

# Hypomagnesemia in ICU

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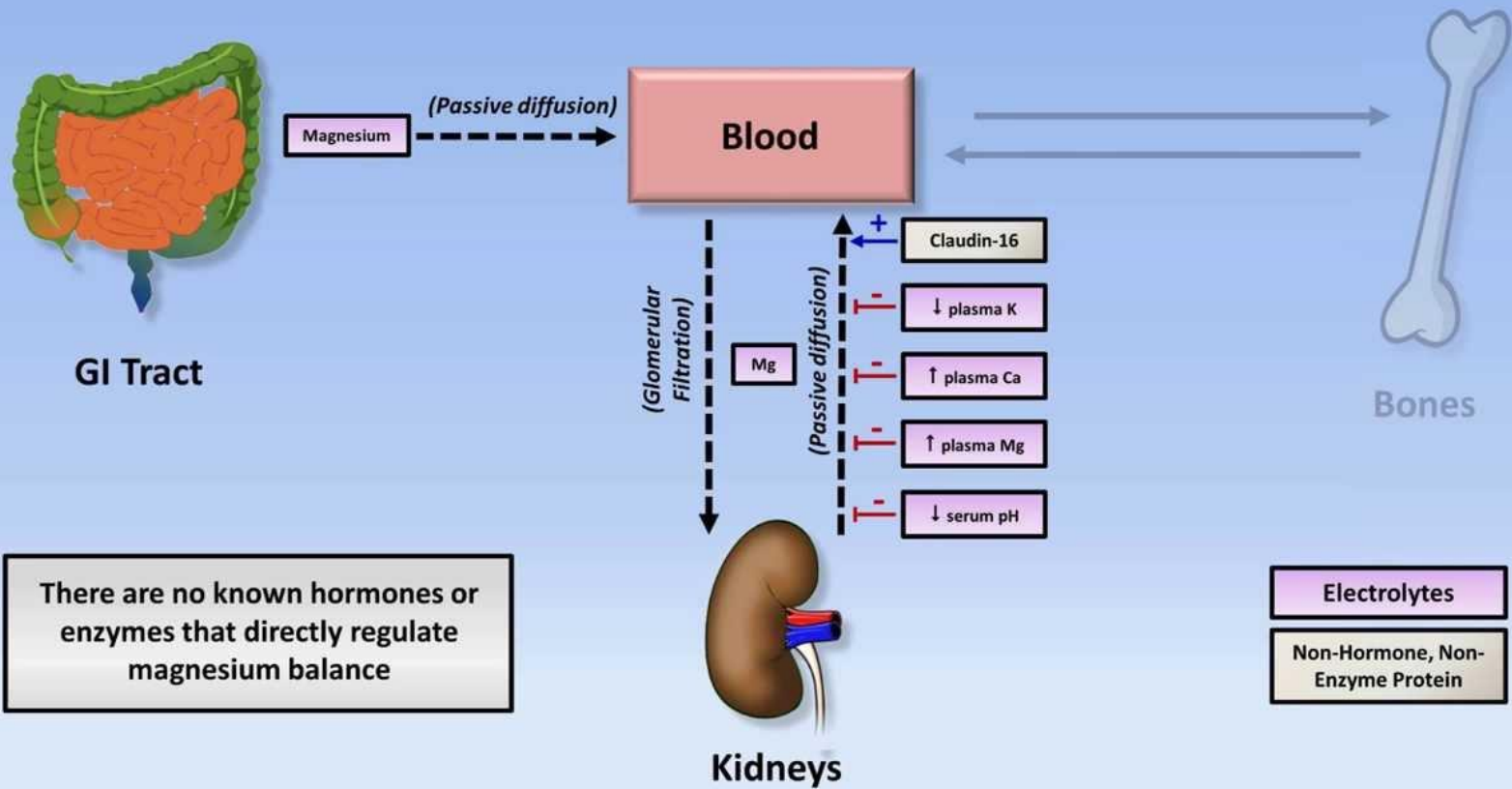
# INTRODUCTION

- 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.

- Approximately 60% of body magnesium is stored in bone, and most of the remainder is found in cells. Only 1% is in the ECF.
- As a result, the serum magnesium is a poor predictor of intracellular and total body stores and may grossly underestimate total magnesium deficits.

# Regulation of Mg Homeostasis

## Regulation of Magnesium Homeostasis



The risk of hypomagnesemia can be summarized as follows:

- 2% in the general population
- 10-20% in hospitalized patients
- 50-60% in intensive care unit (ICU) patients
- 30-80% in persons with alcoholism
- 25% in outpatients with diabetes

# Clinical Manifestations of Magnesium Imbalances

## Hypomagnesemia

- **Neuromuscular** – hyperirritability, tetany-like symptoms, tremors, twitching of the face, spasticity, increased tendon reflexes
- **Cardiac** – Hypertension, cardiac dysrhythmias - PVC's, VT (Torsades), VF, and flat or inverted T wave, ST depression (like low K levels)

## Hypermagnesemia

- Neuromuscular – CNS depression, lethargy, drowsiness, weakness, paralysis, loss of deep tendon reflexes
- Hypotension, Complete heart block (3<sup>rd</sup> degree), bradycardia, Widened QRS complex, prolonged QT interval
- Others: Flushing, respiratory depression

# DRUGS

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- **Diuretics** – Loop diuretics, osmotic diuretics, and chronic use of thiazides
- **Antimicrobials** – Amphotericin B, aminoglycosides, pentamidine, capreomycin, viomycin, and foscarnet
- **Chemotherapeutic agents** – Cisplatin
- **Immunosuppressants** – Tacrolimus and cyclosporine
- Proton-pump inhibitors
- Ethanol

# Evidence for Prevalence of Hypomagnesemia in ICU

- Prevalence of hypomagnesemia in critically ill patients in different studies ranges from 20% to 65%
- 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)



# Hypomagnesemia and Outcome Parameters

- The association of hypomagnesemia with various outcome parameters in critically ill patients deserves a special consideration.
- In the present study, within the study group, pts with hypomagnesemia (as compared to pts with normomagnesemia) had higher duration of ICU stay (131.4 vs. 82.6 hours) & mechanical ventilation (47.08 vs. 33.4 hours), higher need for mechanical ventilation (65.21% vs. 47.9%), but all above were not statistically significant. Mortality was similar in both groups (21.7 vs. 23.3%).

- **Kiran et al study**, showed that hypomagnesemic pts had higher mortality [51% vs. 36%(P value=0.02)] & higher need for ventilator support [35% vs. 17%(P value  $\leq 0.009$ )] but there was no association with duration of ICU stay (P >0.65).

- In **Kumar et al study** of 601 patients, hypomagnesemia was associated with higher duration of MICU stay (5.46 vs. 3.93 days,  $P=0.0002$ ), need for mechanical (15.86 % vs. 24.33%,  $P < 0.000$ ) and mortality (38.56% vs. 14.73%,  $P=0.000$ ) but there was no difference in duration of ventilation ( $P=0.36$ ).

# 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

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

- **Upala S et al** published a metaanalysis 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.

- 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% pts 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 ICU Merit Serum Magnesium Level and its Correction

- Apart from rare syndromic presentation of Barter & 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 & risk factors especially if they are on mechanical ventilation.

# Hypomagnesemia in the ICU – Does Correction Matter?

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- **Original Article**

# 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 underrecognized & uncorrected.
- There are no studies, in our knowledge, that have assessed the impact of correction of hypomagnesaemia on outcome of the ICU pt.

# Aims and Objectives:

- To determine the standard Mg levels in a healthy population sample & 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



# 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 sample of the normal population.

- The second phase was conducted in the medical ICU where we prospectively recruited 96 critically ill patients into the study sample from 6th March 2012 to 5th 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
- Normal magnesium levels were taken between 1.7mg/dl –2.4mg/dl (by colorimetric method with Xylidyl blue)

# 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, 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  $p=0.04$ ).

**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)

- Mortality was significantly higher in the comparison group ( $p=0.01$ ) (39.6% vs. 22.9%).

**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	28
31-40	8	3	11
41-50	7	14	21
51-60	24	17	41
≥60	38	50	88
Total	96	96	189
<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	



# 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.

# Diagnostic Testing

- Low serum [Mg<sup>2+</sup>] in conjunction with an appropriate clinical scenario is sufficient to establish the diagnosis of **magnesium deficiency**.
- The etiology of hypomagnesemia usually is evident from the clinical context, but if there is uncertainty, measurement of **urine magnesium excretion** is helpful.

# 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.

- 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

- 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

- Even patients with “normal” Magnesium at admission level may even develop low serum Mg after a few days of ICU stay – hence they 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) had low serum Mg.
- Hypomagnesemia has been known to be associated with Diabetes mellitus, due to increased renal losses of Mg that accompany glycosuria.
- Magnesium supplementation is associated with decreased insulin resistance.

- Chronic alcoholism is one of the predisposing factors for magnesium deficiency, 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.



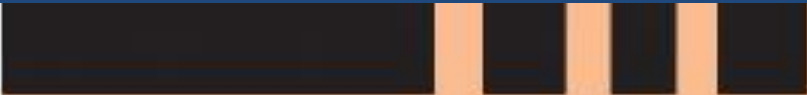
# TREATMENT

- In patients with normal renal function, excess magnesium is readily excreted, and there is little risk of causing hypermagnesemia with recommended doses.
- However, *magnesium must be given with extreme care in the presence of renal insufficiency.*

- The route of magnesium administration depends on whether clinical manifestations from magnesium deficiency are present.
- **Asymptomatic hypomagnesemia can be treated orally**
- Numerous preparations exist, including Mag-Ox 400 (240 mg elemental magnesium per 400-mg tablet)

# Severe symptomatic hypomagnesemia

- Treated with 1 to 2 g magnesium sulfate (1 g magnesium sulfate = 96 mg elemental magnesium) IV over 15 minutes.
- Again, to account for gradual redistribution to severely depleted intracellular stores, replacement therapy may need to be maintained, often for 3 to 7 days.
- Tendon reflexes should be tested frequently, as hyporeflexia suggests hypermagnesemia.




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96402

**MAGNESIUM  
SULFATE**  
*INJECTION, USP*

**50% (1 gram/2 mL)**



For IM or IV Use

**Must be diluted before IV use.**

**2 mL** Single Dose Vial

4.06 mEq/mL

4.06 mOsmol/mL

**Fresenius Kabi USA, LLC**  
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# SUMMARY

- 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.

Thank you !