Hypomagnesemia in Critically Ill Medical Patients

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Abstract

Background: Hypomagnesemia is an important but underdiagnosed electrolyte abnormality in critically ill patients. There are many studies to find the prevalence of hypomagnesemia and its effects on mortality and morbidity in these patients. Most of these studies have been carried out in intensive care units caring for patients with medical and surgical conditions and postoperative patients or those in respiratory intensive care unit, or critically ill cancer patients. This study was carried out on patients admitted to the medical acute care unit in a major tertiary care hospital.

Aims and Objectives

To study serum magnesium levels in critically ill patients and to correlate serum magnesium levels with patient outcome considering the following parameters: length of stay in MICU, need for ventilatory support, APACHE score and mortality.

To identify the primary medical conditions associated with abnormalities of serum magnesium. To identify the factors predisposing or contributing to hypomagnesemia in critically ill patients admitted in a medical intensive care unit.

To detect other electrolyte abnormalities associated with hypomagnesemia, if any.

Results: On admission to MICU 52% patients had hypomagnesemia, 7% patients had hypermagnesemia and 41% patients had normomagnesemia. The patients with hypomagnesemia had higher mortality rate (57.7% vs 31.7%), more frequent need for ventilatory support (73% vs 53%), longer duration of mechanical ventilation (4.27 vs 2.15 days), more frequently had sepsis (38% vs 19%), hypocalcemia (69% vs 50%) and hypoalbuminemia (80.76% vs 70.8%). Patients with diabetes mellitus had hypomagnesemia more frequently (27% vs 14%). The duration of stay in the MICU or APACHE score on admission did not vary in patients with low or normal magnesium.

Conclusions: There was a high prevalence of hypomagnesemia in the critically ill patients. Hypomagnesemia was associated with a higher mortality rate in critically ill patients. The need for ventilatory support was significantly higher in hypomagnesemic patients. Hypomagnesemic patients required ventilator support for longer duration. Hypomagnesemia was commonly associated with sepsis and diabetes mellitus. The duration of MICU stay and APACHE score on admission did not vary in patients with low magnesium and normal magnesium. Hypomagnesemia is more commonly seen in patients with hypocalcemia and hypoalbuminemia.

Methods

A prospective observational study was carried out in the Medical Intensive Care Unit of a tertiary care hospital from April 2004 to May 2005. The study was approved by the Institutional Ethics Committee. Hundred patients admitted to the MICU for critical illness were included in the study after a written informed consent was obtained. These included patients suffering from various medical conditions namely severe infections like complicated malaria, leptospirosis, tetanus, urinary tract infections, cellulitis, meningitis, pneumonia, tuberculosis and mucormycosis; hepatic failure due to acute viral hepatitis or cirrhosis; acute renal failure due to hypovolemia, infections; chronic renal failure; respiratory failure due to chronic obstructive lung disease, interstitial lung disease and ARDS; congestive cardiac failure due to ischemic heart disease or valvular heart disease; cerebrovascular accident secondary to cerebral infarct or hemorrhage; poisonings including organophosphate compounds; snake bite; acute pancreatitis; Guillain-Barre syndrome; malignancy; status epilepticus and diabetic ketoacidosis. Patients who had received magnesium prior to transfer to MICU were excluded.

A blood sample was collected for estimation of serum total magnesium levels on admission to MICU. History and clinical findings were noted for each patient. Other hematological, biochemical and radiological investigations were performed as indicated in every patient. APACHE score was calculated for...
each patient on the day of admission to MICU using APACHE II scoring system. The study did not interfere with the patient management in MICU. Serum total magnesium level was determined by colorimetric method using Titan yellow (method described by Neill and Neely). The normal value of serum total magnesium was between 1.7 to 2.4 mg/dl. For quantitative data the normal deviate (z) test was applied to find the significance of difference between two means. For qualitative data chi-square test was applied to find the significance of difference between two proportions and to find the association between two variables.

**Results**

On admission, 52% (52/100) patients had hypomagnesemia, 7% (7/100) had hypermagnesemia and 41% (41/100) had normal serum magnesium levels. The lowest serum magnesium value recorded was 1.1 mg/dl while the highest value was 2.7 mg/dl. The range of duration of stay in MICU varied from 1 day to 35 days with mean of 7.06 days. The mean duration of stay in MICU of patients with low serum magnesium was 8±7.92 days while that of patients with normal serum magnesium was 6.17±3.84 days and that of patients with high serum magnesium was 5.28 days. The difference was not statistically significant (p>0.05).

73% (38/52) patients with hypomagnesemia needed mechanical ventilatory support, while only 53% (22/41) of the normomagnesemic group needed ventilatory support. The difference is statistically significant (p<0.05). The mean duration of ventilatory assistance for the hypomagnesemic group was 4.27±5.01 days and that for normomagnesemic group was 2.15±3.36 days. Hypomagnesemic patients required ventilatory support for greater number of days as compared to the normomagnesemic patients (p<0.05). The mean APACHE score on admission in the hypomagnesemic group was 14.52±8.23 while that of normomagnesemic group was 15.75±7.60. The difference was not statistically significant. The mortality rate in hypomagnesemic group was 57.7% (30/52); whereas in normomagnesemic group was 31.7% (13/41). Significantly greater mortality rate was observed in hypomagnesemic patients as compared to normomagnesemic patients (p< 0.05). Three patients who died had hypermagnesemia.

Of 52 patients with hypomagnesemia 36 (70%) also had hypocalcemia. Of 48 patients with normal or high magnesium levels, 24 (50%) had hypocalcemia. The incidence of hypocalcemia is significantly higher in patients with hypomagnesemia (p<0.05). Seventy six patients had low serum albumin level of which 42 (55%) had low serum magnesium levels and 34 (44%) had normal magnesium levels. Twenty four patients had normal serum albumin level of which 10 (42%) had hypomagnesemia and 14 (58%) had normal magnesium level. The incidence of hypomagnesemia was significantly higher in hypoaalbuminemic patients (p< 0.05). Twenty five patients had documented hypokalemia on admission, of which 12 had hypomagnesemia, 11 had normomagnesemia and 2 had hypermagnesemia which was not statistically significant.

The occurrence of sepsis was more common in hypomagnesemic patients (20/52 or 38%) as compared to normomagnesemic (8/41 or 19%) and hypermagnesemic patients (1/7 or 14%). Also among the 29 patients with sepsis, the incidence of hypomagnesemia was higher (20/29 or 69%) as compared to the incidence of normomagnesemic (8/29 or 28%) and hypermagnesemic (1/29 or 3%). Out of 20 patients with diabetes mellitus, 14 (70%) had hypomagnesemia and 6 (30%) patients had normomagnesemia. Among 80 patients who were non-diabetic, 38 had hypomagnesemia (47%). Thus diabetic patients have higher incidence of hypomagnesemia as compared to the non-diabetic patients (p< 0.05). The mean random blood sugar in hypomagnesemic diabetic patients was 255 mg/dl; while that in normomagnesemic patients with diabetes was 227 mg/dl. However the difference was not statistically significant. Twenty one patients had history of alcoholism of which 11 had hypomagnesemia (52%) and 10 patients had normal magnesium. Of the 79 non-alcoholic patients 41 had hypomagnesemia (51%). Thus a higher incidence of hypomagnesemia in individuals who are chronic alcoholics though reported in literature was not found in this study.

Results of this study are summarized in Table 1.

**Discussion**

Magnesium is the second most common intracellular cation. It plays an important role in homeostasis. Magnesium is the cofactor for most of the adenosine triphosphate (ATP) reactions because it is the ATP–magnesium complex that is bound to and hydrolyzed by the enzymes. Many factors contribute to hypomagnesemia and magnesium deficiency in critically ill patients; like impaired GI absorption, nasogastric suction, poor content of magnesium in feeding formulae or TPN solutions, administration of drugs like diuretics, aminoglycosides, Amphotericin-B which cause renal wasting of magnesium. Hypermagnesemia is reported less commonly and it is mostly due to renal failure or iatrogenic.

Table 2 gives the prevalence of hypomagnesemia and hypermagnesemia in various studies carried out previously in critically ill patients all over the world and the results of this study. Most of the studies carried out previously have measured total serum magnesium. The prevalence of hypomagnesemia was in the range of 14% to 70%. In the present study 52% patients from ICU were found to have total serum magnesium less than normal. Few studies have measured RBC magnesium as it is a better index of intracellular magnesium as compared with serum magnesium.

It is seen from the table that in the two studies which had measured ionized magnesium, (Huijigen et al and Soliman et al) the prevalence of hypomagnesemia was much lower (14% and 18% respectively) whereas in the studies which have measured total serum or RBC magnesium the prevalence of hypomagnesemia was higher (20% to 70%). Zaloga GP, Zedem et al 15

<table>
<thead>
<tr>
<th>Table 1 : Results of present study</th>
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</thead>
<tbody>
<tr>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>Prevalence</td>
</tr>
<tr>
<td>Mortality rate</td>
</tr>
<tr>
<td>Need for ventilator</td>
</tr>
<tr>
<td>Duration of ventilator</td>
</tr>
<tr>
<td>MICU stay (days)</td>
</tr>
<tr>
<td>APACHE score</td>
</tr>
<tr>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Hypoaalbuminemia</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Alcoholism</td>
</tr>
</tbody>
</table>
Wilkens R al 18 had measured ultrafiltrable magnesium which approximates ionized magnesium.

Hypermagnesemia is found less commonly than hypomagnesemia. It is reported in the range of 4 to 14% in literature and in this study hypermagnesemia was seen in 7% of patients.

The relationship between hypomagnesemia or hypermagnesemia and mortality rate varies from study to study. A higher mortality rate was detected in hypomagnesemic patients as compared to normomagnesemic patients by Chernow et al 19 (41% vs 13%), Rubiez et al 10 (46% vs 25%) and Safavi et al 11 (55% vs 35%). Guerin et al had found no difference in ICU mortality between hypomagnesemic and normomagnesemic groups (18% vs 17%); but noted a higher mortality rate among hypermagnesemic patients. 11 Soliman et al observed that patients who develop ionized hypomagnesemia during their ICU stay have higher mortality rates. 11 In the current study the mortality rate in hypomagnesemic group was 57% which is significantly higher as compared to 31% in the normomagnesemic group and 43% in the hypermagnesemic group (p<0.05). The higher mortality rates in the hypomagnesemic patients can be explained by greater incidence of electrolyte abnormalities especially hypokalemia and cardiac arrhythmias and a strong association of hypomagnesemia with sepsis and septic shock which is a common cause of death in ICU patients.

Hypomagnesemia is known to cause muscle weakness and respiratory failure. It is one of the factors causing difficulty in weaning the patient from the ventilator. 6 In the current study it has been seen that patients with hypomagnesemia needed ventilatory support more frequently and for a longer duration. In a study performed by Fiaccordori et al 7 it was found that patients with low muscle magnesium were on ventilatory support for more number of days. In a study carried out by Molloy et al 8 magnesium was administered to the hypomagnesemic patients and normomagnesemic controls and improvement in respiratory muscle weakness was noted in hypomagnesemic patients while there was no effect on normomagnesemic controls. Safavi et al had found that in patients with hypomagnesemia the duration of mechanical ventilation was longer (7.2 vs 4.7 days, p < 0.01). Munoz et al 9 found that in the neonatal ICU the patients with hypomagnesemia required ventilatory assistance more frequently than normomagnesemic patients.

In the study carried out by Soliman et al 14 there was no difference in the length of ICU stay among the three groups. However the patients who developed hypomagnesemia during their ICU stay had longer duration of stay in the ICU. They also found the length of ICU stay as an independent risk factor for development of hypomagnesemia. In the present study also there was no difference in length of ICU stay among hypomagnesemic, normomagnesemic, hypermagnesemic groups. Similarly APACHE score on admission did not differ significantly among the three groups. In the studies performed by Soliman et al, Guerin et al, Rubiez et al, all of them had noticed that APACHE scores in the three groups were comparable to each other. Soliman et al found that those patients who develop ionized hypomagnesemia during their ICU stay had higher APACHE score on admission.

Magnesium plays an important role in sepsis. Hypomagnesemia is associated with increased release of endothelin and proinflammatory cytokines. 12 Salem et al 12 showed that progressive magnesium deficiency and hypomagnesemia are strongly associated with increased mortality in experimental sepsis and magnesium replacement provides significant protection against endotoxin challenge. Harkema et al 13 had administered ATP-MgCl 2 to the animal models with sepsis and shock in order to restore cellular bioenergetics. It was found to improve the organ function and the survival time. This effect was due to the downregulation of release of inflammatory cytokines (TNF-alpha, IL-6). 14 Sepsis is an independent risk factor for developing hypomagnesemia during ICU stay as found by Soliman et al. 14 In the present study the incidence of sepsis was twice as common in hypomagnesemic patients as compared to normomagnesemic patients (p<0.05).

Hypomagnesemia has been known to be associated with diabetes mellitus. It is due to increased renal losses of magnesium that accompany glycosuria. 4 There is a strong relationship between hypomagnesemia and insulin resistance 26. Magnesium supplementation is associated with decreased insulin requirements. 27 In the present study hypomagnesemia is more common in diabetic patients (p<0.05). However no significant difference was noted between the random blood sugar values on admission in patients with hypomagnesemia or with normomagnesemia. Chronic alcoholism is one of the predisposing factors for magnesium deficiency. Hypomagnesemia is reported in 30% of hospital admissions with alcohol abuse and in 85% of admissions for delirium tremens. 28 Magnesium depletion in alcoholic individuals is due to a number of factors including poor nutrition, alcohol-induced renal tubular dysfunction leading to renal magnesium wasting, pancreatitis, intracellular shift in alcohol withdrawal syndrome. 1 Soliman et al 14 had noted hypomagnesemia in one-third of patients with chronic liver disease and alcoholism. In the present study the prevalence of hypomagnesemia was observed in one-half of alcoholic patients (11/21).

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Magnesium measured</th>
<th>Low magnesium</th>
<th>High magnesium</th>
<th>Normal magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryzen et al</td>
<td>1985</td>
<td>94</td>
<td>Total</td>
<td>51%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chernow et al</td>
<td>1989</td>
<td>193</td>
<td>Total</td>
<td>61%</td>
<td>5%</td>
<td>34%</td>
</tr>
<tr>
<td>Reinhart et al</td>
<td>1989</td>
<td>102</td>
<td>Total</td>
<td>20%</td>
<td>9%</td>
<td>71%</td>
</tr>
<tr>
<td>Rubiez et al</td>
<td>1993</td>
<td>197</td>
<td>Total</td>
<td>20%</td>
<td>7%</td>
<td>73%</td>
</tr>
<tr>
<td>Guerin et al</td>
<td>1996</td>
<td>179</td>
<td>Total and erythrocyte</td>
<td>44%</td>
<td>6%</td>
<td>50%</td>
</tr>
<tr>
<td>Huijigen et al</td>
<td>2000</td>
<td>115</td>
<td>Ionized</td>
<td>14%</td>
<td>12%</td>
<td>74%</td>
</tr>
<tr>
<td>Deheinzelin et al</td>
<td>2000</td>
<td>226</td>
<td>Total</td>
<td>45.6%</td>
<td>-</td>
<td>54.4%</td>
</tr>
<tr>
<td>Soliman et al</td>
<td>2003</td>
<td>422</td>
<td>Ionized</td>
<td>18%</td>
<td>14%</td>
<td>68%</td>
</tr>
<tr>
<td>Safavi et al</td>
<td>2007</td>
<td>100</td>
<td>Total</td>
<td>51%</td>
<td>-</td>
<td>49%</td>
</tr>
</tbody>
</table>
Hypomagnesemia is commonly associated with other electrolyte abnormalities. Whang et al.29 had found hypomagnesemia in 42% patients with hypokalemia, 29% patients with hypophosphatemia, 27% patients with hypernatremia, and 22% patients with hypocalcemia. Hypokalemia, hypocalcemia, hypophosphatemia are said to be the predictors of hypomagnesemia. Hypokalemia seen in hypomagnesemic patients is relatively refractory to potassium supplementation until magnesium deficiency is corrected.30,31 This is due to defective membrane ATPase activity and also because the renal potassium loss is increased in presence of hypomagnesemia. In this study half of the patients (48%) with hypokalemia also had low serum magnesium levels. Hypocalcemia is also commonly associated with hypomagnesemia.6 The mechanism involves defects in synthesis and release of parathyroid hormone (PTH)32 as well as the end organ resistance to PTH.33 Also the magnesium deficiency may directly act on bones to reduce calcium release independent of PTH.34 As with hypokalemia, the hypocalcemia of magnesium depletion is difficult to correct unless magnesium deficits are corrected.30 The present study also found increased incidence of hypocalcemia in hypomagnesemic patients than in normomagnesemic patients.

Summary

Hypomagnesemia is a common electrolyte imbalance in the critically ill patients. Hypomagnesemia is associated with higher mortality rate in critically ill patients and is also associated with more frequent and more prolonged ventilatory support. It was seen in this study that hypomagnesemia is frequently associated with sepsis and diabetes mellitus. Whether hypomagnesemia directly contributes to cellular alterations leading to increased mortality, morbidity and poor patient outcome in critically ill patients or it is just a marker of critical illness is not clear. Although there was a high incidence of hypomagnesemia in the present study, its correction after magnesium supplementation was not included as a part of the study. The potential benefit of magnesium supplementation to prevent or correct hypomagnesemia in critically ill patients requires further study.

References