrolyte abnormalities were followed up to assess their mortality and morbidity. The study procedure did not interfere with the patient management in ICU. Serum magnesium was measured by colorimetric method [xylidyl blue method].

The reference range of serum magnesium is between 1.7 – 2.4 mg /dl [8]. The reference range of other included investigations are glucose[less than 126 mg/dl for fasting and 200 mg /dl for random and postprandial], sodium [136-145 mEq /L], potassium [3.5-5.5 mEq/L], total serum calcium [8.2-10.6 mg/dl], total bilirubin [less than 1.2 mg /dl] and creatinine [0.4-1.3 mg/dl].

Number of days with mechanical ventilation is calculated as the duration of ventilation. Depending upon the serum magnesium levels patients are classified into two groups of hypomagnesemia [less than 1.3 mEq /L and normomagnesemia [1.3-2.1 mEq /L]. All collected data were tabulated and analysed with the standard statistical methods using SPSS software 20. Quantitative data were analysed by unpaired t test, correlation by Pearson's correlation co-efficient test, qualitative values by chi square test and multivariate regression analysis for individual risk assessments.

Results

A total of 170 critically ill medical patients admitted in MICU, with the mean age of 54.5 ± 7.62 in males and 53 ± 4.11 in females have been included in study. The baseline characteristics of the study population has been included in the Table 1.

On admission 61.4% of the Male patients and 39.6% Female patients had low serum magnesium. 63.7%of Male and 36.3 % of Female patients had normal serum magnesium levels. Lowest serum magnesium recorded was 1.11 mg/dl and highest serum magnesium recorded was 1.99 mg/dl. Mortality was significantly high in hypomagnesaemic patients (48.5 % vs. 23.4 % and p value was 0.013) and serum magnesium value was low in patients who died as compared to who survived (1.27 ± 0.13 vs. 1.53±0.32; p value 0.001). Table-2 shows the Percentage of Morbidity & Mortality in patients with normal and low magnesium levels.

Morbidity was also high in patients with low serum magnesium levels as per the APACHE 2 score (13.12 ±3.44 vs. 10.11 ± 1.20; p value 0.001), SOFA score (9.56 ± 2.33 vs 7.77 ±

0.89; p value 0.001) and maximum SOFA score (13.01 ± 4.01 vs. 9.25 ± 1.45 ; p value 0.001). Total duration of hospitalisation (9.98 ± 5.08 vs. 8.27 ± 1.24 days p value 0.024), ICU stay (6.96 ± 3.85 vs. 5.12 ± 1.31 days p value 0.002) and the need of mechanical ventilation (68.9 % vs. 40.4 %; p value 0.003).

The mean duration of mechanical ventilation (4.54 ± 2.98vs. 2.87 ± 1.09 days, p value 0.014). The associated medical conditions like sepsis (61.01% vs 40.4 %, p value 0.046), diabetes (49.2% vs 21.3%, p value 0.004), hypocalcemia (80.5% vs 34.0%, p value <0.001), hypokalemia (82.2% vs 51.1%, p value <0.001) and hyponatremia (62.8% vs 40.4%, p value 0.029). Table-3 shows the Linear regression analysis considering serum Magnesium as dependent variable.

Table-1: Baseline characteristics of the study population

Characteristics	Male [n=106]	Female [n=64]	Total [n=170]	Statistical significance
Mean age (SD)	54.5 (7.62)	53 (4.11)	61.33 (6.98)	P <0.01
Normal BP	91 (85.84)	55(85.93)	146 (85.8)	P= 0.5770
Hypertension	15 (14.15)	9 (14.06)	24 (14.11)	X^2 = 0.165
Normal QT	75 (59.98)	48 (40.05)	123 (72. 3)	P= 0.6844
Prolonged QT	31 (66.18)	16 (35.05)	47 (27.64)	
Diagnosis				
Cirrhosis	16 (15.09)	1 (1.56)	17 (9.41)	Not applicable
CKD	8 (7.5)	4 (6.25)	12 (7.05)	
IHD	13 (12.26)	10 (15.62)	23 (13.52)	
COPD	5 (4.71)	2 (3.12)	7 (4.11)	
DM	3 (2.83)	1 (1.56)	4 (2.35)	
Malaria	4 (3.77)	3 (4.68)	7 (2.17)	
Sepsis	19 (17.92)	18 (28.12)	37 (21.76)	
Stoke	5 (4.70)	6 (9.31)	11 (6.47)	
Others	33 (31.13)	19(29.68)	52 (30.58)	

Table-2: Percentage of Morbidity & Mortality in patients with normal and low magnesium levels [N=170]

Characteristics	Low Mg [n=97]	Normal Mg [n=73]	Statistical significance
Prevalence	56.8%	43.2%	-
Serum Mg level (mg/dl)	1.27 ± 0.16	1.85 ±0.14	<0.001
Age of the patients	59.5 ± 7.62	55.15 ± 4.21	0.216
Gender (%)	Male 61.4% Female 39.6%	Male 63.7% Female 36.3 %	0.892
APACHE 2 score	13.12 ±3.44	10.11 ± 1.20	<0.001
SOFA score	9.56 ± 2.33	7.77 ± 0.89	<0.001
Max. SOFA score	13.01 ± 4.01	9.25 ± 1.45	<0.001
ICU stay	6.96 ± 3.85	5.12 ± 1.31	0.002
Hospital stay	9.98 ± 5.08	8.27 ± 1.24	0.024
Mortality (%)	48.5 %	23.4%	0.013
Need of MV (%)	68.9 %	40.4 %	0.003
MV Duration (days)	3.54 ± 2.98	1.87 ± 1.09	0.014
Sepsis (%)	61.01%	40.4 %	0.046
Diabetes (%)	49.2%	21.3 %	0.004
Hypocalcemia (%)	80.5 %	34.0 %	<0.001
Hypokalemia(%)	82.2 %	51.1 %	<0.001
Hyponatremia (%)	62.8 %	40.4%	0.029

Table-3: Linear regression analysis considering serum Magnesium as dependent variable					
Dependent variable: serum Mg^{++} level	Standardized Coefficients	T	Sig.	95.0% Confidence Interval for B	
	Beta			Lower bound	Upper bound
(Constant)		5.187	0.000	1.404	3.142
Max SOFA	-1.041	-3.432	0.001	-0.189	-0.042
ICU stay	-0.746	-0.974	0.385	-0.319	0.112
Mortality	-0.041	-0.473	0.710	-0.219	0.138
Sepsis	-0.565	-3.513	0.001	-0.625	-0.179
Hypokalemia	-0.157	-0.629	0.598	-0.613	0.333

Discussion

The prevalence of hypomagnesemia in critically ill patients varies from 14-70% in other studies and it was 56.8 % in our study. The relation between mortality and hypomagnesemia was 41 % vs 13 % in a study by Chernow et al [9], 55 % vs 35 % bySafavi et al [10], 46 % vs 26 % by Rubiez et al [11] and are in higher mortality levels. But no significant difference was observed in mortality among hypomagnesemia and normal magnesium level patients in a study by Guerin et al [12] 18 % vs 17 %. The increased morbidities like longer duration of ventilatory assistance, association of sepsis, diabetes, electrolyte abnormalities like hypocalcemia, and hypokalemia may be explained as the reasons for higher mortality in hypomagnesemia patients.

Longer duration of ICU stay in hypomagnesaemic patients was observed by Soliman et al [13] and also they have observed the length of ICU stay as an independent risk factor for hypomagnesemia development. In our study we have observed a high APACHE 2 score and maximum SOFA score among the patients with low magnesium during the ICU period. Soliman et al [13] found that patients with ionized hypomagnesemia during the ICU stay had higher APACHE 2 score on admission. The important factor causing difficulty in weaning patients from ventilatory support is hypomagnesemia, as it causes muscle weakness and respiratory failure [14]. But Guerin et al [12] and Rubiez et al [11] did not find any difference between APACHE 2 score in patients with normal and low magnesium levels. In our study we observed the increased need of ventilatory support in frequency and duration among the hypomagnesaemic patients. The same was observed in a study by C S Limaye et al [15] and Safavi et al. [16].

On administering magnesium in hypomagnesaemic patientsimprovement in respiratory muscle weakness was observed in a study by Molloy et al [17]. Fiaccordori et al [18] observed patients low magnesium levels were on ventilatory support for more days. Munoz et al [19] observed that the need of ventilatory assistance is more frequent, even in neonatal ICU among the hypomagnesaemic patients. Increased mortality in experimental animals with sepsis and shock with the associated hypomagnesemia was observed in a study by Salem et al [20] and the magnesium supplementation provides significant protection against endotoxin challenge. As there is increased release of endothelin and proinflammatory cytokines (TNF – alfa and IL-6), hypomagnesaemia has important role in sepsis.

The administration of ATP – Mg Cl2 to animal models with sepsis and shock restores bioenergetics and improves organ function and better survival in a study by Harkema et al [21] in animal models. Soliman et al has observed that sepsisis an independent risk factor for developing hypomagnesaemia during the ICU stay. In our study we observed the increased incidence of sepsis in patients with low magnesium as compared to the patients with normal magnesium. The association of sepsisis twice as common in patients with hypomagnesaemia was observed by CS Limaye et al [15]. The increased renal losses accompanying glycosuria may cause

the hypomagnesemia and there is a strong relation between hypomagnesaemia and insulin resistance [22].

Among the diabetic patients, hypomagnesaemia is very common and the same was reported in a study by CS Limaye et al [12]. There may be increased requirement of insulin on magnesium supplementation. Hypomagnesemia is associated with the other electrolyte abnormalities. In our study we observed increased association of hypocalcemia, hypokalemia and hyponatremia in patients with hypomagnesemia compared to normo-magnesemic patients. Whang et al [23] and CS Limaye et al [15] also mentioned about increased association of hypocalcemia and hypokalemia among the hypomagnesaemic patients. Even hypokalemia and hypocalcemia are the predictors of hypomagnesemia [23].

In hypomagnesemic patients, hypokalemia and hypocalcemia are refractory to potassium and calcium supplementation till magnesium correction is done [24-25]. Sepsis and organ failure are predominant underlying factors for hypomagnesemia which was evident from the simple linear regression analysis model. Even though mortality was significantly associated with hypomagnesium, it did not correlate significantly with hypomagnesemia in the study. In summary hypomagnesemia in critically ill medical patients is more prevalent and is also associated with increased ratee of morbidity and mortality.

Conclusion

Among the critically ill medical patients, hypomagnesemia is highly prevalent. Moreover hypomagnesemia was associated with the high mortality rate and also with the longer ICU stay, higher APACHE score, frequent ventilatory support, association with sepsis, diabetes mellitus and electrolyte abnormalities like hypocalcemia, hypokalemia and hyponatremia as compared to patients with normal magnesium. The predominant underlying factors causing hypomagnesmia are the sepsis and organ failure.

Limitations The low magnesium levels did not correlate significantly with the mortality in the study, even though mortality rates significantly associated with hypomagnesemia. To confirm the direct correlation of hypomagnesemia and increased mortality and morbidity and the potential benefit of magnesium supplementation to improve the poor patient outcome in critically ill conditions, further studies are required.

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