Magnesium, a key mineral, is the second most abundant intracellular cation. It is a cofactor of various enzymes, is essential for maintenance of membrane potentials and modification of vascular tone. It helps to maintain normal nerve and muscle function and supports a healthy immune system. The total magnesium content in humans is 25 mEq (12.4 mmol) per kilogram of body weight. The normal serum magnesium level ranges from 1.5 to 2.3 mg/dl (0.62 – 0.95 mmol/L).

The importance of magnesium is being increasingly recognized. A number of studies, especially related to critical care, have shown high prevalence of low magnesium levels and have linked the same with poor outcome. Hypomagnesemia may present with neuromuscular, neurologic, psychiatric and cardiac manifestations, which may considerably increase the morbidity of such patients. The etiology of magnesium deficiency in ICU is multifactorial. Drugs (diuretics, aminoglycosides), renal and gastrointestinal losses, comorbidities like diabetes mellitus and chronic alcoholism, metabolic disorders like Barter’s and Gittleman’s syndromes and magnesium redistribution are the postulated causes.

The use of IV magnesium in cardiovascular therapy was explored way back in 1990’s. The results of Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) and a meta-analysis of seven smaller trials depicted a reduction in mortality with a decreased incidence of heart failure and arrhythmias in acute myocardial infarction.

In this issue of the journal, B. Sheba Charles et al determined the magnesium levels in 50 healthy subjects and 96 critically ill study patients. They infused IV magnesium as a therapeutic intervention in 23 patients of hypomagnesemia (serum magnesium ≤1.7 mg/dL). The outcome parameters namely duration of ICU stay, need and duration of mechanical ventilation and overall ICU mortality were compared with a control group of 96 patients satisfying the inclusion-exclusion criteria, admitted serially in the same ICU prior to the study.

In this study the mean serum magnesium in a sample of healthy Indian population was 2.112 mg/dL (range 1.8-2.6 mg/dL) by using colorimetric method with Xylidyl blue. This was found to be marginally higher than the western data. 31.7% of diabetics and 43.7% of alcoholics had hypomagnesemia.

Evidence for Prevalence of Hypomagnesemia in ICU

The prevalence of hypomagnesemia in critically ill patients in different studies ranges from 20% to 65%. This would be influenced by cut off value, method used, study population and the parameter (Total vs Ionized) determined. In a study by Charles et al study, incidence of hypomagnesemia in patients admitted to medical ICU was 23.96% (cut-off value 1.7 mg/dL). A study by Kiran et al using same cut-off and method found 30% incidence of hypomagnesemia in a sample of 150 critically ill patients. 49% of diabetic, 33% of alcoholics and 53% of hypertensives had hypomagnesemia. A study involving 601 patients in a rural ICU in central India by Kumar et al using 1.5 mg/dL as hypomagnesemia cut off and same method found 25.45% (153/601) incidence. An observational study on 102 medical ICU patients by Reinhart et al showed that hypomagnesemia was present in 20% of patients using serum magnesium 0.7 mmol/L (1.7 mg/dL) as cut off. The majority of the studies including the present study have used total serum magnesium levels.

Ideally ionized magnesium levels would be a better option. Soliman et al measured ionized Mg levels daily (normal value, 0.42-0.59 mmol/L) in 446 patients admitted to a university hospital ICU over 3 months. 18% of patients had hypomagnesemia on admission whereas 5.15% (23) patients developed ionized hypomagnesemia during their ICU stay. A much higher incidence of hypomagnesemia – 52% has been reported by Limaye et al in 100 medical ICU patients. A cut-off of 1.7 mg/dL was used. Their colorimetric method used Titan yellow. Chernow et al using a cut-off of 1.5 mEq/dL (1.8 mg/dL) found a 61% (117/193) incidence of hypomagnesemia in 193 postoperative ICU patients.
value (1.8 mg/dL) may be the reason for a higher incidence of hypomagnesemia in this study.

**Hypomagnesemia and Outcome Parameters**

The association of hypomagnesemia with various outcome parameters in critically ill patients deserves a special consideration. In the present study,

vs. 23.3%).

was similar in both groups (21.7

statistically significant. Mortality

vs. 47.9%), but all above were not

for mechanical ventilation (65.21%

hours) and mechanical ventilation

duration of ICU stay (131.4 vs. 82.6

hours) and mechanical ventilation

in the wards had mortality approximately twice as high compared to patients with normal Mg levels (P <0.01).

Chernow study of postoperative hypomagnesemia linked severe hypomagnesemia [<1 mEq/dL (1.2 mg/dL)] with aminoglycoside use, hypokalemia and higher mortality (41%, P=0.02).

However, this association has not been consistently seen. Studies by Guerin et al(14 (179 ICU patients, 4 months), Huijgen et al(15 (115 ICU patients) and Escuela et al(16 (144 ICU patients, 6 months), showed no correlation between hypomagnesemia and mortality.

**Does Correction of Hypomagnesemia Translate into Outcome Benefits**

The study group receiving magnesium correction in Charles et al’s study, as compared to the control group, showed a decrease in mean total duration of ICU stay (by 5.2 hours, P=0.78) and the need for mechanical ventilation (52.08 % vs. 65.25%, P value=0.08), but these were not statistically significant. However the decrease in duration of mechanical ventilation by 22.11 hours (P value=0.04) and mortality reduction by 16.7% (P value=0.01) was statistically significant.

Similarly, Dabbaghet al published in 2006 the results of a prospective observational study on 71 patients consecutively admitted to the ICU and showed that mortality was significantly lower in patients who received Mg supplementation at dose >1 g/day.

**Is any Meta-analysis Available to Clarify the Issue?**

Upala S et al published a meta-analysis of 6 studies involving 1550 patients. There was a statistically higher risk of mortality and need for mechanical ventilation in critically ill patients with hypomagnesemia. (Relative risk of 1.9 and 1.65 respectively) with a higher length of ICU stay (4.1 days, P value=0.01).

In a similar meta-analysis done by Jessica Fairley et al, relevant studies from 1975 to 2014 were included. Risk of mortality was significantly increased with hypomagnesemia (odds ratio, 1.85; 95% confidence interval, 1.31-2.60). No consistent associations existed between magnesium administration and outcome.

A 18 months prospective observation study on prolonged mechanical ventilation (PMV) in a tertiary care medical ICU (45/397 mechanically ventilated patients) by Vora C et al revealed hypomagnesemia in 40.9% patients requiring PMV. The other electrolyte abnormalities observed were hypocalcemia - 84.4%, hypokalemia – 31.1% and hypophosphatemia – 23.8%. Occurrence of multiple electrolyte abnormalities including hypomagnesemia in PMV patients is noteworthy.

**Which Patients in the ICU Merit Serum Magnesium Level and its Correction**

Apart from the rare syndromic presentation of Barter and Gittelman’s (presenting with hypomagnesemia, hypokalemia, metabolic alkalosis and occasional hypocalcemia/hypophosphatemia), patients having combination of above electrolyte disorders or persistent hypokalemia and hypocalcemia, chronic ethanol abusers, diabetes mellitus,
patients of sepsis and prolonged mechanical ventilation warrant a search for hypomagnesemia and its subsequent correction. In cardiac ICUs, the same could be extrapolated to patients with ventricular arrhythmias including Torsade de pointes. All tertiary care centers should monitor serum magnesium levels in critically ill patients with above comorbidities and risk factors especially if they are on mechanical ventilation.

In the present study, by designing it as “a before and after study”, Charles et al. have very cleverly bypassed the ethical hurdle of doing an interventional study. The small sample size might not have allowed the difference in the outcome parameters within the hypomagnesemic and the normomagnesemic study group patients to be statistically significant. Also hypermagnesemia was not considered as a separate group and clubbed with normomagnesemia. Future multicenter studies involving larger sample size, estimating ionized rather than total serum magnesium level and keeping hypermagnesemia as a separate entity may provide additional evidence to the conundrum of magnesium care of critically ill.

References