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Serum magnesium levels and its correlation with unfavourable outcomes of critically ill patients admitted at intensive care unit

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Abstract

Introduction: Deficiency of Magnesium leads to activation of neuroendocrine pathways which induces systemic stress response, which in turn takes part in the pathogenesis of numerous disease and also implicated in an increased mortality rate among ICU patients. The above said effects of Magnesium on immune system play a crucial role in the pathogenesis of sepsis. In hypomagnesemic state, cardiac tolerance to reduced oxygen level is reduced significantly. Electromechanical activities of cardiac smooth muscles and vascular endothelial cells can get affected largely by small changes in free Magnesium levels.

Objectives: To determine and corelate serum magnesium levels and unfavourable outcomes of critically ill patients admitted at intensive care unit.

Materials and Methods: A Prospective observational study was conducted to find the Serum magnesium levels and its correlation with unfavourable outcomes among 100 critically ill patients admitted at intensive care unit, ESICMC&PGIMSR Medical College Hospital during the period of Jan 2021 to June 2022.

Results: Critically ill patients who were admitted in MICU, ESICMC & PGIMSR Medical College, males were 58 and females 42, mean age was of males were 63.09 years and females were 69.7 years. There was no significant difference between the male and female study participants.

There was a significant difference present related to mean Apache score between the comatose (27.8) as compared to the non-comatose (20.58) patients. There was no significant difference related to the intubation days between the comatose and non-comatose patients.

There was significant negative correlation between the Serum Mg values and Apache score ($r=-0.422$, $p<0.008$). The Hypomagnesemia was present with the lowest GCS score as compare to the normal /Hyper magnesemia.

Conclusion: Hypomagnesemia was associated with longer duration of ventilator support and ICU stay, and higher APACHE II score in critically ill patients.

Keywords: Serum magnesium levels; critically ill-patients; APACHE Score.

Introduction

In the human body Magnesium is known to be the fourth abundant cation and next to potassium which is known to be second most abundant cation intra cellularly [1]. And it helps in completing reaction as cofactor nearly for 300 enzymes more commonly involving transferring of phosphate group; it is the major intracellular divalent cation. And it also helps in the formation of ATP. And maintain neuromuscular excitability and maintenance of cardiac function is also its major action. With ATP, Intracellular magnesium will form key complex and acts as an important cofactor for transporters, enzymes, and nucleic acids needed for normal cellular function, energy metabolism and replication. The normal concentration of serum magnesium is between the ranges of 1.8 to 2.5 mg/dl [2], In that 30% will be bound to the protein and 15% is loosely bound to the many other anions and phosphate. According to studies during the ICU stay 20 to 65% of critically ill patients develop hypomagnesemia [3]. It is very important to consider Hypomagnesemia, as it is very common in patients with critical illness.

Patients with hypomagnesemia on admission have been found to have an important impact on mortality and morbidity according to many important studies. Such patients have a higher APACHE II Score, which has a poor prognosis. Hypomagnesemia is an important factor causing prolonged stay in critically ill patients admitted in ICU. It causes an increased need for ventilator support, and increased number of days on ventilator. Various studies have supported it and is an overall factor which increases the mortality and morbidity of the patients. Our present study aims to look at the above said factors and to determine the impact of hypomagnesemia in critically ill medical patients in a centre for tertiary care(4)

The body contains the total magnesium of around 21-28grams. 53% of total magnesium is found in bone, 19% in non muscular tissue and 1% in extracellular fluid. The majority of serum magnesium is bound to chelators such as ATP, ADP, proteins and citrate. Approximately 33% of serum magnesium is bound to proteins and 5-10% is not bound. In the regulation of intracellular magnesium, this unbound form play an essential role. In the regulation of serum magnesium kidneys play an important role. 60% of filtered magnesium is getting absorbed from the loop of Henle. So it is the major site for magnesium homeostasis. Only 120 mg of magnesium is excreted through urine as against 2400 mg of filtered magnesium.

Magnesium is primarily found within the cell where it acts as a counter ion for the energy-rich ATP and nuclear acids[6]

Thus, one should keep in mind that ATP metabolism, muscle contraction and relaxation, normal neurological function and release of neurotransmitters are all magnesium dependent. It is also important to note that magnesium contributes to the regulation of vascular tone, heart rhythm, platelet-activated thrombosis and bone formation [7]

It has long been suspected that magnesium may have a role in insulin secretion owing to the altered insulin secretion and sensitivity observed in magnesium-deficient animals [8]

Recent epidemiological studies have suggested that a relatively young gestational age is associated with magnesium deficiency during pregnancy, which not only induces maternal and foetal nutritional problems but also leads to other consequences that might affect the offspring throughout life [9]

The incidence of hypomagnesemia varies from 20% to 65% in intensive care unit (ICU) patients. The pathology of magnesium deficiencies is multifactorial including gastrointestinal disorders, renal loss, renal diseases, drug induced loss, metabolic acidosis, and other causes.1,5 In addition, critically ill patients have several potential risks of magnesium dysregulation. It was significantly associated with increased and prolonged need for mechanical ventilation, difficulty to wean, prolonged ICU stay and increased mortality in critically ill patients.9-11

Hypermagnesemia is less common and mostly due to renal failure or iatrogenic.

Prevalence of hypermagnesemia was reported to be 7.3%.12 It can lead to severe muscle weakness, respiratory depression, hypotension, cardiac arrhythmia and ultimately progress to cardiac arrest.13. Hence, an attempt was made to study serum magnesium levels in critically ill patients on admission in ICU and its correlation with patient's need and duration for ventilator support, duration of ICU stay, incidence of cardiac arrhythmias and mortality.

Magnesium consumption

Humans need to consume magnesium regularly to prevent magnesium deficiency, but as the recommended daily allowance for magnesium varies, it is difficult to define accurately what the exact optimal intake should be. Values of ≥300 mg are usually reported with adjusted dosages for age, sex and nutritional status. The Institute of Medicine recommends 310–360 mg and 400–420 mg for adult women and men, respectively. Other recommendations in the literature suggest a lower daily minimum intake of 350 mg for men and 280–300 mg magnesium for women (355 mg during pregnancy and lactation)[10][11]

While drinking water accounts for ∼10% of daily magnesium intake [12], chlorophyll (and thus green vegetables) is the major source of magnesium. Nuts, seeds and unprocessed cereals are also rich in magnesium [13]

Legumes, fruit, meat and fish have an intermediate magnesium concentration. Low magnesium concentrations are found in dairy products. It is noteworthy that processed foods have a much lower magnesium content than unrefined grain products[14]

The salts of magnesium are used in the form of magnesium hydroxide, magnesium citrate, magnesium sulphate or magnesium chloride, in laxatives or antacids.

Chemical characteristics of magnesium

In the periodic table: it is a group 2 element.

Atomic mass: 24.305Da

Specific gravity at 20 degree C: 1.738

Boiling point: 1090 degree C

Melting point: 648.8 degree C

When comparing to potassium, sodium and calcium, it binds with hydration water tightly. So it is hard to dehydrate the hydrated magnesium, also the radius of hydrated magnesium is 400 times larger than that of dehydrated form. When compared to calcium, sodium and potassium, for the magnesium ions the difference between hydrated and dehydrated state is very prominent. Although ionic radius of dehydrated magnesium is small, it is biologically

relevant. Lot of peculiarities of magnesium can be explained by the above simple fact including its antagonistic behaviour to calcium in spite of the similar charge and chemical reactivity. For example, unlike calcium which readily traverses through narrow channels in biological membranes, the magnesium cannot be able to do so. Because magnesium cannot be stripped of its hydration shell.

Physiological functions of magnesium:

In muscle contraction, by stimulating the calcium activated ATPase of the sarcoplasmic reticulum, the magnesium stimulates the calcium reuptake. Also magnesium modulates cell proliferation and insulin signal transduction. It is also important for cell adhesion and transmembrane conductance of calcium and potassium ions. By maintaining the conformation of nucleic acids, it is important for the structural function of proteins and mitochondria.

Regulation of magnesium influx and efflux: The intra and extracellular magnesium is being exchanged at various rates in myocardium, kidneys, skeletal muscles, brain and lymphocytes. In mammalian heart, adipocytes and kidney the total intracellular magnesium is completely exchangeable with extracellular magnesium within 3-4hours. But in man, this equilibrium takes place very slowly.

Magnesium absorption and excretion: The intestine, bone and kidneys play a major role in magnesium homeostasis. Like calcium, magnesium gets absorbed in the gut & stored in bones, and excess of magnesium gets excreted mainly through kidneys and also small amount in faeces. Two transport mechanisms are there for the reabsorption of magnesium from the gut. They are:

1. Passive para cellular mechanisms: these are driven by means of electrochemical gradient & solvent drag. The majority of magnesium is absorbed in the small intestine by this mechanism.
2. Minor fraction of Mg is absorbed via TRPM6 &TRPM7. These are members of long transient receptor potential channel family. Only about 24-76% of consumed magnesium is absorbed from the gut & the remaining amount is eliminated through faeces. The rate of absorption of Mg from the gut is directly proportional to serum magnesium levels, it does not depend upon total Mg intake. If concentration of Mg is low inside the lumen, active trans cellular transport will take an upper hand.

Pathophysiology: To diagnose hypomagnesemia, measurement of serum magnesium levels and 24 hours of urinary magnesium excretion are the most important laboratory tests.

Chronic hypomagnesemia

Diagnosis of chronic hypomagnesaemia is difficult as there may be only a slightly negative magnesium balance over time. There is equilibrium among certain tissue pools, and serum concentration is balanced by magnesium from bone. Thus, there are individuals with a serum magnesium concentration within the reference interval who have a total body deficit for magnesium. Magnesium levels in serum and 24-h urine samples may be normal, and so parenteral administration of magnesium with assessment of retention should be considered if in doubt [7].

Hypomagnesaemia has been linked to poor condition (malignant tumours, cirrhosis or cerebrovascular disease)

The following conditions are associated with chronic latent magnesium deficiency.

1. Atherosclerosis
2. Essential hypertension
3. Acute coronary syndrome
4. Renal calculi
5. Malignant tumours
6. Dyslipidemia
7. Psychiatric disorders and
8. Premenstrual syndromes.

Clinical features of hypomagnesemia

Early signs include nausea, vomiting, anorexia, easy fatigue and weakness. Other manifestations include agitation, tremors, fasciculations, depression, hypokalemia and cardiac arrthmias. In severe hypomagnesemia tingling, numbness, cramps, muscle contractions, seizures, sudden onset of altered behaviour caused by excess electrical activity of the brain, changes in personality, irregularities in heart beat and coronary spasm can occur. Other electrolyte imbalances such as hypokalemia and hypocalcemia may accompany severe hypomagnesemia.

Aims and Objectives

To determine and corelate serum magnesium levels and unfavourabe outcomes of critically ill patients admitted at intensive care unit.

Materials and Methods

A Prospective observational study was conducted to find the Serum magnesium levels and its correlation with unfavorable outcomes among 100 critically ill patients admitted at intensive care unit, ESICMC&PGIMSR Medical College Hospital during the period of Jan 2021 to June 2022.

Ethical Clearance

A protocol of the intended study was submitted to the Institutional Ethical Committee and Review Board, ESICMC&PGIMSR Medical College Hospital and ethical clearance was obtained.

Permission and Consent

Necessary permissions were obtained from concerned authorities of hospital before conducting the study. Informed consent was obtained from the participants after explaining the procedure and purpose clearly.

Training and Calibration

Principal investigator was trained and calibrated prior to start of the study to ensure reliability. The investigator evaluated a group of 5 patients for the feasibility of taking variables and outcome assessment. The Kappa co-efficient value (k) for intra examiner reliability for the investigator was 0.86-0.88. The overall intra-examiner reliability was good and these values reflected high degree of conformity in observation.

Patient Selection Criteria

Inclusion criteria:

1. Critically ill adult patients above the age of 18 years, admitted in MICU.
2. With APACHE II score of 18 or more.

Exclusion criteria:

1. Patients who had received blood products.
2. Patients who had received magnesium infusion.
3. Patients who are not willing to participate in this study

Sample Size Calculation:

1. Sample Size:

Cochran formula for minimum Sample Size=**N** = $\frac{Z^2 * P * (1-P)}{e^2}$

Where Z=1.96, z value for 5% confidence level

P= proportion in the target population having given characteristic. Here, P=0.80 e= Precision at 6%

= (1.96^2*0.80*0.14)/$(0.10)^2$ =100

Hence Minimum Sample Size =100

Study Procedure

A Total Of 100 Critically Ill Patients Admitted In A Intensive Medical Care Unit, ESICMC & PGIMSR Medical College Hospital During The Period Of Jan 2021 To June 2022. Critically Ill Adult Patients Aged More Than 18years Were Included. Written And Informed Consent Was Obtained From All Patients.

Patient's age, gender, diagnosis, duration of stay, clinical parameters and mechanical ventilation were recorded. Patients who had received blood products, magnesium or calcium infusions before sampling have been excluded from the study. Inclusion of the patients in this study did not affect the routine patient care in the IMCU. Acute Physiology and Chronic Health Evaluation (APACHE II) score have been calculated for each patient on the day of admission to Intensive care unit. Venous blood samples of around 4.5ml was taken to assess serum magnesium levels, within the first 24hours of admission in to the MICU.

Statistical Analysis: The data collected were entered into excel spread sheet and it was analyzed using the Statistical Package for Social Sciences (SPSS) version 24. .Descriptive and inferential statistics was done. Continuous variables were presented as mean ± SD, and categorical variables were presented as absolute numbers and percentage. Data was checked for normality before statistical analysis and found the normal data set. Independent t test was used to find out the mean difference of clinical findings. Pearson's correlation was used to find the relationship between the variables. Statistical significance was considered at p <0.05 (confidence interval of 95% was taken).

Results

Table 1: Gender wise mean difference of laboratory variables

	Sex	Mean	Std. Deviation	Std. Error Mean	Mean df	p-value
GCS	Male	9.17	3.43	0.72	0.99	0.09
	Female	8.18	3.38	0.82		
Apache PS	Male	22.74	7.47	1.56	1.79	0.41
	Female	24.53	7.49	1.82		
Intubation (days)	Male	9.04	3.43	0.72	0.22	0.52
	Female	8.82	4.23	1.03		
Total	Male	17.59	6.81	1.56	0.64	0.85
	Female	18.225	6.47	1.78		
SMg	Male	2.809	1.06	0.22	0.27	0.11
	Female	2.537	1.27	0.32		
SCa+	Male	12.022	2.74	0.57	0.45	0.21
	Female	11.569	2.58	0.65		

Independent t test, sig2 tailed, p<0.05

Table 2: Disease Severity wise mean difference of the hospital related variables

	GCS CAT	Mean	Std. Deviation	Std. Error Mean	Mean df	P value
Apache PS	(GCS<8)	27.88	6.84	1.71	7.30	0.00
	(GCS≥8)	20.58	6.41	1.31		
Intubation (days)	(GCS<8)	9.75	4.19	1.05	1.33	0.45
	(GCS≥8)	8.42	3.40	0.69		
SMg	(GCS<8)	2.25	0.88	0.22	-0.76	0.00
	(GCS≥8)	3.01	1.21	0.25		
SCa+	(GCS<8)	11.23	1.61	0.40	-1.04	0.03
	(GCS≥8)	12.26	3.15	0.66		

Graph 1:

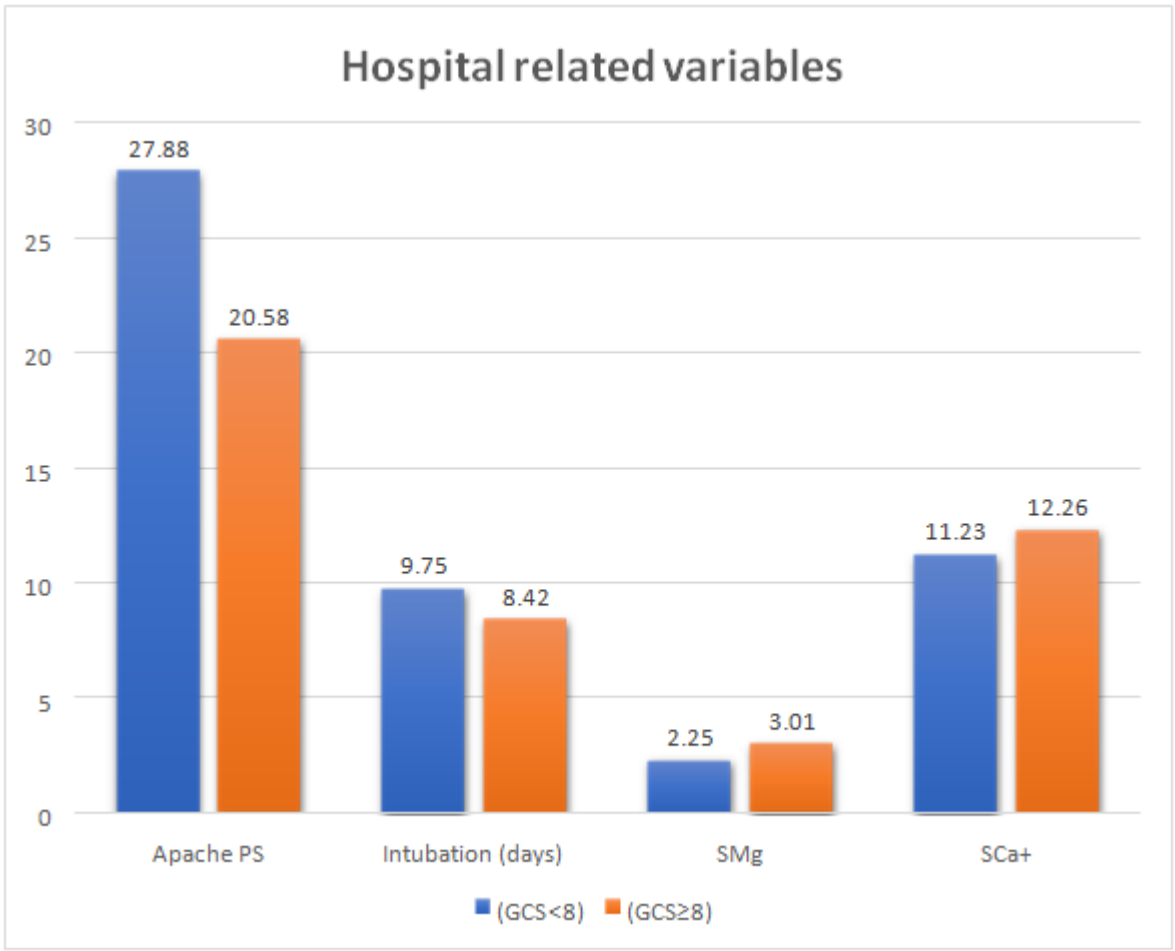


Table 2 shows the significant difference present related to mean Apache score between the comatose (27.8) as compared to the non-comatose (20.58) patients. There was no significant difference related to the intubation days between the comatose and non comatose patients

Table 3: Patients severity status and laboratory value comparison

	GCS CAT	Mean	Std. Deviation	Std. Error Mean	mean df	Pvalue
Arterial Ph	(GCS<8)	7.54	0.20	0.05	0.18	0.00
	(GCS≥8)	7.36	0.12	0.02		
Na+	(GCS<8)	134.63	7.48	1.87	2.13	0.40
	(GCS≥8)	132.50	8.01	1.63		
K+	(GCS<8)	3.79	0.92	0.23	0.06	0.86
	(GCS≥8)	3.73	1.24	0.25		
Creatinine	(GCS<8)	3.22	2.06	0.51	0.51	0.48
	(GCS≥8)	2.72	2.24	0.46		
PCV	(GCS<8)	37.75	8.21	2.05	-1.50	0.95
	(GCS≥8)	39.25	8.97	1.83		
TC	(GCS<8)	9564.38	5978.47	1494.62	2405.05	0.60
	(GCS≥8)	7159.33	2960.06	604.22		

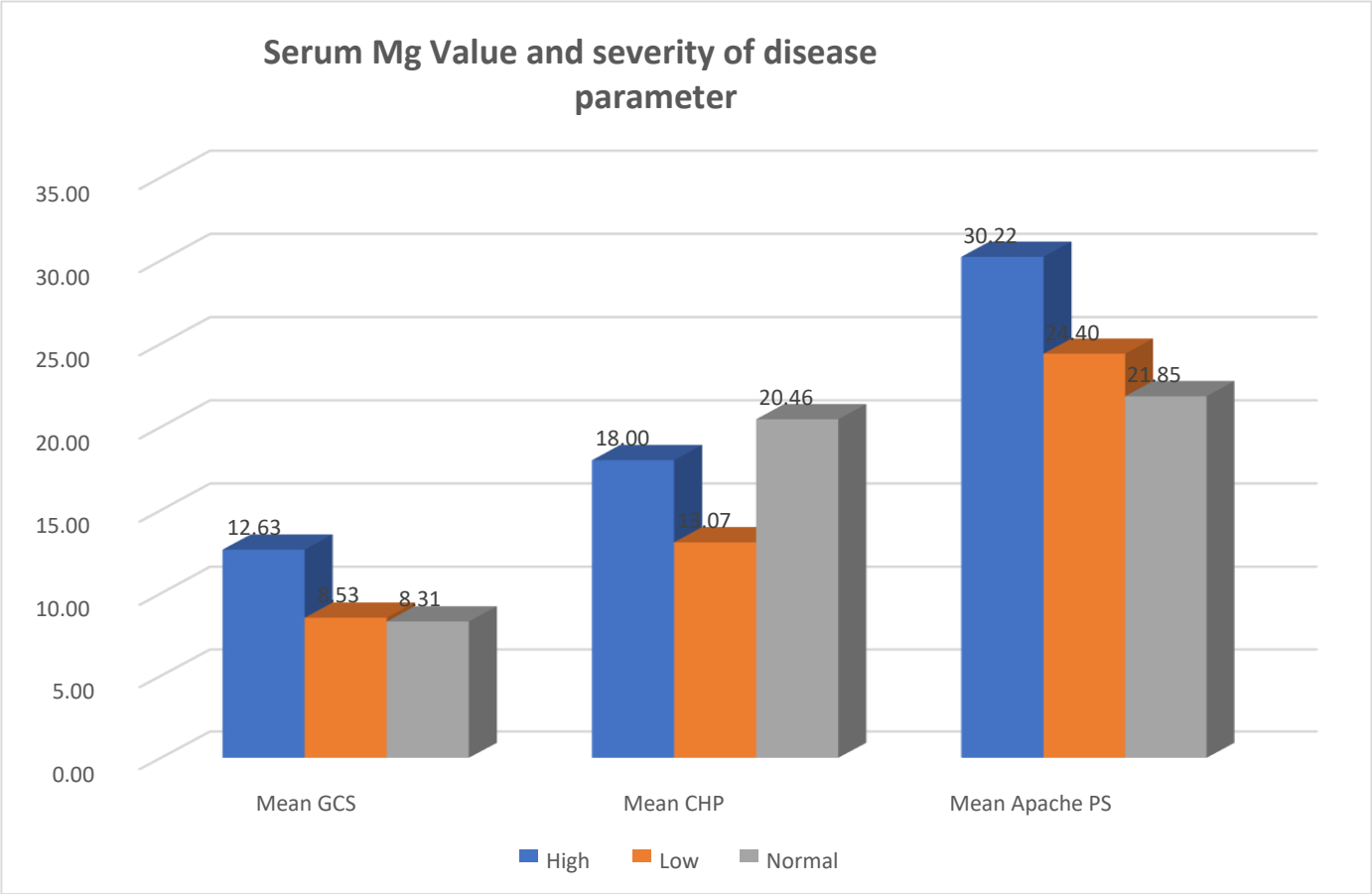
Related to the Serum Mg, the significant difference present between the comatose (2.25) as compared to the non-comatose (3.01) patients. Similarly, the significant difference present related to mean serum calcium values between the comatose (11.23) as compared to the non-comatose (12.26) patients.

Table 4: Serum Mg Value and severity of disease parameter

Serum Mg	High	Low	Normal	Grand Total	p-value
Mean GCS	12.63	8.53	8.31	11.45	<0.001
SD	5.12	3.44	3.52	5.05	
Mean CHP	18.00	13.07	20.46	17.58	0.441
SD	6.46	5.99	4.70	6.48	
Mean Apache PS	30.22	24.40	21.85	28.26	0.002
SD	8.17	7.66	9.31	8.78	

Independent t test

Graph 2:



Discussion

In mystudy,100 critically ill patients who were admitted in MICU, ESICMC&PGIMSR Medical college, males were 58 and females 42, mean age was of males were 63.09 years and females were 69.7 years. There was no significant difference between the male and female study participants related to mean difference of GCS , Apache PS, CHP Score, intubation days and serum Magnesium.

There was a significant difference present related to mean Apache score between the comatose (27.8) as compared to the non-comatose (20.58) patients. There was nosignificant difference related to the intubation days between the comatose and non comatose patients. There was significant negative correlation between the serum Mg values and Apache score ($r=-0.422$, $p<0.008$).

The Hypomagnesemia was present with the lowest GCS score as compare to the normal /Hyper magnesemia.

They concluded that among the elderly patients admitted in ICU hypomagnesemic patients, when compared with normomagnesemic patients had higher duration of ICU stay .The necessity for mechanical ventilation, average duration of ventilation were higher in hypomagnesemic patients when compared to normomagnesemic individuals. Low serum magnesium levels were associated with severity of disease.. So serum magnesium level monitoring may have impact on prognostic and therapeutic implications especially in elderly patients.

Conclusion

Hypomagnesemia was associated with longer duration of ventilator support and ICU stay, and higher APACHE II score in critically ill patients.

Summary

- Hypomagnesaemia was associated with longer duration of ventilator support and ICU stay, and higher APACHE II score in critically ill patients.
- There was no significant difference between the male and female study participants related to mean difference of GCS, Apache PS, CHP Score, intubation days and serum Magnesium.
- There was no significant difference related to the intubation days between the comatose and non comatose patients.
- The Hypomagnesaemia was present with the lowest GCS score as compare to the normal /Hyper magnesemia.
- serum magnesium level monitoring may have impact on prognostic and therapeutic implications especially in elderly patients.

Limitations

- Sample size was small due to financial and time constraint.
- The study was conducted only in patients admitted at a single tertiary care center.
- A few dynamic changes in serum value due to fluid administration were not studied.

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