Original Research Article

Prevalence of admission hypomagnesemia in critically ill patients

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Abstract

Introduction: In critically ill patients, hypomagnesemia is a serious but underdiagnosed electrolyte abnormality. There are several studies to assess the prevalence of hypomagnesemia in these patients and its effects on mortality and morbidity. The majority of these experiments were performed in intensive care units for patients with medical and surgical complications, postoperative patients, cardiac intensive care units, or patients with serious cancer.**Aims:** To co-relate low serum Magnesium levels with the following outcomes in critically ill medical patients admitted to ICU.**Materials and methods:**A hospital based cross sectional study in Patients attending the Medical Intensive Care unit in Osmania General Hospital for a period of two years from September 2012-September 2014. 160 patients of age more than 18 years with Critically ill medical patients with various medical illnesses and APACHE II score more than 20 were selected study.**Results:** Out of 160 patients on admission, 106(66.3%) patients had hypomagnesemia, and 54 (33.7%) had normal serum magnesium levels. The mortality rate in hypomagnesemia group was 64.8%; whereas in normomagnesemia group was 35.2% Significantly greater mortality rate was observed in hypomagnesemic patients as compared to normomagnesemic patients (p=0.058). of 106 patients with hypomagnesemia, 73(69%) also had hypocalcemia. Of 54 patients with normal magnesium levels, 28(52%) had hypocalcemia (p=0.03). Of 106 patients with hypomagnesemia 84(80%) had hypoalbuminemia. 34 (63%) cases of normomagnesemic patients had hypoalbuminemia which is significant.**Conclusion**: Early diagnosis of hypomagnesemia in critically ill patients is a must to avoid adverse outcomes. Monitoring of serum magnesium levels may have prognostic, perhaps therapeutic implications. High incidence of hypomagnesemia should be kept in mind while treating critically ill patients.

Keywords: Hypocalcaemia ,Hypoalbuminemia , Hypomagnesemia .

Introduction

Hypomagnesemia is a common, often overlooked electrolyte imbalance in critically ill patients[1].Magnesium is the fourth most abundant intracellular cation after potassium. Magnesium (Mg) is pivotal in the transfer, storage, and utilization of energy as it regulates and catalyzes > 300 enzyme systems[1].Magnesium deficiency has been associated with a number of clinical manifestations such as atrial and ventricular arrhythmias, cardiac insufficiency, coronary spasm, sudden death, skeletal, respiratory muscle weakness, bronchospasm, tetany, seizures, and other neuromuscular abnormalities and a number of electrolyte abnormalities, including hypokalemia, hypocalcemia, hyponatremia, and hypophosphatemia.Hypomagnesemia is one of the most common electrolyte disturbances in hospitalized patients, especially in the critical ill. The Prevalence of hypomagnesemia (measuring total serum magnesium) has a wide range (11% to 61%)[2].Many factors contribute to hypomagnesemia in critically ill patients such as impaired GI adsorption, 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[3,4]. Magnesium plays an important role in sepsis. Hypomagnesemia is associated with increased release of endothelin and proinflammatory cytokines. Hypomagnesemia has been known to be associated with diabetes mellitus. It is a strong relationship between hypomagnesemia and insulin resistance. The severity of hypomagnesemia can be assessed using subjective clinical evaluation and biochemical markers of organ dysfunction. Acute Physiology and Chronic Health Evaluation (APACHE) II score is commonly used to assess severity of illness and to predict outcome in critically ill medical patients.The scoring systems may identify high-risk groups among the critically ill, to whom therapeutic interventions may be directed in order to reduce morbidity and mortality, and comparisons may be made of the benefit of such interventions[5].There is a paucity of data evaluating serum magnesium at admission as a predictor of morbidity or mortality.The purpose of this study was to define the prevalence of admission hypomagnesemia in critically ill patients and to evaluate the relationship of magnesium level to organ failure, length of stay, electrolyte disturbance, ventilator need, duration of mechanical ventilation, and mortality rate.

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Materials and methods

A hospital based cross sectional study in Patients attending the Medical Intensive Care unit in Osmania General Hospital for a period of two years from September 2012-September 2014. Ethical clearance was obtained from the Osmania Medical College.

Inclusion Criteria:

- Age more than 18 years.
- Critically ill medical patients with various medical illnesses and APACHE II score more than 20.

Exclusion Criteria:

- Patients who received magnesium supplements prior to ICU admission .

Prevalence of hypomagnesemia in critically ill patients admitted to medical ICU as cited from the review, study article[1] is 52% and Sample size was estimated to be approximately a minimum of 160.Written informed consent was taken from the patients. Inclusion in the study did not change the routine patient management in the ICU. Data was collected by pretested semi structured questionnaire, clinical examination and investigations.All patients fulfilling the inclusion criteria were investigated by all or few of the following in the clinical context of their diseases.Renal function tests, compete blood picture with peripheral smear, Liver function tests including Gamma glutamyl transferase, Random, fasting, postprandial blood sugars, Hba1c for diabetics, Prothrombin time, INR, activated plasma thromboplastin time, Blood, urine endotracheal tube/sputum culture and sensitivity, Serum procalcitonin, serum lactate, arterial blood gas analysis, ECG, 2D ECHO and Radiological investigations like chest x-ray, ultrasound abdomen and CT scan brain was done to patients in study.Serum magnesium level was estimated by photometric colorimetric method. Normal value of serum total magnesium was between 1.7 to 2.4mg/dl

Statistical analysis: It was estimated using N-master software considering the prevalence of hypomagnesemia among critically ill medical patients as 52%. Relative precision (allowable error) -15%. Confidence interval-95%**.** Assuming relative precision of 15% and confidence interval of 95% sample size was estimated as minimum of 160 patients.Data was entered in MS excel and analyzed using SPSS version 17.All quantities data like age, vital signs and serum magnesium levels were represented as mean and standard deviation with 95% confidence intervals.All qualitative variable like severity of critical illness, baseline medical conditions etc. Were presented as frequencies and percentages. Proportion of critical ill patients having hypomagnesemia and various types of outcomes were presented as frequency and percentages.Serum Mg levels between two groups were correlated with the duration of the ICU stay , need for ventilator and the other quantitative prognostic between various groups of serum magnesium levels and clinical outcomes.Correlation and regression statistic were applied to assess the correlation between low serum magnesium levels and various prognostic variables.Chi Square test of significance was applied to test association between various groups of serum magnesium levels and clinical outcomes.Difference were considered statistically significant if P-value was less than 0.05.

Results

Table 1: Age distribution of patients studied.

Age in years	**Numbers of Patients N=160**	**Percent %**
<30	38	23.8
31-40	48	30.0
41-50	24	15.0
51-60	14	8.8
61-70	21	13.1
71-80	11	6.9
>80	4	2.5
TOTAL	**160**	**100.0**
Gender		
Male	112	70.0
Female	48	30.0
Medical Comorbid is		
Diabetes	54	33.0
Hypertension	51	32.0
COPD	27	17.0
IHD	25	16.0
BPH	18	11.3
CVA	17	10.6
Hypothyroidism	15	9.4
Malignancy	6	3.8
CKD	3	1.9

COPD- chronic obstructive pulmonary disease, CVA-cerebrovascular accident, IHD- Ischemic heart disease, BPH- Benign prostatic hypertrophy, CKD- Chronic kidney disease.

Mean ± SD of age in study is 36.50 ± 10.25. male : female ration is 2.1:1 . Males constituted 70% of the patients, 30% were females. Common comorbid conditions were diabetes (33%) followed by hypertension(31%), C.O.P.D(17%), coronary artery disease (16%). Comparing variables between hypomagnesemia 66% and normomagnesemics 34%, those with hypomagnesemia had median age of 46.16 years, 37% were diabetics, 84% had sepsis, mean

Table 2: Symptoms and Signs of presentation in study

Symptoms	**Number of Patients**	**Percent %**
Fever	96	64.0
Altered Sensorium	81	50.6
Breathlessness	72	45.0
Oliguria	72	45.0
Cough	47	29.4
Seizures	44	27.5
Pain Abdomen	37	23.0
Bleeding Tendencies	36	22.0
Dysuria	32	20.0

Loose Stools	11	6.90
Physical Signs		
Tachycardia	136	85.0
Pallor	125	78.0
Tachypnea	122	76.0
Hypotension	72	45.0
Icterus	56	35.0
Febrile Episode	52	32.0

Fever and tachycardia are most important findings in study.

Table 3: Clinical Diagnosis at admission:

Clinical Diagnosis	Number of Patients	Percentage %
Sepsis	68	42.5
Drug Intoxication	24	15.0
Snake Bite	14	9.00
Acute Coronary Syndrome	14	9.00
Meningoencephalitis	12	7.50
Acute Pancreatitis	10	6.20
Hepatic Encephalopathy	10	6.20
Gullian Barre Syndrome	4	2.50
Myasthenia Gravis	4	2.50
Status Epilepticus	4	2.50
Status Asthmaticus	2	1.25

Most of the patients in study are diagnosed with sepsis and followed by drug intoxication.

Table 4: Comparison between survivors and non survivors

Parameters	Survivors	Non Survivors	P-value
Age (In years)	44.5	44.4	0.753
Sepsis(68)	21	47	<0.01
Apache II Score	15.36	22.14	<0.01
Magnesium	2.2	1.6	0.006
Potassium	5.26	4.58	0.799
Calcium	8.56	8.28	0.037
Phosphorus	2.89	2.92	0.953
Albumin	3.39	3.72	<0.01

Sepsis, Apache II Score and Albumin are significant when compared in survivors and non survivors and all other parameters are insignificant.

Table 5: Comparison between normal and hypomagnesemic patients

Parameters	LOW mg	Normal MG	p-value
No of Patients	106(66.2%)	54(34%)	-
SERUM Mg2+ Levels	1.44	2.13	-
Age(Years)	46.16 yrs.	34.61	-
Diabetes	39(37%)	17(32%)	0.53
Sepsis	89(84.%)	46(85.2%)	0.84
Apache II Score	24.2+/-1.99	23.8+/-1.64	0.197
ICU Stay (Days)	10.6+/-6.5	8.95+/-5.6	0.084
Mortality (%)	70(64.8%)	38(35.2%)	0.058
Need For Ventilation	78(73%)	26(53%)	0.001
Hypoalbuminemia	84(80%)	34(63%)	0.02
Hypocalcaemia	73(69%)	28(52%)	0.03
Duration of Ventilation	7.9	6.7	0.07

Out of 160 patients on admission, 106(66.3%) patients had hypomagnesemia, and 54 (33.7%) had normal serum magnesium levels. The lowest serum magnesium value recorded was 1mg/dl while the highest value was 2.8 mg/dl with mean level of 1.95+_0.28. The range of duration of stay in ICU varied from 11 day to 34 days with mean of 14+/-6.8 days. The mean duration of stay in ICU of patients with low serum magnesium was 10.6+/-6.51 days while that of patients with normal serum magnesium was 8.95+/-5.65 days. The difference was not statistically significant (p=0.084). Patients with hypomagnesium needed mechanical ventilator support, 7.91+/-7.28 days while only 6.76+/-5.02 days of the normomagnesemic group needed ventilator support. The difference is not statistically significant (P=0.084). Hypomagnesemic patients required ventilator support for greater number of days as compared to the normo-magnesemic patients. The mean APACHE II score on admission in the hypomagnesemic group was 24.2+/-1.99 while that of normomagnesemic group was 23.8+/-1.64. The difference was not statistically significant. The mortality rate in hypomagnesemic group was 64.8%; whereas in normomagnesemic group was 35.2% Significantly greater mortality rate was observed in hypomagnesemic patients as compared to normomagnesemic patients (p=0.058). of 106 patients with hypomagnesemia, 73(69%) also had hypocalcemia. Of 54 patients with normal magnesium levels, 28(52%) had hypocalcemia (p=0.03). Of 106 patients with hypomagnesemia

84(80%) had hypoalbuminemia.Whereas 34 (63%) p=0.02 of normomagnesemic patients had hypoalbuminemia. The incidence of hypocalcemia and hypoalbuminemia is common in hypomagnesemic patients.

Discussion

Magnesium is the second most common intracellular cation. Many factors contribute to 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.Most of the studies carried out previously have measured total serum magnesium. In this present study we also measured total serum magnesium. In the present study prevalence of hypomagnesemia was in 66%, whereas in study done by C.S Limye et al[6] it was 52%.Few studies have measured RBC magnesium as it is a better index of intracellular magnesium compared with serum magnesium. In a study done by Guerin et al[7], Prevalence of low magnesium considering RBC magnesium was 66% whereas total serum magnesium was only 44%. As seen from two studies done by Huijigen et al[8].According to, Soliman et al[9] in which ionized magnesium was measured 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%). One study assessed the use of ionized magnesium concentrations in critically ill children. As in the adult population, almost 60% of patients had ionized levels less than 0.4 mmol/L. Interestingly, of the children with ionized hypomagnesemia, 60% had normal total magnesium determinations. The authors found no correlation between ionized magnesium concentrations and ionized calcium, pH, albumin, potassium, or serum creatinine Furthermore, the usual replacement doses of magnesium did correct total magnesium levels to the normal range but not ionized levels. Other studies have found no difference in ionized magnesium measured in whole blood, plasma, or serum[9].The use of ionized magnesium levels is not universally accepted[8].Despite the poor correlation between total and ionized magnesium, some have questioned the role of ionized levels. They point out that other studies have shown that ionized hypomagnesemia may not correlate with total body magnesium deficiency based on results of magnesium loading tests.Zalora GP, Wilkens R et al[10] had measured ultrafiltrable magnesium which approximates ionized magnesium. Hyper-magnesemia is found less commonly than hypomagnesemia. It is reported in the range of 4 to 14% in literature and in the study done by C.S. Limaye etal[6] hypermagnessemia was seen in 7% of patients but none of the patients in our present study had hypermagnesemia, similar results were reported with a study done by Safavi et al[11].The relationship between hypomagnesemia and mortality rate varies from study to study. A. higher mortality rate was detected in hypomagnesemic patients as compared to normomagnesemic patients in studies done by Chernow et al[12] (41% vs 13%)[4], Rubiez et al[13] (46% vs 25%) and Safavi et al[11] 55% vs 35%)[2] Similar results were seen in our present study (65% vs 35%) 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 factor causing difficulty in weaning the patient from the ventilator.In the current study it has been that patients with hypomagnesemia needed ventilatory support more frequently and for a longer duration. In a study performed by Fiaccordori et al[14] it was found that patients with low muscle magnesium were on ventilator support for more number of days.Safavi et al[11] had found that in patients with hypomagnesemia the duration of mechanical ventilation was longer (7.2 vs 4.7 days, p<0.01) but in our study the duration of ventilator stay between the 2 groups was not statistically significant (7.9 vs 6.7 days, p=0.074). in the study carried out by Mousavi etal86 there was significant difference in ICU stay among the Mg group compared to those with normal Mg group . (18 vs 11 days, p=0.037). In the present study also there was considerable difference in length of ICU stay among low Mg&, normal Mg groups but was not statically significant (10.6 vs 8.9 p=0.08).In a study by Safavi et al[11] hypomagnesemic patients had more severe organ dysfunction and higher APACHE II Score then those with normomagnesemia (14 vs 10) patients. This may be explained by a strong association of hypomagnesemia with sepsis and sepsis and septic shock, a common cause of death in the ICU patient. In our present study the difference in APACHE II score among the 2 groups was considerable but not statistically significant(24 vs 23,p=.197).Magnesium plays an important role in sepsis. Hypomagnesemia is associated with increased release of endothelin, proinflammatory cytokines[8]. Salem et al[6] 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[15] 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). Sepsis is an independent risk factor for developing hypomagnesemia during ICU stay as found by Soliman et al[9].In the study conducted by C.S.Limaye et al[6]. the incidence of sepsis was twice as common in hypomagnesemic patients as compared to normomagnesemic patients (p<0.05). In our present study the difference in the incidence of sepsis among those with low and normal mg levels was considerable but not statistically significant. (p=0.84)Hypomagnesemia has been known to be associated with diabetes mellitus. It is due to increased renal losses of magnesium that accompany glycosuria. There is a strong relationship between hypomagnesemia and insulin resistance.

Magnesium supplementation is associated with decreased insulin requirements. In the present study hypomagnesemia is more common in diabetic patients (p<0.05). However no significant difference was noted in the present study between those with normal and low magnesium values with regards to prevalence of diabetes mellitus (P=0.53).Among the endocrine and metabolic disorders associated with magnesium deficiency, diabetes mellitus is the most common. Many studies have shown that mean plasma levels are lower in patients with both type 1 and type 2 diabetes compared with nondiabetic control subjects. The various cause of low magnesium in diabetics include diets low in magnesium, osmotic dieresis causing high renal excretion of magnesium, insensitivity to insulin affecting intracellular magnesium transport and thereby causing increased loss of the extracellular magnesium, rampant use of loop and thiazide diuretics promoting magnesium wasting, diabetic autonomic neuropathies, and reduced tubular reduced tubular reabsorption due to insulin resistance.Intracellular magnesium plays a key role in regulating insulin action, insulin mediated glucose uptake, and vascular tone. Reduced intracellular Mg concentrations result in a defective tyrosine-kinase activity, postreceptorial impairment in insulin action, and worsening of insulin resistance in diabetic patients. Cellular magnesium is a critical cofactor for the activities of various enzymes involved in glucose transport, glucose oxidation, insulin release, and is a cofactor for ATP ase and adenylate cyclase enzymes. Chronic magnesium deficiency has also been associated with elevated concentrations of TNF-alpha, and this may also contribute to post receptor insulin resistance. 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 86.

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. Soliman et al[3] had noted hypomagnesemia in one-third of patients with chronic liver disease and alcoholism in a study by C.S.Limaye et al hypomagnesemia was observed in one-half alcoholics. In the present study 60% alcoholics had hypomagnesemia.

Hypomagnesemia is commonly associated with other electrolyte abnormalities. Whang et al had found hypomagnesemia in 42% patients with hypokalemia, 29% patients with hypophosphatemia, 27% patients with hyponatremia and 22% patients with hypocalcemia. Hypokalaemia, hypocalcemia, hypophosphatemia are said to be the predictors of hypomagnesemia. Hypokalaemia seen in hypomagnesemic patients is relatively refractory to potassium supplementation until magnesium deficiency is corrected. 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 (44%) with hypokalemia also had low serum magnesium levels.

Potassium channel efflux is inhibited by magnesium. Thus hypomagnesemia results in an increased efflux of potassium in kidney, resulting in a hypokalaemia. This condition is believed to occur secondary to the decreased normal physiologic magnesium inhibition of the ROMK channels the apical tubular membrane

In this light, hypomagnesemia is frequently the cause hypokalaemia patients failing to respond to potassium supplementation. For example, patients with diabetic ketoacidosis should have their Magnesium levels monitored to ensure that the serum loss of potassium, which is driven intracellularly by insulin administration, is not exacerbated by additional urinary losses. Hypocalcemia is also commonly associated with hypo-magnesemia8. The mechanism involves defects in synthesis and release of parathyroid hormone89 as well as the end organ resistance to PTH. Also the magnesium deficiency may directly act on bones to reduce calcium release independent of PTH89. As with hypokalemia, the hypocalcemia of magnesium depletion is difficult to correct unless magnesium deficits are corrected. The present study also found increased incidence of hypocalcemia in hypomagnesemia patients than in normomagnesemia patients Release of calcium from the sarcoplasmic reticulum is inhibited by magnesium. Thus hypomagnesemia results in an increased intracellular calcium level. This inhibits the release of parathyroid hormone which can result in hypoparathyroidism and hypocalcemia Furthermore, it makes skeletal and muscle receptors less sensitive to parathyroid hormone.

Conclusion

Hypomagnesemia in critically ill patients is associated with more frequent and prolonged ventilator support.Critically ill diabetics with poor glycaemiccontrol had significant hypomagnesemia.All diabetics with critical illness should undergo regular monitoring of serum magnesium levels.Hypomagnesemia was frequently associated with severe sepsis.Hypomagnesemia was associated with hypocalcaemia and hypoalbuminemia.Tachycardia, APACHE II score, hypoalbuminemia and hypomagnesemia were independent prognostic markers of in hospital mortality.Early diagnosis of hypomagnesemia in critically ill patients is must to avoid adverse outcomes.Monitoring of serum magnesium levels may have prognostic, perhaps therapeutic implicationsHigh incidence of hypomagnesemia should be kept in mind while trading critically ill patients.

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