

Original Research Article

Prevalence of hypomagnesemia in children admitted to pediatric intensive care unit and its correlation with patient outcome

Siddappa F. Dandinavar, Suma D.*, Vinod H. Ratageri, Prakash K. Wari

Department of Paediatrics, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India

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***Correspondence:**

Dr. Suma D.,

E-mail: sumadevaraj26@gmail.com

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ABSTRACT

Background: Magnesium deficiency is common in critical illness and is said to be associated with increased need for mechanical ventilation, mortality and prolonged ICU stay. The knowledge of hypomagnesemia is essential as available data is scarce and it could have prognostic and therapeutic implications. This study was undertaken to estimate the prevalence of hypomagnesemia at the time of admission in PICU and its correlation with length of PICU stay, duration on mechanical ventilator and outcome at the end of hospital stay-death or discharge.

Methods: This is a prospective observational study including 343 children aged 1month to 12years admitted to PICU. Detailed history taking and clinical examination was done for all enrolled children. At admission, blood was collected for estimation of serum magnesium. Patients were categorized into three groups i.e., hypomagnesemia, normomagnesemia and hypermagnesemia and data was analysed.

Results: Out of 343 children, 28% had hypomagnesemia, 7.3% had hypermagnesemia and 64.7% had normomagnesemia. Hypomagnesemia was more common in neurological disorders. No association was found between magnesium and length of mechanical ventilation. PICU stay was significantly longer in hypomagnesemia group ($p=0.031$). 37.5% patients with hypomagnesemia also had hypocalcemia and 35.4% had hypokalemia. Mortality rate was higher in those with hypomagnesemia (30.2%) compared to those with normomagnesemia (22.1%).

Conclusions: Patients with hypomagnesemia had increased duration of PICU stay, other associated electrolyte abnormalities and higher mortality. Hence monitoring of magnesium levels in critically ill patients is indicated.

Keywords: Children, Hypomagnesemia, Intensive care unit, Mortality, Outcome, PICU

INTRODUCTION

Magnesium (Mg) is the second most abundant intracellular cation and the fourth most common cation in the body.¹ It activates about 300 enzymes and is involved in most reactions of carbohydrate, lipid, nucleic acid and protein metabolism, regulation of cellular permeability and neuromuscular excitability.²

Magnesium deficiency frequently develops in a wide variety of clinical conditions such as protein-energy

malnutrition, malabsorption, hypoalbuminaemia, sepsis, etc., which are commonly seen in children in developing countries. Magnesium disturbances are also likely following prolonged gastrointestinal suctioning, blood transfusion, catecholamine excess, diuretic and aminoglycoside therapy etc., which are operative in the intensive care patients. Magnesium deficiency is therefore likely to be frequent in critically ill patients.³ Studies have shown a wide variation (20%-70%) in prevalence of hypomagnesemia in the intensive care unit setting.⁴ There is a strong, consistent clinical evidence,

largely from observational studies, that hypomagnesemia is significantly associated with increased need for mechanical ventilation, prolonged ICU stay and increased mortality.⁵ Critically ill patients are predisposed to both symptomatic and asymptomatic magnesium deficiency that can lead to some important clinical consequences such as hypokalemia, cardiac arrhythmias, hypocalcemia, neurotoxicity and psychiatric problems, leading to increased morbidity and mortality.⁶ The available data on altered Mg levels in pediatric intensive care unit (PICU) setting is scarce, especially from developing countries. This study was undertaken to estimate the prevalence of hypomagnesemia at the time of admission in critically ill children admitted to PICU in a tertiary care hospital and its association with patient outcome with respect to length of PICU stay, need for mechanical ventilator support and its duration and outcome at the end of hospital stay-discharge or death.

METHODS

This prospective observational study was conducted in the Department of Paediatrics, Karnataka Institute of Medical Science, Hubballi, from 1st January 2017 to 31st December 2017.

Inclusion criteria

- Children between ages 1 month and 12 years admitted to the PICU were included in the study.

Exclusion criteria

- Patients with known congenital renal magnesium wasting (e.g., Bartter syndrome and Gitelman syndrome), patients who had already received replacement for hypomagnesemia in last 24 hours, patients with surgical conditions, trauma patients, patients transferred to other PICUs, patients with PICU stay of less than 24 hours were excluded from the study.

After obtaining clearance from ethical committee, children who were satisfying the inclusion criteria were enrolled in to the study. A written informed consent was taken from the parents or guardians of the children included in the study. All enrolled children underwent detailed history taking and clinical examination. The details including age, gender, anthropometry, admission disease category (neurological, respiratory, cardiovascular, gastrointestinal and others) were recorded in a structured proforma. At admission, 5ml venous blood was collected in a serum vacutainer, centrifuged and serum was sent for estimation of magnesium. Other routine investigations like complete hemogram, renal function test, serum electrolytes-sodium, potassium, calcium and other relevant investigations as required for case management were performed. All the enrolled subjects received treatment according to the PICU protocol.

Study enrolment did not change the normal treatment procedure. All patients were followed until death or discharge from hospital. The patient outcome was measured by length of PICU stay and hospital stay, need and duration of mechanical ventilator support, outcome at the end of hospital stay i.e., death or discharge. Biochemical analysis for Magnesium was done using fully auto-analyzer XL 300. Magnesium level was estimated by XYLIDYL BLUE method using Erba kits. The results were expressed in mg/dL. Subjects were divided into three Groups based on their Serum Magnesium concentration defined as below

- Normal: 1.5-2.3mg/dL
- Hypomagnesemia: <1.5mg/dL
- Hypermagnesemia: >2.3mg/dL.

Statistical analysis

Data was entered into Microsoft Excel sheet and statistical analysis was done using SPSS version 22 software. Categorical data was represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation (SD).

ANOVA (analysis of variance) was the test of significance used to identify the mean difference between more than two groups for quantitative data. p value (probability that the result is true) of <0.05 was considered as statistically significant.

RESULTS

Three forty-three children admitted to the Pediatric Intensive Care Unit in the Department of Paediatrics, KIMS Hubli from 1st January 2017 to 31st December 2017, who met the inclusion criteria were enrolled into the study.

Table 1: Baseline characteristics of the study population.

	Number (n= 343)	Percentage
Gender		
Female	149	43.4
Male	194	56.6
Age		
<1 year	134	39.2
1 to 5 years	110	32.1
6 to 10 years	72	20.9
>10 years	27	7.8
Disease category		
Neurological	125	36.4
Respiratory	92	26.8
Others	80	23.3
Cardiovascular	27	7.9
Gastrointestinal	19	5.5

There were 56.6% males and 43.4% females. Male to female ratio was 1.3:1. Majority of the subjects were aged <1 year (39.2%) followed by 32.1% between 1 to 5 years and 28.7% were aged >5 years. Majority of the subjects were admitted to PICU with neurological complaints (36.4%) followed by respiratory disorders (26.8%) (Table 1). Out of 343 patients, 222 (64.7%) patients had normal magnesium levels with a mean of 1.9mg/dl. 96 patients were found to have hypomagnesemia which accounts for 28%. The mean magnesium levels were 1.2mg/dL. 25 (7.3%) patients were found to have hypermagnesemia, mean magnesium being 2.8mg/dL (Figure 1). The lowest measured magnesium level was 1mg/dL and highest level was 4.1mg/dL. There was no statistically significant association between hypomagnesemia and gender, age, disease category of admission and sepsis. Among children aged ≤5 years, 26.8% had severe acute malnutrition in hypomagnesemia group. In those with normal magnesium levels, 24% had severe acute

malnutrition and 27.3% had severe acute malnutrition in those with hypermagnesemia.

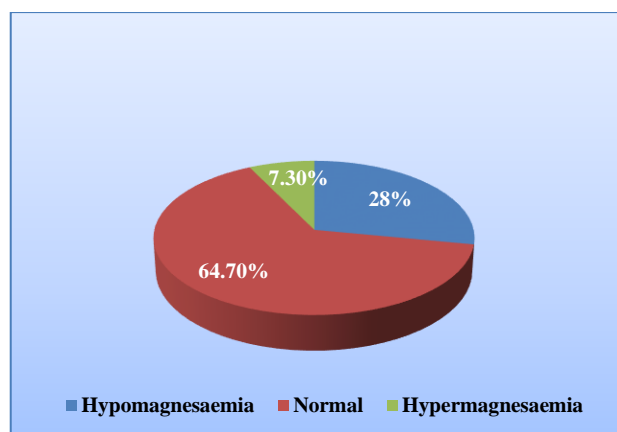


Figure 1: Distribution of magnesium (N=343).

Table 2: Results.

	Serum Magnesium						P value
	<1.5 mg/dl (n=96)		1.5 to 2.3 mg/dl (n=222)		>2.3 mg/dl (n=25)		
Gender (%) (n=343)							
Female	41	42.7%	96	43.2%	12	48%	0.888
Male	55	57.3%	126	56.8%	13	52%	
Age (%) (n=343)							
<1 year	43	44.8%	82	36.9%	9	36%	0.224
1 to 5 years	28	29.2%	69	31.1%	13	52%	
6 to 10 years	19	19.8%	51	23%	2	8%	
>10 years	6	6.2%	20	9%	1	4%	
Disease category (%) (n=343)							
Neurological	43	44.8%	76	34.2%	6	24%	0.081
Cardiovascular	5	5.2%	18	8.1%	4	16%	0.198
Respiratory	25	26%	60	27%	7	28%	0.974
Gastrointestinal	4	4.2%	14	6.3%	1	4%	0.701
Others	19	19.8%	54	24.3%	7	28%	0.577
Sepsis (%) (n=343)							
Present	21	21.8%	35	15.7%	4	16%	0.411
Severe acute malnutrition (%) (n=243)							
Present	19	26.8%	36	24%	6	27.3%	0.879
Associated electrolyte imbalance (n=343)							
Hypocalcemia (%)	36	37.5%	57	25.7%	6	24%	0.087
Hypokalemia (%)	34	35.4%	51	22.9%	7	28%	0.070
Outcome (n=343)							
Duration of PICU stay days (mean±SD)	4.29	3.62	3.27	3.11	4	2.25	0.031*
Duration of hospital stay days (mean±SD)	9.85	5.63	8.59	5.72	8.96	4.32	0.184
Requirement of mechanical ventilator (%)	33	34.4%	58	26.1%	7	28%	0.326
Duration of mechanical ventilation days (mean±SD)	3.90	2.82	3.69	3.56	2.42	0.97	0.543
Discharge (%)	67	69.8%	164	77.9%	20	80%	0.262
Death (%)	29	30.2%	49	22.1%	5	20%	

*statistically significant

There was no significant association between serum magnesium and severe acute malnutrition.

The range of duration of stay in PICU varied from 1 to 19 days with a mean of 3.62 ± 3.24 days. Children with hypomagnesaemia had a significantly longer mean duration of PICU stay of 4.29 ± 3.62 days in comparison with 3.27 ± 3.11 days in those with normal magnesium levels and 4 ± 2.25 days in hypermagnesaemia subjects ($p=0.031$). The range of duration of stay in hospital was 1 to 35 days. Mean duration of hospital stay in those with hypomagnesaemia was 9.85 ± 5.63 days, 8.59 ± 5.72 days in those with normal magnesium levels and in those with hypermagnesaemia; it was 8.96 ± 4.32 days ($p=0.184$).

In the hypomagnesaemia group, mechanical ventilation was needed in 34.4% subjects while 26.1% in normal magnesium group and 28% in hypermagnesaemia group needed mechanical ventilation respectively. There was no significant association between duration of mechanical ventilation and serum magnesium levels. Other electrolyte imbalances were more common in subjects with hypomagnesaemia in comparison with the other two groups. Hypocalcaemia was the most commonly seen associated electrolyte abnormality in hypomagnesaemia group (37.5%). 25.7% subjects in the normal magnesium group and 24% with hypermagnesaemia also had hypocalcaemia. 35.4% of subjects with hypomagnesaemia had hypokalaemia compared to 22.9% in normomagnesaemia group and 28% in hypermagnesaemia group. In the study, overall mortality was 24.2% (83 out of 343). Mortality among those with hypomagnesaemia was 30.2%. Among those with normal magnesium levels, 22.1% died and 20% died in hypermagnesaemia group (Table 2).

DISCUSSION

Hypomagnesaemia is said to be a common finding in the intensive care setup. It is frequently associated with sepsis, prolonged PICU stay, more frequent need for and longer duration of mechanical ventilation and increased mortality.⁷ The knowledge regarding prevalence of hypomagnesaemia is essential as early identification and correction of the same could have prognostic and therapeutic implications.⁸ Most of the data presently available are from studies done in adult intensive care units with data from pediatric population being scarce.

In the present study, out of 343 subjects, hypomagnesaemia was present in 96 (28%) subjects while 222 (64.7%) had normal magnesium levels and 25 (7.3%) had hypermagnesaemia. This is comparable to the findings of Chen et al where hypomagnesaemia was seen in 27.27% of their study subjects with 64.71% in normomagnesaemic and 8% in hypermagnesaemic groups respectively.⁹ A study by Broner et al involving 98 paediatric patients admitted to ICU found Mg to have highest prevalence of abnormal values compared among all ions measured. They found a prevalence of 25.6%

hypomagnesaemia with 56.7% having normal and 17.8% having high magnesium values.¹⁰ Most of the studies, including the present study, have measured total serum magnesium. The interplay between serum total and ionized Mg levels during specific critical illnesses and their treatment is not completely known. Serum magnesium does not necessarily reflect total body magnesium, since Mg is mainly intracellular and ionized Mg is the biologically active form.¹¹ The heterogeneous patient population in every study and the fact that serum Mg measurement is not a reliable indicator of real magnesium status of the body could be the reason for wide ranging incidence of hypomagnesaemia in various studies. Hypermagnesaemia is found less commonly than hypomagnesaemia, in the range of 4 to 14% as reported in the literature. In this study, hypermagnesaemia was seen in 7.3% of patients which is comparable to the reports of other studies.^{9,12}

There were 194 (56.6%) males and 149 (43.4%) females in the present study, with male to female ratio of 1.3:1. Hypomagnesaemia was more common in infants (44.8%) compared to other age groups. No correlation was found between age and magnesium levels. Saleem et al identified age greater than one year as a risk factor for hypomagnesaemia.⁴ Hypomagnesaemia was more frequently reported among patients with neurological disorders compared with the rest of the cases ($p < 0.05$) by Singhi et al.⁵ Deshmukh et al also found the incidence of hypomagnesaemia in PICU to be more in patients with convulsions and patients with severe grades of altered sensorium.¹³ In the present study, it was noted that 44.8% subjects in the hypomagnesaemia group had neurological complaints compared to 34.2% subjects in the normal magnesium group ($p > 0.05$). Serum magnesium levels are said to be significantly low in children with moderate and severe malnutrition as found by Singla et al. Hypomagnesaemia in malnourished children may be due to inadequate intake, malabsorption, diarrhoea, and infection.¹⁴ In present study, no such difference was found. 26.8% children had severe acute malnutrition in hypomagnesaemia group in comparison with 24% in normal magnesium group and 27.3% in hypermagnesaemia group ($p > 0.05$). These results are similar to the findings of Saleem et al (39.2% vs 38%; $p > 0.05$).⁴ Magnesium plays an important role in sepsis. Hypomagnesaemia is associated with increased release of endothelin and proinflammatory cytokines. Many studies have found a significantly higher incidence of sepsis in hypomagnesaemic patients.^{7,9} The incidence of sepsis in present study was 21.8% in subjects with hypomagnesaemia compared to 15.7% and 16% in subjects with normal magnesium levels and hypermagnesaemia respectively. Subjects with hypomagnesaemia were found to have significantly longer duration of PICU stay (4.29 ± 3.62 days) compared to those with hypermagnesaemia (4.00 ± 2.25 days) and normal magnesium levels (3.27 ± 3.11 days) ($p = 0.031$). A similar finding of increased duration of PICU stay in hypomagnesaemia patients was also reported by

Deshmukh et al, Chen et al, and Kumar et al.^{9,13,15} On the contrary, Limaye et al reported no difference in length of ICU stay among hypomagnesemic (8.00 ± 7.92 days) and normomagnesemic (6.17 ± 3.84 days) groups ($p > 0.05$).⁷ In present study, no significant difference in duration of hospital stay was found in those with hypomagnesemia ($p > 0.05$). Hypomagnesemia is known to cause muscle weakness and respiratory failure leading to difficulty in weaning the patient from the ventilator and hence may lead to prolonged duration of mechanical ventilation.¹¹ In study by Kumar et al, 56.86% patients with hypomagnesemia needed mechanical ventilatory support and in normomagnesemic group, 24.33% needed ventilatory support ($p < 0.05$). No significant difference was found in the mean duration of ventilatory assistance among the groups.¹⁵ In the present study, 34.4% subjects with low magnesium needed mechanical ventilation support when compared to 26.1% in those with normal magnesium and 28% in the high magnesium group. The duration of mechanical ventilation in the low magnesium group was similar to those with normal and high magnesium levels ($p > 0.05$).

Hypomagnesemia was found to be associated with other electrolyte disturbances in one third of the cases in the present study. Hypocalcemia was the most commonly seen associated electrolyte abnormality in hypomagnesemia group in the current study. Of the 96 patients with hypomagnesemia, 37.5% also had hypocalcemia. 56% of hypomagnesemic group also had hypocalcemia in study by Saleem et al.⁴ Limaye et al found 69% of hypomagnesemic patients to also have hypocalcemia.⁷ Hypocalcemia is seen frequently as magnesium deficiency impairs parathyroid glandular function and may lower serum concentrations of vitamin D, leading to hypocalcemia. Hypocalcaemia of magnesium deficiency cannot be corrected by treatment with calcium alone.¹⁶ In the present study, 35.4% patients with hypomagnesemia also had hypokalemia. Saleem et al found 31% incidence of hypokalemia in the low magnesium group.⁴ This could be due to underlying disorders that cause both magnesium and potassium loss, such as diuretic therapy, vomiting and diarrhea or nasogastric suctioning. Moreover, renal potassium losses are increased in hypomagnesemic patients. This hypokalemia is said to be relatively refractory to isolated potassium supplementation until magnesium deficiency has been corrected.¹⁶

Mortality was taken as an important indicator of outcome in the present study. Overall mortality in the study group was 24.2%. In the hypomagnesemia group, 30.2% (29 out of 96) succumbed to the illness while 22.1% (49 out of 222) and 20% (5 out of 25) died in normomagnesemia and hypermagnesemia group respectively ($p > 0.05$). The relationship between hypomagnesemia and mortality rate is varied from study to study. A significantly higher mortality rate was detected in hypomagnesemic patients as compared to normomagnesemic patients in most studies.^{6,7,8,9} Soliman et al observed that there was no

association between ionized Mg levels on admission and mortality, but patients who develop ionized hypomagnesemia during their ICU stay had higher mortality rates.¹⁷ The higher mortality rates in the hypomagnesemic patients could be due to a greater incidence of electrolyte abnormalities like hypokalemia, hypocalcemia and cardiac arrhythmias and a strong association of hypomagnesemia with sepsis and septic shock which is a common cause of death in ICU patients.⁷ However, varying results are reported by Safavi et al, Broner et al and Escuela et al who found no association between hypomagnesemia at admission and mortality rates.^{8,10,18}

Huijjen et al found no correlation between low extracellular or intracellular Mg and clinical outcome and suggested that the absence of correlation with clinical outcome could mean hypomagnesemia is merely an associated finding not directly related to the disease condition.¹⁹ Some possible explanation for lack of correlation between magnesium and clinical outcome in different studies could be the heterogenous patient population in every study and also the fact that serum Mg measurement is not a reliable indicator of the real magnesium status of the body. The limitations of the study were that serum magnesium levels were recorded only on the day of admission to intensive care unit. Follow up magnesium levels were not done. Total serum magnesium level was measured instead of ionised magnesium.

CONCLUSION

One third of patients admitted to PICU had altered magnesium levels. Hypomagnesemia was more in patients with neurological disorders compared to other disease categories. Hypomagnesemia was commonly associated with hypocalcemia and hypokalemia. Presence of hypomagnesemia was associated with significantly longer duration of PICU stay. Those with hypomagnesemia needed mechanical ventilation support more frequently than the normal and hypermagnesemia groups. Mortality rate is higher in those with hypomagnesemia compared to those with normomagnesemia and hypermagnesemia.

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