

Original Article

Hypomagnesemia is associated with increase in mortality and morbidity in ICU: Can serum magnesium level be used as prognostic marker in critically ill ICU admitted patients?

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Abstract

Objective: Hypomagnesemia is one of the common electrolyte disorders found in critically ill patients. It is often an incidental finding and usually its importance is ignored. This study was designed to assess the significance of the "impact of hypomagnesemia" on the mortality and morbidity of the ICU patients. Hence the efficacy of hypomagnesemia as prognostic marker was also tested.

Method: Prospective cohort study done at the department of Critical Care Medicine, of a tertiary care hospital in the city of Dhaka, Bangladesh (from January 2014 to December 2014) aiming to find out of the differences in mortality & morbidity between two groups of patients one with low and other with normal Mg level.

Result: 95 adult ICU admitted patients were included in the study and 38% of the study subjects were found to be Hypomagnesemic. The Hypomagnesemic group of patients needed more frequent ventilator support (75% vs 52.54%, $p < 0.02$) and the duration of mechanical ventilator support was also prolonged (3.88 ± 4.10 vs 2.25 ± 3.18 , $p < 0.04$, in days). Hypomagnesemic group also needed prolonged ICU stay (9.13 vs 6.27, $p < 0.01$) and total hospital stay (14.94 vs 10.47, $p < 0.007$, days). Hypomagnesemic group of patients had more abnormal total leukocyte count (69.4% vs 47.5%, $p < 0.05$) and more frequent use of inotropic support (61.1% vs 38.9%, $p < 0.05$). The 28 days mortality rate in Hypomagnesemic patients were also high (33.3% vs 11.86%, $p < 0.01$).

Conclusion: In this study it was observed that Hypomagnesemia was significantly associated with adverse outcome. So it is better not to ignore this important confounder to predict the outcome of the critically ill ICU admitted patient. Considering the increasing demand of more accurate prognostic marker in critically ill patient, it maybe the high time to utilize serum Mg level systematically for outcome prediction.

Key words: Hypomagnesemia, ICU, mortality and morbidity.

Introduction:

Magnesium is a very important cation of the human body. It is the fourth most abundant cation in the body and the second

most abundant intracellular cation after potassium. Magnesium (Mg) has a very important role in transfer, storage and utilization of energy. More than 300 enzyme systems are regulated and catalyzed by it.^{1, 2} Magnesium deficiency is known to be associated with a number of electrolyte abnormalities e.g. hypokalemia, hypocalcemia, hyponatremia and hypophosphatemia. It is also associated with a lot of clinical manifestations such as atrial and ventricular arrhythmias, cardiac insufficiency, coronary vasospasm, sudden death, skeletal and respiratory muscle weakness, bronchospasm, tetany, seizures and other neuromuscular abnormalities.^{3,4,5,6} It serves as a co-factor for several enzymes required for electrolyte homeostasis and is also necessary for membrane stability, cell division, and generation of action potentials.⁷

Malnutrition in the intensive care unit (ICU) patients is a widely acknowledged problem that may intensify underlying illnesses and increase the risk of complications.⁸ Nutritional assessment upon admission to the ICU is necessary to identify patients at risk and to guide nutritional support during ICU stay.⁹ This disorder is often overlooked, although it should probably be searched for systematically because of its significance in predicting prognosis of patients.¹⁰

Magnesium deficiency commonly occurs in critical illnesses and correlates with higher mortality rate and worse clinical outcome in the intensive care unit patients.^{11,12} Magnesium

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also regulates enzymes controlling intracellular calcium, which ultimately affects smooth muscle vasoconstriction, important to the underlying pathophysiology of several critical illnesses.¹¹ Magnesium deficiency results primarily from gastrointestinal or urinary Mg losses, but malnutrition and decreased dietary Mg intake may hasten the development of Mg depletion.¹³ Magnesium therapy is supported by clinical trials in the treatment of symptomatic hypomagnesemia and preeclampsia and is recommended for torsade de pointes.¹¹

Hypomagnesemia occurs in 40% of the hospitalized patients,⁵ approximately 60% of postoperative patients,⁷ about 65% of medical ICU patients,¹⁴ and up to 90% of surgical ICU patients.¹⁵ Hypomagnesemia has been implicated in the development of cardiovascular dysfunction and the systemic inflammatory response syndrome in ICU patients.¹⁵ This study has been conducted to determine the level abnormalities in serum magnesium in critically ill patients at the time of initial ICU evaluation and to study the association of these values with patient's prognosis in terms of mortality and morbidity.

The patients who are admitted to ICU are unstable & critically ill. Most of them need extensive resuscitation & organ support along with expensive interventions & medications. Most of the times it is very important to undergo an initial assessment & to calculate a predictive outcome of the patient. The calculated predicted outcome is then applied for the priority selection of patient's interventions & medications. In a third world country like Bangladesh where most of the people have very low income & limited resources, the calculated outcome prediction may have a great value to utilize the limited resource judiciously.

Till date there are many different scoring systems to predict the outcome of the critically ill ICU patients, but magnesium level is not included to any one of them. Recently the researchers are showing more interest on serum Magnesium level as a predictive marker. Yet more research needed especially in Bangladesh. Moreover this study may help to create physicians awareness to keep an eye on serum magnesium level which is frequently ignored till today.

MATERIALS AND METHODS:

It was a Prospective cohort study where samples were collected by consecutive sampling method. The study was done during the period of January 2014 to December 2014.

The all new admission at intensive care unit who are over 18 years and stays at ICU > 24 hrs were included in the study. The patients recently treated with magnesium (within last 7 days) and with Increased serum creatinine (Serum creatinine > 1.2 mg/dl) during admission were excluded from the study.

This prospective cohort study was carried out at the Department of Critical Care Medicine, at a tertiary care hospital in Dhaka city, aiming at finding out the significant mortality & morbidity differences between low & normal magnesium level groups in critically ill ICU admitted patients. The cohort was selected from the critically ill ICU

admitted patients by some selection criteria. From the cohort one group was exposed to hypomagnesemia and another group was not exposed to hypomagnesemia. The exposed and unexposed groups were identical to each other. They were all selected after ICU admission and they did not show significant difference of their diagnosis patterns, age distribution and initial mean APACHE II score. After selection of cohort they were followed up for 28 days. The mortality & morbidity within 28 days were recorded. The morbidity was defined as the length of ICU and hospital stay, need and duration of mechanical ventilator support and the occurrences of severe sepsis/septic shock. The study period was of 12 months.

From the study population a total 8 patients were found to be hypermagnesemic (S. Mg level > 2.4 mg/dl). The hypermagnesemic patients were excluded from the study calculation. Normal plasma magnesium concentration was defined as 1.7-2.4 mg/dL (0.7-0.9 mmol, or 1.5-2.0 mEq/L). Hypomagnesemia was defined as the Mg level <1.7 mg/dl & normomagnesemia was defined as the Mg level between 1.7 to 2.4 mg/dl. The overall outcome variables were statistically analyzed to find out any significant difference between the groups.

As it was a prospective cohort study we included as many patients as we could at the given time frame. The cost of the relevant laboratory tests were carried out by the patients as part of their routine management (All the required tests are usually routinely done in the department).

All the enrolled subjects received treatments according to the ICU protocol. Study enrollment did not change the normal treatment procedure. All hypomagnesemic patients were routinely treated with I/V MgSO₄. The dose was, In case of mild hypomagnesemia, 4% MgSO₄ (w/v) 100ml I/V daily, whereas the same dose was given 12 hourly in case of severe hypomagnesemia. The serum levels were repeated to reassess the Mg status and any persistent hypomagnesemia or iatrogenic hypermagnesemia were handled accordingly.

The outcome was measured by 28 days mortality, length of ICU and hospital stay, need of inotropic support, need and duration of mechanical ventilator support. Appropriate data were collected by using a preformed data sheet. Other necessary data were collected from history sheet and investigation reports.

Collected data were processed and analyzed using Statistical Packages for Social Sciences (SPSS) software version 17. Parametric variables were expressed as mean± standard deviation; non parametric variables were presented as frequency and percentage. Spearman's co-relation test was used for correlation analysis, P value <0.05 was considered statistically significant.

Ethical approval from the proper ethical approval committee was obtained prior to the commencement of the study. Informed written consents were taken from the appropriate persons. The researcher only collected, processed, analyzed & interpreted the data. Patient's confidentiality was strictly maintained.

RESULTS:

During the study period data was collected from 95 study samples. Total 38% (n=36) study subjects had hypomagnesemia and 62% (n=59) had normal magnesium level. From the study subjects 51 patients were male and 44 patients were female. Total 38.9% of the male patients were hypomagnesemic whereas that was present in 61.1 % cases of

female subjects. That means Hypomagnesemia was significantly high in female subjects ($p < 0.05$).

The hypomagnesemic and normomagnesemic group of patients were identical to each other. The mean age and mean APACHE II score did not show significant difference between two groups. The diagnosis patterns and co morbidities also did not show any significant difference in chi square test.

Table 1: Shows distribution the disease between two groups:

Systems	Magnesium status		Total	*p value
	Hypomagnesemia	Normomagnesemia		
Pneumonia	05(13.89)	17(28.81)	22	
COPD	02(5.56)	05(8.47)	07	
Stroke	08(22.2)	10(16.9)	18	
CLD	04(11.1)	08(13.6)	12	0.21
Post surgical	08(22.2)	04(6.8)	12	
Others	09(25.0)	15(25.4)	24	
Total	36(100)	59(100)	95	

(Percentages are mentioned within parenthesis)

*Chi-square test

Table 2: Demographic data, disease severity, and outcome according to Mg at admission:

	Low Mg	Normal Mg	p Value
No. of patients n(%)	36(38%)	59(62%)	-
Age, yrs	52.47(±20.84)	55.10(±17.89)	-
APACHE II score (Mean ± SD)	15.75(±6.10)	14.92(±7.91)	0.58
Serum sodium (Mean ± SD)	129.75(±11.87) mmol/L	137.66(±9.52) mmol/L	0.001
Serum potassium (Mean ± SD)	3.52(±0.78) mmol/L	3.95(±0.56) mmol/L	0.003
Serum calcium (Mean ± SD)	7.67 (±1.13) mg/dl	8.22(±0.94) mg/dl	0.01
CRP (Mean ± SD)	167.77(±119.61)	117.09(±96.93)	0.02
Albumin (Mean ±SD)	2.66(±0.72)	2.98(±0.52)	0.01
Abnormal total leukocyte count, n (%)	69.4%	47.5%	0.03
Need ventilator, n (%)	75%	52.54%	0.02
Inotropic support, n(%)	61%	38.9%	0.03
Duration of MV, days (Mean ±SD)	3.88(±4.10)	2.25(±3.18)	0.04
ICU stay days (Mean ±SD)	9.13(±5.70)	6.27(±5.59)	0.01
Hospital stay days (Mean ±SD)	14.94(±7.78)	10.47(±7.60)	0.007
Mortality, n (%)	33.3%	11.86%	0.01

The hypomagnesemic patients needed mechanical ventilator support more frequently (75% vs 52.54%) and for more prolonged duration (3.88± 4.10 vs 2.25 ± 3.18) than the normomagnesemic group. The occurrences of sepsis and septic shock were also likely to be high in Hypomagnesemic group of the study subjects as there were increased frequency abnormal total leukocyte count (69.4% vs 47.5%, $p < 0.05$)

and more frequent requirement of inotropes (61.1% vs 38.9%, $p < 0.05$). The mean length of ICU (9.13 vs 6.27, $p < 0.01$) and hospital (14.94 vs 10.47, $p < 0.007$, days) stay (in days) were also high in the hypomagnesemic group. The mortality rate was also high in Hypomagnesemic group of the study subjects (33.3% vs 11.86% $p < 0.01$), the odds ratio of hypomagnesemia for mortality in this study is 3.71.

DISCUSSION:

In human body Magnesium is the 4th most abundant cation.¹⁶ Though its deficiency is a common electrolyte imbalance, till date it is under diagnosed. Magnesium depletion can be present in about one half of all ICU patients. Many study showed that these patients may have significantly higher morbidity and mortality. To identify this type of electrolyte disorder we have to look for the risk factors for this problem. These include poorly controlled diabetes mellitus, alcohol ingestion, severe diarrhea and steatorrhea.¹⁷ Use of a number of pharmacologic agents that induce renal Mg wasting (such as diuretics and aminoglycosides) and sepsis.¹⁸ Manifestations of Mg deficiency include hypokalemia, hypocalcemia, neuromuscular hyper excitability, respiratory muscle weakness and intractable arrhythmias. Mg deficiency may also play a role in the genesis of myocardial ischemia.^{15, 18}

The aim of this study was to find the prevalence of hypomagnesemia in critically ill patients and to evaluate the relationship of magnesium level to organ failure, length of ICU and hospital stay, electrolyte disturbance, need and duration of mechanical ventilation and 28 days mortality rate. That means to evaluate the morbidity and mortality in relation of magnesium level.

This study found that in case of hypomagnesaemia mean age was 52.47(±20.84) years and in case of normomagnesemia it was 55.10 (±17.89) years and the mean age did not show significant difference statistically. Hypomagnesaemia had female preponderance (61.1% vs 38.9%, p<0.05). In a study by Mousavi et al.¹⁹ the mean age of hypomagnesemic patients was found 60.54 ± 2.06 yrs and there were 252 males (55.7%) and 121 (44.3%) females.

In the present study 38% of the patients had hypomagnesemia and 62% had normomagnesemia. Musavi et al.¹⁹ study found 33% of the patients having hypomagnesemia and 53.8% normomagnesemia is comparable with our study.

In the current study we also found that there was no significant difference between hypo and normomagnesemic group in terms of disease distribution, common co morbidity patterns and mean APACHEII score. Those two groups also did not differ significantly in terms of mean age.

In this study it was found that, there was significantly more use of mechanical ventilator support in hypomagnesemic patient group compared to normomagnesemic (75% vs 52.54%) group. Musavi et al.¹⁹ also found increased rate of mechanical ventilator use in hypomagnesemia (91.1% vs 66.7%). Both the studies showed that the patients with lower serum magnesium levels had increased frequency of mechanical ventilator use.

In case of severe sepsis and septic shock the current study found that, abnormal leukocyte count was more frequent in hypomagnesemia (69.4% vs 47.5%, p<0.05) and they also needed inotropic support more frequently (61.1% vs 38.9%, p<0.05) than normomagnesemia, which ultimately indicates that the hypomagnesemic patients are more prone to develop sepsis and septic shock. Similar result was found by

Limaye et al.²⁰ They showed that occurrence of sepsis were more common in hypomagnesemic patients, among the 29 patients with sepsis hypomagnesemia was higher (20/29 or 69%) as compared to normomagnesemia (8/29 or 28%). The present study found that hypomagnesemia is significantly associated with more frequent use of inotropic support which was 61.1% in hypomagnesemic patients (p<0.05). Compared with Safavi and Honarmand et al.²¹ It was found that severe sepsis and septic shock (48%) were most common in hypomagnesemia. The occurrence of hypomagnesemia also was particularly common in patients with sepsis and septic shock. Sepsis was one of the independent risk factors for developing hypomagnesemia during the ICU stay. Magnesium may play an important role in sepsis, as magnesium ions are essential for several important immunologic functions and serve as a natural calcium antagonist, an important step in propagating cellular injury.²² In animal models, magnesium deficiency increases the production of inflammatory cytokines with increase in lethality associated with endotoxin challenge.^{23,24} Showed that progressive magnesium deficiency and hypomagnesemia are strongly associated with increased mortality in experimental sepsis and magnesium replacement therapy provides significant protection from an endotoxin challenge.

Mean length of mechanical ventilation days was higher in hypomagnesemic patients than normomagnesemic (3.88±4.10 vs 2.25±3.18) group. The mean mechanical ventilation days was inversely correlated with serum magnesium level (p>0.04). The mean length of ICU stay was 9.13(±5.70) days in hypomagnesemia. The mean length of hospital stay was 14.94(±7.78) days in hypomagnesemia and 10.47(±7.60) days in normomagnesemia (p>0.007). In the study carried out by Soliman et al.¹⁸ the patients with hypomagnesemia had longer duration of stay in the ICU. They also found that hypomagnesemia was an independent risk factor for the longer ICU stays.

In this study there was significantly increased mortality rate in hypomagnesemic patients compared to normomagnesemia (33.3% vs 11.86%; p<0.01). The relationship between hypomagnesemia and the mortality rate varies from study to study. A higher mortality rate was detected in hypomagnesemic patients when compared with normomagnesemic patients by Chernow et al.⁷ (41% vs. 13%), Rubeiz et al.²⁵ (46% vs. 25%) and Safavi and Honarmand et al.²¹ (55% vs. 35%). But Guérin et al.²⁶ found no difference in ICU mortality between hypomagnesemic and normomagnesemic groups (18% vs. 17%). Soliman et al.¹⁸ observed that patients who develop ionized hypomagnesemia during their ICU stay have higher mortality rates (2-3 times higher). Dabbagh et al.¹² observed higher mortality rates in critically ill-patients with daily magnesium supplementation index (DMSI) <1 g/day in comparison to DMSI > 1 g/day (43.5% vs. 17%). Limaye et al.²⁰ observed that mortality rate in hypomagnesemic group was 57% when compared with 31% in the normomagnesemic group. Our results showed significant difference in ICU mortality between patients with hypomagnesemia and normomagnesemia on admission.

SUMMARY:

This prospective cohort study was carried out in the Department of Critical Care Medicine (ICU), in a tertiary care hospital in Dhaka city, aiming at finding out the significant mortality & morbidity differences between low & normal magnesium level group, in critically ill patients admitted in ICU. A cohort from critically ill ICU admitted patients were selected by some selection criteria. The cohort had two groups, one of them had hypomagnesaemia and another group had normomagnesaemia. The cohort was followed up for the next 28 days. The 28 days mortality & morbidity was assessed & recorded. The mortality was defined as the mortality within 28 days of ICU admission. The morbidity was defined as the length of ICU and hospital stay, need for mechanical ventilation and duration of ventilation support and need for inotropic support. The two cohorts were similar to each other in terms of age, co morbidity, disease distributions and initial mean APACHE II score as statistically they showed no significant differences. The study period was of 12 months.

Total 38% of the study subjects were Hypomagnesemic and this group of patients needed mechanical ventilator support more frequently (52.54% vs. 75%, $p < 0.02$), required prolonged ventilator support (3.88 ± 4.10 vs 2.25 ± 3.18 , $p < 0.04$), prolonged ICU stay (9.13 vs 6.27, $p < 0.01$) and prolonged hospitalization (14.94 vs 10.47 , $p < 0.007$) compared to normomagnesaemia (in days). Incidence of severe sepsis and septic shock were also more common in hypomagnesaemia as it had significant association with abnormal total leukocyte count (69.4% Vs 47.5%, $p < 0.05$) and more frequent use of inotropic support ($p < 0.05$). The mortality rate in hypomagnesemic patients was also significantly high (33.3% vs 11.86% $p < 0.01$).

CONCLUSION :

In this study it was observed that hypomagnesaemia is a common electrolyte imbalance in our study subjects. After summarizing all the observations of this study it can be stated that hypomagnesaemia is significantly associated with increased mortality and morbidity.

RECOMMENDATIONS :

In this study we found that serum hypomagnesaemia is a very common disorder in critically ill patients and it has significant relationship with the outcome of ICU patients, even after proper correction. So we can make the following recommendations.

- Firstly, every ICU admitted patient should be checked for serum Mg level routinely.
- Secondly, we may propose a modified APACHI score which should include separate point for Serum Mg level.
- Finally, as there was limitation of time and budget our sample size was very small to draw a final conclusion. A general consensus is also important to develop a widely accepted modified scoring system. Further multicentre study with large sample size may be done in future to overcome the problem.

Limitations of our study

1. It was a single center study.
2. Short duration of study.
3. Fewer number of study subjects.
4. Serum Mg level should have been substratified among the hypomagnesaemia group to increase the sensitivity of cut off value of serum Mg level to improve the prognostic accuracy.

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