

## ORIGINAL ARTICLE

# Hypomagnesemia in the ICU – Does Correction Matter?

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## Abstract

**Background:** Magnesium is a cation that is constantly being rediscovered. A number of studies have linked low magnesium levels to poor outcome of critically ill patients. Despite this hypomagnesemia continues to be under-recognized and uncorrected. There are no studies, in our knowledge, that have assessed the impact of correction of hypomagnesaemia on the outcome of the ICU patient.

### Aims and Objectives:

To determine the standard Mg levels in a healthy population sample and to correlate it with western data.

To estimate the admission Mg levels in critically ill patients admitted to the ICU and to determine if routine correction of hypomagnesaemia altered their outcomes as compared with the retrospectively collected data of a similar group of patients admitted to the same ICU prior to the routine testing of Mg levels.

This was an observational study carried out in the intensive care unit of a tertiary hospital in south India

**Results:** The mean serum magnesium in a sample of healthy Indian population was noted to be 2.112 mg/dl, which is consistent with that of the western data. Among the critically ill admitted to the medical ICU, the incidence of Hypomagnesemia (defined as serum Mg<sup>+2</sup> of  $\leq 1.7$  mg/dl on admission), was 23.96%. The study group in whom serum Magnesium was routinely corrected, showed a decrease in the mean total duration of ICU stay (94.265 vs. 99.443 hours with  $p=0.78$ ); the need for mechanical ventilation (52.08% vs. 65.625%) and the duration of Mechanical Ventilation (36.64 vs. 58.75 hours with  $p=0.04$ ). Mortality was significantly higher in the comparison group ( $p=0.01$ ) (39.6% vs. 22.9%).

**Conclusions:** The range of Magnesium levels in a healthy Indian population matches that of the west despite variations in diet and lifestyle. Routine screening and replacement of magnesium in critically ill patients with hypomagnesaemia resulted in reduction of morbidity and statistically significant reduction in overall ICU mortality.

## Editorial Viewpoint

- Hypomagnesemia continues to be under-recognized and uncorrected.
- This study shows incidence of hypomagnesemia of 24% in critically ill.
- Correction of hypomagnesemia reduces the duration of ICU stay and mechanical ventilation and mortality as well.

metabolic acidosis, hypocalcemia and hypomagnesemia etc. apart from many other nonfatal complications which increase the morbidity.<sup>1</sup> Magnesium is also used commonly in treatment of hypertension in pregnancy, acute asthma, muscle spasticity and constipation. Yet, hypomagnesemia often remains unrecognized in the critically ill patients,<sup>3</sup> hence magnesium has been called the “forgotten cation.”<sup>4</sup>

Magnesium is the second-most abundant intracellular cation and, overall, the fourth-most abundant. It plays a fundamental role in many functions of the cell, including energy transfer, storage and metabolism; maintenance of normal cell membrane function; and the regulation of parathyroid hormone secretion. Systemically, magnesium lowers blood pressure and alters peripheral

## Introduction

Hypomagnesemia can result in well-known complications like ventricular arrhythmias<sup>1,2</sup> including Torsades de pointes, widened QT interval,<sup>2</sup> coronary artery vasospasm, convulsions,

neuromuscular weakness, inability to wean off the ventilator and several metabolic abnormalities including

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vascular resistance. Magnesium is involved in nearly every aspect of biochemical metabolism, activates almost all enzymes involved in phosphorus reactions and acts as a molecular stabilizer of ribonucleic acids. Because it is bound to adenosine triphosphate inside the cell, shifts in its intracellular concentration may help to regulate cellular bioenergetics, such as mitochondrial respiration. Extracellularly,  $Mg^{+2}$  ions block neurosynaptic transmission by interfering with the release of acetylcholine.  $Mg^{+2}$  ions also may interfere with the release of catecholamines from the adrenal medulla and has been proposed as an endogenous endocrine modulator of the catecholamine component of the physiologic stress response.<sup>5</sup>

## Methodology

A descriptive observational study was carried out in two phases in a tertiary care hospital in south India, which provides service to a population that is both urban and rural, between Jan 2012 and Jun 2012.

The initial phase estimated the serum magnesium levels in a sample of the normal population. We randomly selected 50 hospital job applicants and tested their serum magnesium levels. All the persons were >18 years of age and medically fit with no known co-morbidities. The mean serum magnesium of this group was calculated.

The second phase was conducted in the medical ICU where we prospectively recruited 96 critically ill patients into the study sample from 6<sup>th</sup> March 2012 to 5<sup>th</sup> Jun 2012. Critically ill patients who included men and non-pregnant women admitted in the MICU >18 years with an APACHE II score > 10 were included. Terminally ill patients, those with end stage renal failure with oliguria and non-medical patients were excluded. The total

serum magnesium levels were measured in all these patients using the colorimetric method with Xylidyl blue. Normal magnesium levels were taken between 1.7mg/dl – 2.4mg/dl.

The patients whose serum magnesium levels were below 1.7mg/dl were identified and given intravenous replacement therapy as per the ICU protocol. The target post correction serum Mg was 1.7 mg/dl. The study did not interfere with the management of these patients in the ICU. The correction was done using I.V Magnesium sulphate (8-32 milli equivalents as infusion over 4-12 hours, depending on the severity). Patients were monitored throughout the infusion for possible side effects like sweating, flushing, bradycardia and hypotension. The patient's vitals including the blood pressure, pulse rate, respiratory rate, deep tendon reflexes, mental status and urine output were monitored and serum Mg levels were monitored till normal level was achieved to avoid hypermagnesemia. Serum Mg levels were not repeatedly checked once the desired value was achieved post correction. None of the patients developed any side effects during the magnesium infusion. The outcomes documented in the study group were:

1. Duration of ICU stay
2. Need for mechanical ventilator support
3. Duration of mechanical ventilation
4. Overall ICU mortality.

This outcome data was compared with that of data collected retrospectively from a comparison group of 96 ICU patients, with similar inclusion and exclusion criteria who had been admitted to the same facility prior to the initiation of routine screening of serum Magnesium levels (from 1<sup>st</sup> Jan 2012 to 6<sup>th</sup> March 2012). A randomized controlled study was not done as it would have been unethical, given the evidence

regarding low Mg levels and poor outcome. This can therefore be considered a “before and after study”.

## Statistical Analysis

Descriptive statistical analysis was carried out for the study. The study and the comparison group were noted to be statistically comparable with respect to the age distribution with a  $p=0.061$ , sex distribution with a  $p=0.104$  and the diagnostic frequency distribution with a  $p=0.181$  (Table 1). The average APACHE score was also statistically comparable (approximately 14.5 in the control group versus 15.1 in the study group). All the patients included in the study had an APACHE score of >10. Analysis of variance (ANOVA) has been used to find the significance of the study parameters between the test group and the comparison group. Chi square test has been used to find the significance of the study parameters on categorical scale between the two groups. All data analysis was performed with a SPSS statistical package (SPSS 16.0, SPSS Inc. Chicago II. USA). Microsoft word and Excel have been used to generate graphics, tables etc.

## Results

Estimation of Serum Magnesium In Normal Population. The average serum magnesium in the normal population sample was noted to be 2.112 mg/dl. The maximum value noted was 2.6mg/dl and the minimum was 1.8mg/dl. Our study group consisted of predominantly young females less than 35 years of age belonging to middle class. Hence age and sex related bias may be expected. However even in this small group, the serum  $Mg^{+2}$  was noted to be within the published normal range for general population as mentioned in all the previous studies; which were mostly done on the Western population whose diet and life style vary significantly from that of Indian population. Further studies

**Table 1: Comparison of the two groups with respect to age, sex and diagnosis**

Group	Study group	Control group	Total
<b>Age:</b>			
18-30	19	12	31
31-40	8	3	11
41-50	7	14	21
51-60	24	17	41
≥60	38	50	88
Total	96	96	192
<b>Sex:</b>			
Male	64	53	117
Female	32	43	75
Total	96	96	192
<b>Diagnostic frequency:</b>			
Cerebrovascular accident	10	10	20
Acute coronary event	8	10	18
Sepsis	21	23	44
Poisoning	11	7	18
Seizures	4	1	5
Acute on chronic respiratory dis.	10	9	19
Diabetic ketoacidosis	0	1	1
Snake bite	6	0	6
Miscellaneous	26	35	61
Total	96	96	192
<b>Apache score:</b>			
Average	14.5	15.1	

with higher number of recruits with a wider range of age group are however necessary. There was no significant difference in the serum magnesium level between the younger and the older age groups as well as between the male and female sex, in our study.

Incidence of low serum magnesium at admission to the ICU: The average age of the patients in the study group was 54±19.25 years with a maximum of 90 years and a minimum of 18 years. (61/96) 63.54% were males. 36.46% (35/96) were females. The average age of the patients in the comparison (control) group were 58.48±18.54 years with a maximum of 96 years and a minimum was 19 years. 55.21% (53/96) were males and 44.79% (43/96) were females. The frequency of different diagnoses was found to be similar in both the

**Table 2: Comparison of the outcomes between the study and control groups**

Results of the present study	Study group	Control group	Significance
Incidence of hypomagnesemia	23.96%	Not known	
Duration of ICU stay (hrs)	94.27	99.44	No (P=0.78)
Duration of mechanical ventilation (hrs)	36.64	58.75	Yes (P=0.04)
No. of cases ventilated	50	63	No (P=0.16)
Mortality rate	22.9%	39.6%	Yes (P=0.01)

groups. The average APACHE score was also statistically comparable (14.5 in the control group versus 15.1 in the study group). The basic characteristics of the study and the control groups were statistically comparable with respect to the age distribution with a p=0.061 and sex distribution with a p=0.104 as well as the diagnostic frequency distribution with a p=0.181.

The serum magnesium level was estimated in the study group and the incidence of hypomagnesemia ( $\leq 1.7\text{mg/dl}$ ) was 23.95% (23/96). The lowest serum Mg value recorded was 0.9mg/dl while the highest was 5mg/dl. The average pre correction serum magnesium in these hypomagnesemic patients was 1.522 mg/dl. 16 patients had a serum Mg  $\geq 2.5\text{mg/dl}$  and only one had  $>4\text{mg/dl}$  and none above 5mg/dl. Normal and High Magnesium were taken together as a set in our study. Clinically significant Hypermagnesemia is  $>5\text{ mg/dl}$ <sup>3,4</sup> according to various studies done earlier. Studies show that Hypermagnesemia<sup>4</sup> which is most of the time either iatrogenic or secondary to renal failure; is found less commonly than hypomagnesaemia.

Comparison of parameters before and after the routine screening and correction of serum magnesium: As shown in Table 2, the mean duration of ICU stay in the in the study group was 94.265 hours as compared to 99.443 hours in the comparison group. The duration of ICU stay was relatively less (by 5.178 hours) in the study group. (p = 0.78). The number of cases requiring mechanical ventilation in the study group was lower than in the control group. Only 52.083% (n=50) required ventilator

support after routine magnesium correction was initiated as against 65.625% (n=63) in the control group (p=0.08). The duration for mechanical ventilation was 36.64 hours in the study group as compared to 58.75 hours in the control group. The difference is statistically significant (p=0.04). The study group required 22.11 hours less duration of mechanical ventilation (Table 1). The mortality rate was 22% in the study group where as it was 38% in the control group; hence 16.7% lower after routine screening and correction of serum Mg<sup>+2</sup> was introduced in the ICU. This was statistically significant with a p=0.01.

Comparison of parameters "within" the study group – with respect to serum magnesium: The mean duration of ICU stay (difference of 48.837 hours) (p=0.189) as well as the Mean Duration of Mechanical Ventilation (difference of 13.667 hours) (p=0.349) were found to be higher in patients with low serum magnesium level as compared with those with normal serum magnesium (Table 3). Within the study group, total 50 out of the 96 required mechanical ventilation. Of these, 15 had low serum magnesium i.e, 30% of the total of ventilated cases were hypomagnesemic. 65% of the total cases with hypomagnesemia in the study group required ventilation as compared to 47.94% of the cases having normal levels of serum magnesium (p=0.16). There was no statistically significant difference in the final mortality rate between patients with hypomagnesemia (21.73%) as compared to those of normomagnesemia (23.28%). This finding is very important to be noted, as routine correction

**Table 3: Comparison of the outcomes 'within' the study group – according to the magnesium status**

Magnesium status (within the study group)	Duration of stay (hours)	Duration of mechanical ventilation (hours)	Need for mechanical ventilation
Normal	82.57	33.37	35/73 (47.94%)
Low	131.40	47.03	15/23 (65.21%)

done after screening in the study group might have improved the final mortality rate among the hypomagnesemics.

## Discussion

### How to Measure Hypomagnesemia

The method of measuring Mg levels has been a subject of debate as researchers feel that magnesium being a predominantly intracellular ion, estimating total serum Mg levels may not be accurate. Toffaletti<sup>6</sup> in 1995, noted a substantial increase in requests for serum Mg estimation and the interest has only been rising since then. Huijgen et al<sup>7</sup> found that normal or high levels of total magnesium were always associated with normal ionized Mg levels. However the positive predictive value of a low total Mg was only 29%. The RBC magnesium and ionized Mg are considered better measures of intracellular Mg but they cannot be easily estimated. Most studies still use total serum Mg.<sup>5,8,9</sup> On review of literature, the "gold standard" for establishing hypomagnesaemia is probably the magnesium loading test, where the level of absorption of administered Mg indicates the magnesium depletion in the body. This test needs further evaluation in the ICU patients. In our study we measured total Magnesium in the study group.

### Prevalence of Hypomagnesemia and the Impact of routine Mg Replacement

The prevalence of hypomagnesemia in various studies<sup>5</sup> carried out in the critically ill patients was in the range of 14-70%. In our study; 23% had hypomagnesemia on admission (defined as estimated total serum Mg<sup>+2</sup> of  $\leq 1.7$ mg/dl). Studies that measured ionized magnesium

reported lower prevalence of hypomagnesaemia (Huijgen 14% , Soliman 18%)<sup>7,9</sup> than those that had estimated total Mg or RBC Mg, where the prevalence was 20 -70% .

Hypermagnesemia has been found to be less common<sup>10</sup> and ranges from 4% - 14%. Interestingly, it has been associated with higher mortality in some studies. We found hypermagnesemia prevalent in 17.7% patients but the levels did not exceed the critical level of 5mg% and no change in clinical outcome was noted. Hence these patients have been taken into the normomagnesemic group.

On analyzing 'within' the study group, hypomagnesemia cases were noted to have higher mean duration of total ICU stay (difference of 48.837 hours) (p=0.189) as well as mean duration of Mechanical Ventilation (difference of 13.667 hours) (p=0.349). 65% of hypomagnesemia cases in the study group required ventilator support as against 47.9% in those with normal magnesium levels. Similar findings were also documented in another prospective observational study done by CS Limaye et al.<sup>5</sup> Safavi et al<sup>8</sup> described a 'retrospective observational study' which was done on 100 patients  $\geq 16$  years old, admitted to the ICU at a University Hospital over 2 years period. Hypomagnesemic patients were observed to have higher APACHE II and SOFA scores at admission (p < 0.01 for both), a higher maximum SOFA score during their ICU stay, a more need to ventilator (p < 0.05), longer stay in the ICU and longer duration of mechanical ventilation (p < 0.01) as well as higher mortality rate (55% vs. 35%) when compared with the normomagnesemic patients.

In the current study, there was no

statistically significant difference in the final mortality rate between patients with hypomagnesemia (21.73%) as compared to those of normomagnesemia (23.28%) 'within' the study group. This is important to be noted as a probable consequence of routine correction of low serum magnesium post admission. A higher mortality rate<sup>8,9</sup> can be explained by greater incidence of electrolyte abnormalities especially hypokalemia<sup>11</sup> and cardiac arrhythmias<sup>2,12</sup> and a strong association with sepsis<sup>5</sup> and septic shock.

When these parameters were compared before and after the introduction of routine screening and correction at admission to the ICU, the total mean duration of ICU stay was found to be relatively less (by 5.177 hours) in the study group, as compared to the control group. However this was not statistically significant (p=0.78). But the mean difference of Duration of Mechanical Ventilation in MICU was statistically significant (p=0.04). Post routine magnesium correction, there was 22.11 hours less requirement of mechanical ventilation. The overall ICU mortality was higher without routine correction of serum magnesium i.e, in the control group (39.6%) as against 22.9% in the study group and the difference was noted to be statistically significant (p=0.01).

Many factors contribute to hypomagnesaemia in a patient admitted to ICU like impaired GI absorption, nasogastric suction, poor content of Mg in the feeding formulae or total parenteral nutrition solutions, use of Proton pump inhibitors routinely and administration of drugs like diuretics, amino glycosides, Amphotericin B which cause renal wasting.<sup>(11)</sup> Even patients with "normal" Magnesium at admission level may even develop low serum Mg after a few days of ICU stay – hence we opine further

that routine screening of serum magnesium should be done at least intermittently during the stay in ICU; not just at admission.

We also observed that 56.52% of hypomagnesemics were Diabetics. 31.7% of Diabetics included in the study group (70% in a study by CS Limaye et al<sup>5</sup>) had low serum Mg. Hypomagnesemia has been known to be associated with Diabetes mellitus, due to increased renal losses of magnesium that accompany glycosuria.<sup>11</sup> Magnesium supplementation is associated with decreased insulin resistance.

30.43% of the hypomagnesemic study subjects were noted to be alcohol dependent and 43.7% of the alcohol dependents had hypomagnesemia. These findings are comparable to all the earlier studies.<sup>5,9</sup> Chronic alcoholism is one of the predisposing factors for magnesium deficiency,<sup>11</sup> reported in 30% of hospital admissions with alcohol abuse and in 85% of admissions for delirium tremens. This is due to a number of factors including poor nutrition, alcohol-induced renal tubular dysfunction leading to renal magnesium wasting, pancreatitis and intracellular shift in alcohol withdrawal syndrome.

Of all the complications of low serum Mg<sup>+2</sup> noted in this study, generalized weakness, gastrointestinal manifestations of anorexia and vomiting were predominant followed by

neuromuscular manifestations i.e muscle weakness and depression. Metabolic abnormalities such as hypocalcemia and hypokalemia were also frequently associated.

## Conclusion

Magnesium remains an important but often sidelined cation in the critically ill patient. Average serum Magnesium levels in the Indian Population are similar to that in the West. However further studies with larger numbers are required in this regard. Low Mg levels on admission were noted in 23% in our study group. Correction of these levels improved patient outcome by reducing the length of ICU stay, the need and duration of mechanical ventilation. The overall ICU mortality reduction was statistically significant.

Therefore we recommend routine screening at admission, followed by regular monitoring of magnesium levels, as hypomagnesaemia could develop later too. We could not repeat the serum magnesium repeatedly, after initial correction, due to cost constraints. The other limitations of our study are the sample size, and the optimization of the dose of Magnesium supplementation.

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