Understanding the Role of Serum Magnesium Level and its Influences on the Outcome in Patients with Sepsis in a Medical ICU

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ABSTRACT

BACKGROUND

Sepsis is a life-threatening condition caused by a dysregulated host response to infection. About 2 million cases of sepsis occur annually in United States. The clinical features include signs of infection with organ dysfunction. Magnesium (Mg) is a vital cation for immune system in fighting against infection via inflammatory response and nitric oxide production. Studies have shown that hypomagnesemia is a potential risk factor of infections thereby resulting in sepsis. The present study was undertaken to evaluate the serum magnesium level, its manifestation and outcome among sepsis patients.

METHODS

The study included 100 patients of sepsis admitted over a period of 18 months. Various data such as clinical history, examination, serum magnesium level and other necessary parameters of the patients included in the study were analysed using simple statistical methods.

RESULTS

The mean age of the study population was 62.300 ± 11.4623 years. 63% were male and 37% female. Among study population, 39%, 46% and 15% patients were diagnosed as hypomagnesaemic, normomagnesaemic and hypermagnesaemic respectively. The mortality rate was 76%, 18% and 5% among hypomagnesaemic, normomagnesaemic and hypermagnesaemic patients respectively. Significantly greater mortality and high SOFA score were observed among hypomagnesaemic group.

CONCLUSIONS

The incidence of hypomagnesemia is common in sepsis patients. It is mandatory to monitor serum magnesium levels in sepsis patients in order to prevent the serious manifestations of hypomagnesemia thereby influencing the final outcome.

KEYWORDS

Sepsis, Organ Dysfunction, Magnesium, Hypomagnesemia, Hypermagnesemia

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BACKGROUND

Sepsis is a commonly encountered fatal entity. In 2016, in order to detect sepsis and septic shock, clinicians used "Sepsis-3" clinical criteria which included a suspected infection and acute organ dysfunction, defined as an increase by two or more points from baseline (if known) on the sequential (or sepsis-related) organ failure assessment (SOFA) score. Sepsis is life-threatening organ dysfunction caused by dysregulated host response to infection.

Criteria for Sepsis

Suspected (or documented) infection and an acute increase in ≥2 sepsis-related organ failure assessment (SOFA) points. Systemic inflammatory response syndrome (SIRS) is defined as the presence of ≥2 of the following conditions.[1] (SIRS criteria)**.** One point for each of the following (score range, 0-4)-

1. Fever (oral temperature >38^0 C) or hypothermia (<36^0 C)
2. Tachypnoea (>20 breaths/min.)
3. Tachycardia (heart rate >90 beats / min)
4. Leucocytosis (>12,000/mm^3) or leucopenia (<4000/mm^3) or >10% bands;

SIRS can be due to infectious or non-infectious aetiology.[2] SOFA Score is a 24-point measure of organ dysfunction that uses six organ systems (renal, cardiovascular, pulmonary, hepatic, neurologic, hematologic), where 0–4 points are assigned per organ system.[1] Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities lead to substantially increased mortality risk. Criteria for septic shock include sepsis plus the need for vasopressor therapy to elevate mean arterial pressure to ≥65 mmHg with a serum lactate concentration >2.0 mmol/L despite adequate fluid resuscitation.

Magnesium has got a vital role in sepsis and SIRS especially in critically ill patients.[3] Hypomagnesemia results in functional impairment of various organs and systemic inflammatory response syndrome.[4] Magnesium deficiency also results in enhanced release of various cytokines resulting in serious inflammation and increases the risk of mortality.[5,6,7] Many factors lead to magnesium depletion in critically ill sepsis individuals admitted to ICU like decreased assimilation of magnesium, nasogastric aspiration, lack of adequate nutrient or total parenteral nutrition compounds, use of drugs like diuretics, gentamycin, amikacin and amphotericin-B which results loss of magnesium via kidneys. Magnesium is one among the frequently encountered electrolyte abnormalities yet it is overlooked among the ICU patients.[8] Many studies found that low serum magnesium had been associated with increased duration of hospital stay, mortality,[8,9] mechanical ventilation and increased duration of stay under mechanical ventilatory support among critically ill sepsis patient.[10,11,12]

This study was undertaken with the aim of estimating the level of serum magnesium in the patients who underwent treatment in the ICU satisfying the diagnostic criteria for sepsis and to evaluate the clinical outcome in these patients with relation to the serum magnesium levels.

METHODS

This study was undertaken in critical care unit of General Medicine Department, Silchar Medical College and Hospital, Silchar. This is a hospital based prospective observational study, conducted from April 2018 to September 2019. 333 patients admitted in the medical ICU during the study period were processed and 100 cases fulfilling the definition of sepsis were selected for study. Patient more than 14 yrs. of age suffering from various medical conditions with features of sepsis were included in the study.

Exclusion Criteria

- Patient diagnosed as hypomagnesaemic prior to ICU admission.
- Chronic kidney disease patients.
- Patient receiving blood products, magnesium or calcium infusion before sampling.
- Chronic diarrhoea or malabsorptive states.
- Patients on drugs affecting serum magnesium levels (loop and thiazides, long term Proton pump Inhibitor use like Omeprazole, antimicrobials like Amphotericin and Pentamide, Digitalis, Cyclosporine, Cisplatin and Mycophenolate mofetil.
- Patients admitted with the history of trauma.

Serum magnesium estimated with VITROS 5600 Auto Analyzer. Patients were subjected to a detailed clinical examination and all necessary investigations including estimation of ABG analysis, haematological and biochemical assay comprising of glucose, liver, renal and thyroid function test, and serum electrolytes including sodium, potassium, calcium and magnesium were assessed. Radiological investigations were performed as per indications. The following parameters were noted during the course of ICU stay and patients were classified according to the initial Mg++ level as- Hypomagnesemia (<1.7 mg/dl), Hypomagnesemia (1.7-2.4 mg/dl), and, Hypermagnesemia (>2.4 mg/dl).

Study Variables

Age, sex, diabetic status, alcoholic status, hypertensive status and SOFA Score.

Statistical Analysis

Analysis was performed with IBM "Statistical Package for the Social Sciences Software" (SPSS. Statistics. V21) statistical software. All quantitative data and continuous variables were represented as mean ± standard deviation if they were normally distributed. Differences in the normally distributed variables were assessed using the t-test and the CHI SQUARE TEST was used for testing the relationship and to assess p values between two variables. Probability value of $p < 0.05$ was considered statistically significant. Analysis of

the data collected was based on descriptive statistics. Figures, charts and tables were displayed wherever necessary.

RESULTS

Age Range	No. of Patients
<30	2
30-39	2
40-49	6
50-59	19
60-69	44
70-79	24
≥80	3
Total	100

Table 1. Age Distribution of Study Population

Magnesium Level	Mean Age ± SD (yrs.)
NormoMg	63.143 ± 13.435
HypoMg	60.793 ± 7.724
HyperMg	62.067 ± 9.639

Gender	Mean Serum Magnesium Level (mean ± SD)
Female	1.865 ± 0.630 mg/dl
Male	1.857 ± 0.668 mg/dl

Table 2. Gender and Serum Magnesium Distribution among Cases

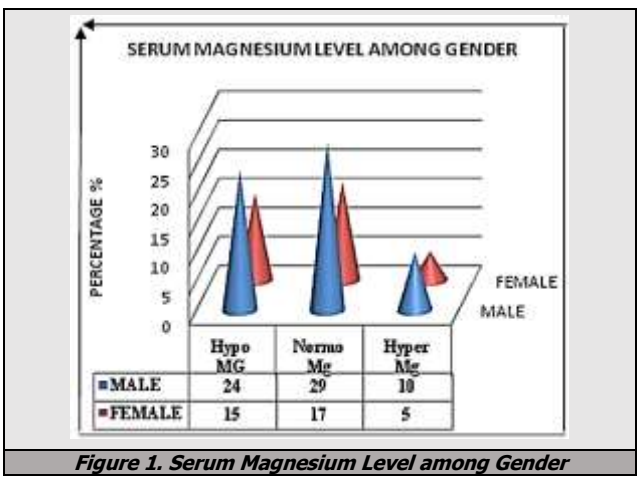

Figure 1. Serum Magnesium Level among Gender

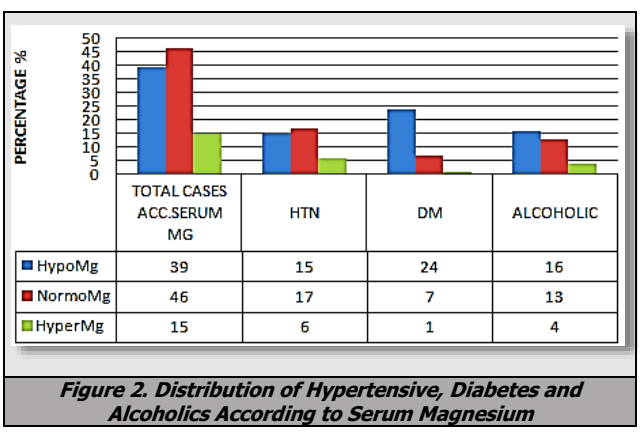

Figure 2. Distribution of Hypertensive, Diabetes and Alcoholics According to Serum Magnesium

The minimum and maximum age of the patients were 18 and 80 years respectively. The mean age of study group was 62.300 ± 11.4623 years. Out of 100 cases, 63% were male and 37% were females. About 38% of males and 40% of female were hypomagnesaemic. Among the study group, 38%, 32% and 33% were hypertensive, diabetic and alcoholic respectively. The chi-square test for association of hypertension and alcoholic status with serum magnesium level in the study population shows an insignificant P value >0.05. Above tables shows that, of all hypomagnesaemic patients, 62% were diabetic and the chi-square test for association of diabetic status and serum magnesium level among cases shows an significant p value <0.05.

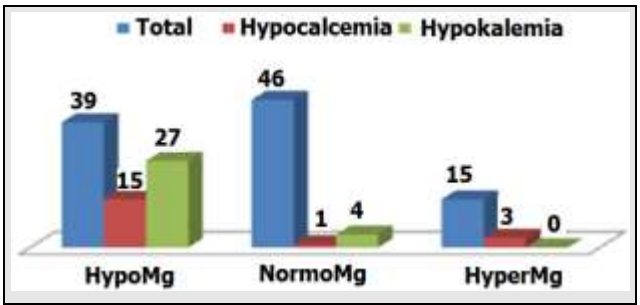

Figure 3. Serum Potassium and Calcium According to Magnesium Level

Among all cases, 31% and 19% were found to be hypokalaemic and hypocalcaemic patients respectively and 87% of hypokalaemic and 78.8% of hypocalcaemic patients were hypomagnesaemic and the chi-square test for association between hypokalaemic and hypocalcaemic status with serum magnesium level in the study population shows a significant p value of < 0.05.

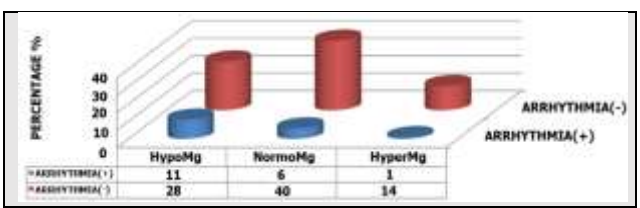

Figure 4. ECG Arrhythmia According to Serum Magnesium

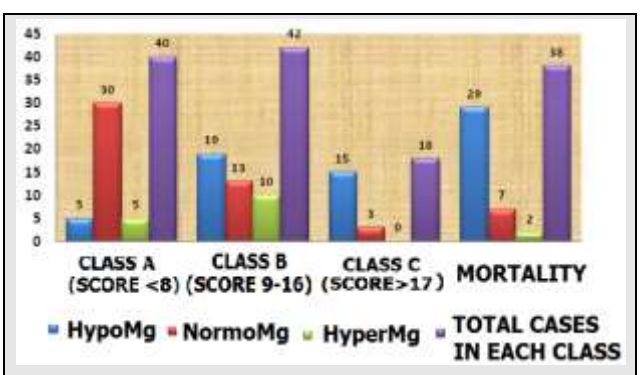

Figure 5. SOFA Score and Mortality

Our study shows that 18% of the study population were arrhythmic patient of which 38.8% were in the age range 60 to 69 years. The mean age of arrhythmic patient was 58.44 ± 13.92 years. The chi-square test for association of ECG changes and serum magnesium level in the study population shows an insignificant p value of >0.05. The chi-square test for association of SOFA score and mortality with serum magnesium level in the study population shows a significant p value of <0.05. Out of 100 cases about 38% patients were non-survivors, of which 67.85% of them were in the age range 60 to 69 years. The mean age of non-survivor patient is 61.393 ± 7.73 years.

DISCUSSION

Association of Magnesium Level with Diabetes Mellitus

This study got 32% of diabetic cases of which 68% were male and 32% were females which is statistically insignificant. Out of all hypomagnesaemic cases, 62% were diabetic and the association of diabetic status and serum magnesium level among cases shows a significant p value <0.05. Similar to our study, C. S. Limaye et al study reveals that patients with diabetes mellitus were more found to be hypomagnesaemic (27% vs. 14%) than non-diabetic. Nadler et al[13] also showed greater prevalence of hypomagnesemia in type 2 diabetics. In several studies it had been shown that type 2 Diabetics were found to be hypomagnesaemic. Magnesium deficiency results in impaired glucose homeostasis, insulin sensitivity[13] and higher risk of developing advanced diabetic retinopathy in type 2 diabetics.[14] The reasons behind magnesium deficiency among diabetes were not clear, few studies reported that it may be because of increased urinary excretion[15,16,17,18] poor absorption of magnesium compared to healthy individuals.[19] Hypomagnesemia in diabetics may be due to renal losses. There is a strong association between low serum magnesium and insulin resistance.[20] so hypomagnesemia itself can be both a cause and a consequence of diabetic complications.

Association of Serum Magnesium with Alcoholics

About 33% of study population are alcoholic, out of which maximum of 45.45% were in the age group 60 to 69 years. The mean age of alcoholic patient is 60.303 ± 11.8861. It had been found in our study that out of all hypomagnesaemic cases, 41% were alcoholic and out of all normomagnesaemic and hypermagnesaemic cases, 28% and 26.6% were alcoholic respectively which were statistically insignificant. The mean serum magnesium levels were 1.7900 ± 0.529 and 1.8937 ± 0.522 in alcoholic and non-alcoholic's respectively. The test for association of alcoholic status and serum magnesium level among all cases shows an insignificant p value >0.05. Numerous studies had revealed that alcoholic patients were associated with low serum level of magnesium. This is because alcohol, an important cause for cirrhosis of liver. In cirrhosis patient, the factors that are responsible for causing hypomagnesemia may be because of prolonged use of diuretics,[21] poor absorption of magnesium in distal jejunum, poor intake and malnutrition and more alcohol intake itself causes magnesium loss by diuresis. CS Limaye et al[13] reveals that the incidence of hypomagnesemia was higher in hypoalbuminaemic patients (p<0.05). Several other causes related to alcoholism leading to the magnesium deficit are vitamin D deficiency, alkalosis and phosphate deficiency. Lack of association in this study is explained by alcoholic in our study group were social drinkers. Duration and quantity of alcohol intake is required for development liver disease and consequently to develop hypomagnesemia.

Association of Serum Magnesium with Disease Severity

Disease severity in our study was assessed by SOFA score. The mean SOFA score of hypomagnesaemic, normomagnesaemic and hypermagnesaemic cases were 15.241 ± 6.174, 9.071 ± 5.898 and 9.733 ± 5.119 respectively. The test for association of SOFA score and serum magnesium among cases shows a significant p value of <0.05. Admission day SOFA score found to differ significantly with serum magnesium level. Patients who had gone to hypomagnesaemic state during their period of ICU stay were noted to have higher SOFA score on admission. Similar to our study, Chen M, et al. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2015 also showed increased SOFA score in hypomagnesaemic cases. The study also had reported that the hypomagnesaemic group was found to have higher SOFA scores (6.86 ± 3.12 vs. 5.46 ± 2.75, t = -2.930, P = 0.004),

Association of Serum Magnesium with Serum Potassium and Calcium

In the present study, 31% and 17% of the total cases were hypokalaemic and hypocalcaemic respectively; maximum were in the age range 60 to 69 years. The mean age of hypokalaemic and hypocalcaemic cases was 60.968 ± 7.54. And 57.647 ± 12.12 years respectively. The test for association of hypokalaemic and hypocalcaemic status with hypomagnesemia shows a direct correlation which were statistically significant (p value <0.05). Similar to our study, several studies had reported that hypomagnesemia is more associated with electrolyte abnormalities mainly potassium and calcium like the study by S. Sudha, S. Bharanidharan et al[22] where they found hypomagnesaemic patients had more incidences of electrolyte abnormalities such as hypokalaemia (20% vs 6.25%) and hypocalcaemia (33% vs. 3%) than normomagnesaemic patients. C S Limaye et al in their study revealed that the occurrence of hypocalcaemia was greater among patients with lower serum magnesium (p<0.05). In contrast Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.[23] reported in their study that the hypomagnesaemic patients had no statistically significant difference in levels of other electrolytes (sodium, potassium, calcium, phosphorus) when compared with normomagnesaemic patients.

Impact of Serum Magnesium on Mortality

Out of 100 cases about 38% were non-survivors, of which 67.85% were in the age range 60 to 69 years. The mean age of non-survivor patients was 61.393 ± 7.73. The mean serum magnesium among survivors and non survivors were 2.074722 ± 0.424430 and 1.3061 ± 0.307 respectively with the former showing a relatively normal value in comparison to the later. The association of mortality and serum magnesium level in our study population was statistically significant (p<.05). In the present study, the majority of deaths occurred in the hypomagnesaemic group in comparison to normomagnesemia and hypermagnesemia, a fact that is also endorsed by studies conducted by other researchers. Soliman et al[24] found that cases which

advanced to hypomagnesemia during their stay in ICU had greater mortality. CS Limaye et al observed that the death rate among hypomagnesaemic patients were significantly higher than (31%) normomagnesaemic and (43%) hypermagnesaemic patients. Significant association between mortality and hypomagnesaemia was found ($p<0.05$). Guerin et al[25] had revealed that there is no difference in mortality among hypomagnesaemic and normomagnesaemic groups (18% vs. 17%), instead they found a greater mortality rate with hypermagnesaemic group.

CONCLUSIONS

Hypomagnesemia is a frequent occurrence and is an important prognostic factor among critically ill serious patients in Medical ICU. Serum magnesium has got inverse relation with SOFA score and vice versa. Thus, hypomagnesemia acts as disease severity index and carries a worse prognosis and leads to unfavourable outcome. Patients with hypomagnesemia had a higher mortality rate. Hypomagnesemia also had a strong association with hypocalcaemia and hypokalaemia. Diabetic patients are more prone to develop hypomagnesemia.

Limitations

The major limitation was small number of patients studied. Total serum magnesium instead of ionized magnesium is measured. Lack of clear-cut guidelines for treatment of magnesium abnormalities. This is a descriptive non interventional study. A large multicentre randomized double-blind interventional trial for magnesium administration among seriously ill patients with hypomagnesemia is required in future to evolve a consensus guideline for management of hypomagnesemia.

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