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Is Intra-Cellular Magnesium Concentration Correlate with Morbidity and Mortality in Critically Ill Patients? A Cross-Sectional Study

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ABSTRACT

Background: Hypomagnesemia is a common electrolyte disturbance among critically ill patient which is associated with increased morbidity and mortality. In this study, correlations between serum and intra-cellular magnesium concentrations at the time of intensive care unit (ICU) admission with ICU complications and mortality were evaluated.

Methods: This cross-sectional study included 70 consecutive adult patients admitted to the intensive care unit of a tertiary referral teaching hospital during a six-month period. Serum and intra-cellular magnesium levels were measured on admission. Clinical information, morbidity, and mortality were followed and recorded during ICU stay until discharge or death.

Results: On admission, 37.14% of patients suffered hypomagnesemia. Low intra-cellular magnesium level was observed in 44.28% of patients. Cardiovascular complications and mortality were significantly higher in patients with lower serum and intra-cellular magnesium levels when compared to patients with normal levels ($P < 0.05$). There was a significant correlation between serum magnesium level on ICU admission and Acute Physiology and Chronic Health Evaluation (APACHE II) score ($r = -0.39$, $P < 0.001$).

Conclusion: Particular attention should be reserved to possible prognostic and therapeutic consequences of magnesium depletion in critically ill patients. Magnesium deficiency was associated with a higher APACHE II score on admission, higher cardiovascular complications, and increased mortality.

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Introduction

Magnesium as a second most abundant intra-cellular divalent cation plays a fundamental role in many human physiological and biochemical functions. Magnesium acts as an essential cofactor required for more than 300 cellular enzymatic reactions involved in metabolism and signal transduction pathways. It is actively involved in carbohydrate, lipid, and protein metabolism (1). Moreover, magnesium has crucial role in modulating vascular smooth muscle tone, endothelial cell function, excitability of a cardiac cell, platelet aggregation, coagulation, fibrinolysis, immunity, and pulmonary function (2-5).

Hypomagnesemia is a common electrolyte disturbance among critically ill patients with both symptomatic and asymptomatic clinical features (6). The prevalence of hypomagnesemia has been reported as high as 61-65% in critically ill patients (7, 8). Patients with diabetes mellitus, sepsis, diuretic use and/or aminoglycoside use are more vulnerable to incidence of hypomagnesemia

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following acute illnesses (7, 9, 10). Hypomagnesemia correlates with respiratory failure, sepsis, cardiovascular complications and prolonged ICU stay (11, 12). However, hypermagnesemia is less frequently reported in critical care setting. The most common predisposing factors of hypermagnesemia are renal failure and iatrogenic administration of magnesium (13). Considering vital role of magnesium, hypomagnesaemia prevalence, and its negative effects on the patients' outcomes, appropriate evaluation of patients at the time of ICU admission is recommended (11,12).

Magnesium is a predominant intra-cellular cation (about 99%) and serum magnesium levels do not always accurately reflect the intra-cellular or total body magnesium content. Therefore, if it is possible, evaluating intra-cellular magnesium level as a surrogate marker of total body magnesium is recommended (1). Hence in this study, correlations between serum and intra-cellular magnesium concentrations at the time of admission with ICU complications and mortality have been evaluated in critically ill patients.

Methods

This cross-sectional study included consecutive adult patients (≥18 years of age) admitted to the intensive care unit of a tertiary referral teaching hospital during a six-month period. The study was registered at Tehran University of Medical Science, Tehran, Iran (code number: TUMs.T-104). Patients who declined research authorization, current or recent (within the last 3 months) use of magnesium supplements, history of prior blood transfusion, and those with recurrent admissions were excluded. A total of 70 consecutive patients were evaluated.

A 5 ml venous blood sample was drawn from peripheral intravenous line of each participant within 1 hour of ICU admission to measure magnesium levels. Intra-cellular (intra-erythrocyte) and serum magnesium levels were measured by atomic absorption spectrophotometer (14). Then, we categorized patients according to the serum and intra-erythrocyte magnesium levels. We defined hypomagnesemia as a total serum magnesium level lower than 1.7mg/dL. Moreover, intra-erythrocyte magnesium concentration less than 4 mg/dL was considered as intra-cellular magnesium deficiency.

Also, following variables were collected from the patients' medical records: demographic data [sex, age, weight, and cause of admission], severity of acute illness (APACHE II) score and Sequential Organ Failure Assessment (SOFA) Score), laboratory data (complete blood count, blood sugar, C-reactive protein, erythrocyte sedimentation rate, liver and renal function tests), and hemodynamic parameters (mean arterial pressure and heart rate).

In our study, the primary outcome was considered ICU mortality which defined as death occurring prior to discharge from the ICU. The secondary outcomes included ICU length of stay (LOS), ICU complications and disease severity scores such as Acute Physiology and Chronic Health Evaluation (APACHE II) and SOFA scores. As ICU complications, we evaluated infectious, cardiac and renal complications.

Infectious complications included ventilator associated pneumonia, urinary tract infections, surgical site infections, and catheter-related blood stream infections. Infection diagnosis was conducted in accordance with Centers for Disease Control and Prevention (CDC) criteria for infection based upon the consensus of two independent intensivists or positive culture results, which resulted in a treatment such as new antibiotic regimen or opening a wound for drainage (15, 16).

All patients received cardiac monitoring by electrocardiogram continuously. Cardiac complications defined as myocardial infarction, cardiac death, cardiogenic shock, pulmonary edema, malignant ventricular arrhythmias, and malignant bradyarrhythmia.

We considered acute renal failure as renal complication. It was defined based on international Kidney Disease Improving Global Outcomes (KDIGO) criteria (17). Included patients were monitored continually by two independent intensivists to evaluate all complications that may occur during their ICU hospitalizations.

Statistical analyses were performed using SPSS version 24.0 software. The Kolmogorov-Smirnov test was used to assess if the continuous variables followed a normal distribution. Continuous variables are reported as mean ± standard deviation (SD) or median [interquartile range] and compared using the independent sample t or Mann–Whitney tests. Categorical variables are presented as counts (percentages) and compared using the chi-squared test or Fisher exact test. Correlations were analyzed by Pearson or non-parametric Spearman correlation test. A p-value of < 0.05 was considered statistically significant.

Results

Over the study period, 70 adult patients who admitted to the ICU, met the inclusion criteria. The mean age (± SD) of patients was approximately 54.51 (± 14.76) years and 42 patients (60%) were male; 70% of patients were medical, and 30% were surgical. Demographic and clinical characteristics and laboratory parameters of the patients at the time of ICU admission were summarized in Tables 1 and 2. The mean value of serum and intra-cellular magnesium levels was 1.96 ± 0.38 mg/dL and 4.01± 0.26 mg/dL, respectively. The ICU mortality rate of this study was 24.28%. The morbidity and mortality rates are summarized in Table 3 and 4.

Table 1. Baseline demographic, laboratory and clinical characteristics of the patients regarding serum magnesium levels.

Variable (unit)	Serum Mg < 1.7 mg/dL (n=26)	Serum Mg ≥1.7 mg/dL (n=44)	P value
Age (years)	62.81±14.59	49.61±12.64	0.16
Sex			0.32
Male	17	25	
Female	9	19	
Weight (kg)	71±10.05	67.43±8.34	0.21
Cause of admission			0.24
Surgical	6	15	
Medical	20	29	
Severity of illness			
APACHE II score	17.46±4.95	12.02±5.28	0.68
SOFA score	6.81±3.85	6.43±3.68	0.99
Cardiac monitoring			
MAP (mmHg)	88.46±17.52	84.27±21.96	0.15
HR (beats per minute)	100.38±17.90	110.93±20.12	0.11
Respiratory rate (breaths per minute)	22.15±6.14	23.09±7.72	0.13
Temperature (°C)	37.59±1.00	37.78±0.85	0.64
CBC			
Hgb (g/dL)	11.46±2.70	10.73±1.32	0.21
WBC ($\times 10^3/\mu L$)	13.91±4.5	12.17±2.59	0.43
Plasma glucose (mg/dL)	183.46±47.43	176.90±39.58	0.31
Urea (mg/dL)	39.34±24.52	36.35±21.76	0.62
Serum creatinine (mg/dL)	1.29±0.42	1.28±0.33	0.12
Erythrocyte sedimentation rate (mm/hr)	54.35±38.09	48±32.02	0.17
C-reactive protein (mg/L)	66.76±42.53	64.70±33.30	0.06

APACHE: Acute Physiology and Chronic Health Evaluation , HR: heart rate, Hgb: hemoglobin, MAP: mean arterial pressure, Mg: magnesium, SOFA: Sequential Organ Failure Assessment, WBC: white blood cell.

Table 2. Baseline demographic, laboratory and clinical characteristics of the patients regarding intra-erythrocyte magnesium levels.

Variable (unit)	RBC Mg < 4 mg/dL (n=31)	RBC Mg ≥ 4 mg/dL (n=39)	P value
Age (years)	63.23±15.20	52±14.87	0.68
Sex			0.56
Male	18	24	
Female	13	15	
Weight (kg)	69.41±10.78	69.54±8.32	0.13
Cause of admission			0.09
Surgical	5	16	
Medical	25	24	
Severity of illness			
APACHE II score	17.73±4.22	15.21±4.63	0.50
SOFA score	6.55±3.98	7.43±4.10	0.61
Cardiac monitoring			
MAP (mmHg)	91.50±16.87	82.28±24.13	0.94
HR (beats per minute)	100.36±19.10	112.79±18.76	0.81
Respiratory rate (breaths per minute)	23.32±6.43	22.43±7.31	0.44
Temperature (°C)	37.77±1.1	37.90±0.87	0.39
CBC			
Hgb (g/dL)	11.57±2.10	10.98±1.40	0.54
WBC ($\times 10^3/\mu L$)	13.99±4.2	14.16±4.81	0.46
Plasma glucose (mg/dL)	184.54±39.42	178.92±49.76	0.59
Urea (mg/dL)	37.41±23.31	35.68±20.16	0.35
Serum creatinine (mg/dL)	1.26±0.58	1.26±0.38	0.87
Erythrocyte sedimentation rate (mm/hr)	59.73±40.52	58.96±34.02	0.39
C-reactive protein (mg/L)	73.12±46.84	76.57±31.45	0.61

APACHE: Acute Physiology and Chronic Health Evaluation , HR: heart rate, Hgb: hemoglobin, MAP: mean arterial pressure, Mg: magnesium, RBC: red blood cell, SOFA: Sequential Organ Failure Assessment, WBC: white blood cell.

There was a significant relationship between male gender and mortality (P = 0.02). Males had higher mortality than females. Patients with higher APACHE II score had significantly higher mortality (P < 0.001). There were significant inverse relationships between serum and intra-cellular magnesium levels with mortality and cardiovascular complications. Both cardiovascular complications and mortality were significantly higher in patients with lower serum and intra-cellular magnesium levels (P < 0.001, P < 0.001, P = 0.02, P < 0.001, respectively). Cardiovascular events including malignant ventricular arrhythmias, myocardial infarction, pulmonary edema and cardiogenic shock were observed in 12 (17.14%) of included patients.

In addition, there was a significant correlation between serum magnesium level on ICU admission and APACHE II score (r = -0.39, P < 0.001). We did not find a significant relationship between magnesium levels with length of ICU stay, infectious and renal complications.

Table 3. Clinical outcomes of the patients regarding serum magnesium levels.

	Serum Mg < 1.7 mg/dL (n=26)	Serum Mg ≥1.7 mg/dL (n=44)	P value
Cardiac complications	10 (14.28)%	2 (2.85%)	< 0.001
Myocardial infarction	2 (2.85%)	1 (1.42%)	0.30
Ventricular arrhythmias	4 (5.71%)	1 (1.42%)	0.06
Pulmonary edema	2 (2.85%)	0	0.13
Cardiogenic shock	2 (2.85%)	0	0.13
Mortality	16 (22.85%)	1 (1.42%)	< 0.001

Table 4. Clinical outcomes of the patients regarding intra-erythrocyte magnesium levels

	RBC Mg < 4 mg/dL (n=31)	RBC Mg ≥ 4 mg/dL (n=39)	P value
Cardiac complications	9 (12.85%)	3 (4.28%)	0.02
Myocardial infarction	1 (1.42%)	2 (2.85%)	0.58
Ventricular arrhythmias	4 (5.71%)	1 (1.42%)	0.11
Pulmonary edema	2 (2.85%)	0	0.19
Cardiogenic shock	2 (2.85%)	0	0.19
Mortality	15 (21.42%)	2 (2.85%)	< 0.001

Discussion

Magnesium plays an important role in the human body's physiological and biochemical functions and critically ill patients are vulnerable population to magnesium deficiency (18). In this study, correlations between serum and intra-cellular magnesium levels at the time of ICU admission with ICU complications and mortality were evaluated. In our study, 37.14% of the Iranian critically ill patients suffered hypomagnesemia at the time of ICU admission. However, the prevalence of intra-cellular magnesium deficiency was higher (44.28%). Cardiovascular complications and mortality were significantly higher in patients with lower serum and intra-cellular magnesium levels when compared to patients with normal levels. Ventricular arrhythmias were the most common complication. There was a significant correlation between serum magnesium level on ICU admission and APACHE II score.

The prevalence of hypomagnesemia and its effects on mortality and morbidity have been assessed in surgical and medical critically ill patients in previous studies. The prevalence rate of hypomagnesemia ranges from 18% to 65% (8, 10). Hypomagnesemia was associated with more sepsis episodes, need of mechanical ventilation support and for a longer duration, prolonged ICU stayed, higher APACHE and SOFA scores, and increased mortality rate (7, 9, 10, 13, 19-23). Although, Escuela et al., study reported no association between hypomagnesemia and mortality (24). Only in one previous study, association between intra-erythrocyte magnesium level and mortality in critical care setting was evaluated. In Guérin et al., study, low levels of serum and intra-erythrocyte magnesium did not correlate with higher mortality (25).

In a recent systematic review and meta-analysis, association between magnesium imbalance (hypo or hyper) and mortality rate in critically ill patients has been evaluated. In this analysis, hypomagnesemia was significantly correlate with requirement for mechanical ventilation, length of ICU stay and mortality (11). The most plausible explanation for hypomagnesemia related morbidity or mortality refers to the key role of magnesium in cellular metabolism and function. Magnesium plays a fundamental role at neuromuscular junction and conduction (26). Therefore, magnesium is obligatory for the regulation of muscular contraction and magnesium deficiency is a recognized cause of respiratory insufficiency due to muscle weakness (11, 26). Magnesium deficiency correlates with higher risk of cardiovascular complications (11, 27). Magnesium can regulate the contractility of endothelium and vascular smooth muscle tone. In addition to its role in blood pressure modulation, magnesium deficiency is known to be possible causes of coronary artery vasospasm, ventricular arrhythmias and sudden cardiac arrest. Hypomagnesemia can directly affect cardiac cell electrophysiology through its impact on ion channel function and second messenger system (3, 28).

Another magnesium significant action is modulation of sepsis development (11, 29). Low magnesium status results in increased release of endothelin and pro-inflammatory cytokines and consequently inflammatory responses (2,

13). Finally, magnesium deficiency is associated with the development of insulin resistance and impaired glycemic control among diabetic and nondiabetic patients (11, 26).

All these factors may be simultaneously involved in hypomagnesemia related morbidity and mortality especially in critically ill patients. There is currently little evidence and guidance regarding whether magnesium supplementation would improve clinical outcome and survival rate in critically ill patients. Large, well-designed, randomized controlled trials are needed in order to further address this issue.

To the best of our knowledge, this was first study evaluated the effects of serum and intra-cellular magnesium deficiency on morbidity and mortality in critically ill patients.

However, potential limitations of our study need to be considered. Our study evaluated relatively small number of patients in comparison with previous studies. Intra-cellular magnesium level was measured in erythrocytes, because the lack of a reliable and noninvasive method for measuring tissue magnesium level. However, some previous studies reported no association between intra-erythrocyte magnesium concentration and tissue stores (30). Measurement of ionized magnesium fraction which is presumed to be biologically active is recommended (1).

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