

Correlation between Serum Magnesium and Lactate Levels at the Time of ICU Admission and Early Phase of Sepsis

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Background: As the fourth abundant electrolyte in the body, magnesium has critical roles in aerobic metabolism and regulation of the immune system. Few studies investigate the association between magnesium status of critically ill septic patients and lactate acidosis in the intensive care unit (ICU). In this study, serum magnesium level and lactate level were evaluated at both admission time and time of sepsis.

Methods: This was a prospective, cross-sectional study conducted at general ICU of a tertiary referral teaching hospital. Hypomagnesemia was defined as a serum magnesium concentration of less than 1.7 mg/dL. Mann-Whitney test and independent-sample t-test were used to analyze nonparametric and parametric data, respectively.

Results: Of 50 sepsis patients, 32 patients were normomagnesemic, and 18 were hypomagnesemic. Hypomagnesemic patients have significantly higher lactate serum level at the time of sepsis compared to normomagnesemic patients [2.32 (1.96-3.29) vs. 1.94 (1.80-2.15) mg/dl respectively, $p < 0.001$]. There were significant differences between normomagnesemic and hypomagnesemic septic patients in Acute Physiology and Chronic Health Evaluation (APACHE) II score at sepsis time (9.44 ± 4.33 vs. 11.67 ± 3.83 , $p = 0.46$), and Sequential Organ Failure Assessment (SOFA) score [3 (3.00-5.00) vs. 4 (3.75-6.25), $p = 0.04$]. Also, 28-day mortality because of sepsis (50% respectively, $p < 0.001$), duration of mechanical ventilation [12.00 (4.00-14.25) days respectively, $p < 0.01$] and ICU stay [14.00 (12.75-17.25) days respectively, $p < 0.01$] were significantly higher in hypomagnesemic groups.

Conclusion: Admission hypomagnesemia in sepsis patients may increase serum lactate concentration, duration of ventilation, duration of ICU stay and mortality.

Keywords: Hypomagnesemia; Lactate level; Sepsis; Mortality

Fourth abundant cation in the body is magnesium (Mg) that acts as a cofactor for more than 300 biological reactions [1-2]. The larger fraction magnesium in the human body, about 60%, is present on bone and 40% is in muscle, soft tissue, and the liver [3]. Magnesium is crucial to many ATP-generating reactions such as mitochondrial ATP synthase and Na⁺/K⁺-ATPase and is essential for normal mitochondrial function [1, 4]. Until now, many physiological roles of magnesium have been discovered such as involvement in energy metabolism and protein and nucleic acid synthesis [5-6].

Several disease and clinical conditions, also various medications such as antibiotics, antihypertensive agents, and proton pump inhibitors may lead to magnesium loss and

hypomagnesemia [7-9]. Hypomagnesemia is one of the commonest but underdiagnosed electrolyte abnormality in critically ill patients such as sepsis patients, with an estimated prevalence between 20% to 65% [10-12].

Sepsis is defined as a dysregulated host response to infection that results in life-threatening organ dysfunction [13]. Sepsis affects more than 30 million people in the world [14]. Acute increase in Sepsis-related Organ Failure Assessment (SOFA) score of 2 or more as a result of infection is defined as organ dysfunction and associated with greater mortality [13]. Sepsis mortality is about 20-30%, which has dropped significantly over the last decade [15].

Low level of magnesium activates neuroendocrine pathways, which induce a systemic stress response and is related to the longer length of stay and increased mortality in critically ill sepsis patients [16-18]. A retrospective study conducted by Safavi et al. on critically ill patients found an association between hypomagnesemia and an increase in need of mechanical ventilation and also days of mechanical ventilation [19].

Also, experimental studies on the animal model have shown magnesium deficiency, associated with an increase in cytokines concentration such as tumor necrosis factor α , substance P, interleukin 1, and calcitonin gene-related peptide. Furthermore, magnesium is important for the macrophage activation process. Therefore, the effects of magnesium on the immune system are important in the

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pathogenesis of sepsis [20-23].

In sepsis patients, elevated serum lactate often reflects inadequate tissue oxygen delivery, impaired aerobic respiration, accelerated aerobic glycolysis, and reduced hepatic clearance [24]. Increase in lactic acid production due to magnesium deficiency, occurs because of a shift to anaerobic metabolism from oxidative phosphorylation in mitochondria [25]. In a study by Moskowitz et al., magnesium deficiency was described as a risk factor for lactate production in critically ill patients [26].

In this study, we aimed to evaluate the association between serum magnesium and lactate level in sepsis patient. Also, we assessed whether hypomagnesemia in sepsis patients was associated with poor sepsis outcome in critically ill sepsis patients.

Methods

A prospective, cross-sectional study was conducted at general ICU of Imam Khomeini hospital, a tertiary referral teaching hospital affiliated to Tehran University of Medical Sciences. The institutional review board and the ethics committee of Tehran University of Medical Sciences approved this study (code number: IR.TUMS.PSRC.REC.1396.4390).

All Critically ill septic adult patients (18-65 years old) admitted to ICU between January 2018 and December 2018 were included in this study. Based on sepsis-3 criteria, in this study, an acute change in total SOFA score of 2 or more points was considered as sepsis [13]. Patients who did not meet sepsis-3 criteria during ICU stay were excluded in this study.

Demographic information including age, sex, weight, and cause of ICU admission, serum lactate concentration, total serum magnesium concentration, Sequential Organ Failure

Assessment (SOFA) score, and Acute Physiology And Chronic Health Evaluation (APACHE) II score of patients who admitted to ICU, was recorded.

A 10-mL peripheral venous blood sample was drawn at admission and the first day of sepsis. EDTA-containing blood samples were centrifuged for 10 minutes at 3000 rpm. Spectrophotometry technique was used to measure magnesium concentration.

Admission hypomagnesemia was defined as a serum magnesium concentration of less than 1.7 mg/dL.

In order to assess the serum lactate level, blood samples were centrifuged 10 minutes at 3000 rpm. To stabilize plasma samples until test was performed, potassium oxalate or sodium fluoride were added and refrigerated in 2-8 degree centigrade.

Biorexfars lactate kit was used to analyze of lactate in separated plasma. Spectrophotometry technique at 546 nanometers was used to measure serum lactate level.

As sepsis occurred, total serum magnesium concentration and serum lactate level were recorded. Routine laboratory data including complete blood red cell count, total bilirubin, and creatinine also, heart rate, mean arterial pressure, respiratory rate, SOFA score, APACHE II score, need for mechanical ventilation, duration of ventilation and 28 days mortality of septic patients were recorded.

Also, ventilation days defined as the number of days on mechanical ventilation and oxygenation parameters such as blood gas analysis, blood pH, and blood oxygen saturation, were recorded.

The primary outcome and primary exposure was first sepsis day lactate concentration and admission serum magnesium concentration, respectively.

Statistical analyses were performed using SPSS version 19.0 software. Kolmogorov-Smirnov test was applied to all data to confirm normality of the distribution of data. Mann-Whitney test and independent-sample t-test were used to analyze nonparametric and parametric data, respectively. Chi-square test was used to analyzed the association between patients magnesium level at admission to ICU and categorical variables. Pearson's correlation coefficient was used to evaluate the relationship between serum concentration of magnesium and serum lactate concentration. A P value of <.05 was considered statistically significant.

Results

During this study, 50 patients (age, between 18 and 65 years) were included. The mean age (SD) of patients in the normomagnesemia and hypomagnesemia groups was 47.53 (7.36) and 52.94 (8.37) years old respectively.

At the time of admission, 36% of patients had hypomagnesemia. Highest and lowest serum magnesium level at admission was 2.70 mg/dl and 1 mg/dl respectively. There was no difference in sex between patients with hypomagnesemia and patients with normomagnesemia at admission to ICU ($p=0.39$). Admission APACHE II score of hypoagnesemic and normomagnesemic patients was not significantly different (11.67 ± 3.83 vs. 9.44 ± 4.33 , $p=0.46$), but there was a significant difference in admission SOFA score [4 (3.75-6.25) vs. 3 (3.00-5.00), $p=0.04$]. Patients in the normomagnesemia and hypomagnesemia groups had comparable serum lactate concentrations at the first day of sepsis [1.94 (1.80-2.15) vs. 2.32 (1.96-3.29) mg/dl respectively, $p<0.001$].

Duration of mechanical ventilation was significantly more in patients with hypomagnesemia compared to patients with a normal serum concentration of magnesium [12.00 (4.00-14.25) vs. 3.00 (0.00-8.00) days respectively, $p<0.01$]. All other routine clinical laboratory tests are summarized in (Table 1).

During 28 days follow-up, 13 patients died because of sepsis. 28-day mortality was statistically different between the normomagnesemia and hypomagnesemia groups (12.5% vs. 50% respectively, $p<0.001$). Furthermore, median (range) length of ICU stay in hypomagnesemic patients was significantly more than normomagnesemic patients. [14.00 (12.75-17.25) vs. 10.00 (8.25-14.25) days respectively, $p<0.01$].

Admission serum lactate concentration of patients with hypomagnesemia and first sepsis day lactate concentration were significantly greater than patients with normal magnesium level at admission [1.25 (0.99-1.82) vs. 0.77 (0.62-1.06) mg/dl respectively, $p<0.01$] and [2.32 (1.96-3.29) vs. 1.94 (1.80-2.15) mg/dl respectively, $p=0.04$]. Also, there was a significant difference in first sepsis day lactate concentration of sepsis patients with hypomagnesemia compared to normomagnesemia in time of sepsis diagnosed [3.11 (2.02-3.93) vs. 1.96 (1.79-2.23), $p<0.01$].

There was a significant negative correlation between admission serum concentration of magnesium and admission serum lactate concentration ($r=-0.534$, $p<0.001$).

Table 1- Demographic, laboratory and clinical data of patients at admission to ICU

Parameter	Normomagnesemia (n=32)	Hypomagnesemia (n=18)	P value
Age (years); mean± SD	47.53 ± 7.36	52.94 ± 8.37	0.93
Gender; number (%)			
Male;	20(69.00)	9 (31.00)	0.39
Female	12 (57.10)	9 (42.90)	
Weight (kg); mean ± SD	76.41 ± 8.54	73.61 ±9.67	0.43
Cause of ICU admission; number (%)			
Surgical	20 (60.60)	13 (39.40)	
Medical	12 (70.60)	5 (29.40)	0.77
APACHE -II score; mean ± SD, at the time of ICU admission	9.44 ± 4.33	11.67 ± 3.83	0.46
APACHE -II score; median (Range), at the time of early phase of sepsis	13.00 (8.25-18.00)	20.50 (19.75-25.25)	<0.001
SOFA score; median (Range), at the time of ICU admission	3 (3.00-5.00)	4 (3.75-6.25)	0.04
WBC (× 10 ³ /μL); mean ±SD	12.71 ±4.59	11.13 ±5.42	0.36
Hgb (g/dL); median (Range)	10.30 (9.00-15.52)	9.60 (8.65-12.32)	0.52
INR; median (Range)	1.50 (1.30-2.31)	1.60 (1.43-2.10)	0.58
Bilirubin (mg/dl); median (Range)	1.05 (0.80-1.40)	1.10 (0.90-1.90)	0.17
Serum creatinine concentration (mg/dL); mean ±SD	1.05 ± 0.31	1.01 ± 0.34	0.29
Temperature (°C); median (Range)	37.70 (37.50-37.87)	37.70 (37.50-38.30)	0.23
HR (bpm); median (Range)	93.50 (80.50-107.00)	94.00 (81.75-105.00)	0.94
RR (bpm); median (Range)	17.00 (12.50-20.00)	20.00 (17.25-22.00)	0.01
MAP (mmHg); mean ±SD	92.91 ± 15.12	99.94 ±17.21	0.86
Mechanical ventilation (day); median (Range)	3.00 (0.00-8.00)	12.00 (4.00-14.25)	< 0.01
Duration of ICU stay (day); median (Range)	10.00 (8.25-14.25)	14.00 (12.75-17.25)	< 0.01
28-day mortality; number (%)	4 (12.50)	9 (50.00)	< 0.001

Discussion

Magnesium is second intracellular cation in the human body and acts as a cofactor for numerous enzymatic reactions such as thiamine three-phosphate enzyme and ATP reactions. Thiamine pyrophosphate, the active form of thiamine, is a cofactor for pyruvate dehydrogenase and α -ketoglutarate dehydrogenase in citric acid cycle. Therefore, magnesium has an important biological role in aerobic metabolism and ATP reactions such as mitochondrial ATP synthase and Na⁺/K⁺-ATPase. Energy metabolism, protein and nucleic acids synthesis and effects on the immune system are examples of magnesium critical roles in the human body. Magnesium ions play important roles in immunological functions including lymphocyte proliferation, macrophage activation, adherence and bactericidal activity of granulocyte. Mg has an anti-inflammatory effect through activating PI3K β , PI3K δ and PI3K γ . Also, magnesium is essential for normal mitochondrial function [1, 2, 4-6, 20-23].

Hypomagnesemia is a common electrolyte disorder among ICU patients with sepsis and observational studies showed that it is significantly associated with poor clinical outcomes. Previous studies on critically ill patients in ICU, reported different prevalence of admission hypomagnesemia varying from 20% to 65% [12, 19, 26-30]. In this study population, 36% of patients had hypomagnesemia at admission to ICU.

Magnesium depletion can lead to the inhibition of energy production by inhibition of the Krebs pathway. As a result pyruvate shifts to lactate production and hyperlactatemia occurred [18].

One of the manifestations of sepsis is hyperlactatemia. During sepsis and septic shock liver hypoperfusion occurred and resulted in decreasing lactate clearance. Also Inflammatory immune cells, hypoperfusion and tissue hypoxia increased lactate production. Moreover, hyperlactatemia occurred due to more release of endogenous epinephrine and norepinephrine during sepsis. Drugs such as epinephrine, propofol and fluid administration as primary

resuscitation strategy in sepsis could affect lactate levels [18]. Before starting sampling, all included patients were resuscitated on the basis of international guideline for management of sepsis and septic shock [13]. According to the results, type and mean dose of fluid therapy and suspected medications did not have any significant difference between both groups.

Magnesium deficiency and hypomagnesemia in critically ill patients can be due to a variety of medical situations and medications. Gastrointestinal loss, alcoholism, poorly controlled diabetes mellitus, reduced kidney perfusion due to hypovolemia and hypotension, heart failure due to sepsis associated fluid and electrolyte abnormalities, inappropriate fluid administration, activation of the vasopressin and renin-angiotensin-aldosterone system and also medications such as antibiotics (especially aminoglycosides) and diuretics are common risk factors associated with hypomagnesemia [7-9, 31].

Hypomagnesemia manifestations include hypocalcemia, hypokalemia, arrhythmias, dysphagia, anemia, changes in CNS (central nervous system), increased cytokine concentration and neuromuscular irritability [3]. Mg has a critical role in regulation of cardiovascular hemostasis. Mechanical and electrical activities of cardiac and vascular muscle membranes can be affected by small changes of free Mg in these cells. Furthermore, hypomagnesemia correlates with hyperexcitability and respiratory muscle weakness. In a cohort study by Mousavi et al., duration of ventilation was higher in the hypomagnesemic patient compared to patients with normal serum magnesium [27]. Another study by Safavi et al. indicated higher duration of mechanical ventilation in patients admitted to ICU with hypomagnesemia compared to patients with normal magnesium level [19]. In our study, the duration of ventilation was higher among patients admitted with hypomagnesemia.

Also, previous researchers investigated the impact of magnesium status on ventilation dependency, duration of ventilation, sequential organ failure assessment score and acute physiology and chronic health evaluation score [19]. Our data show greater APACHE II score in sepsis patients admitted with hypomagnesemia and greater SOFA score in hypomagnesemic patients at admission compared to patients who were admitted with normal magnesium level.

One of the main sepsis pathogenesis is systemic inflammation. Magnesium deficiency can lead to an increase in serum level of tumor necrosis factor alpha (TNF α), inflammatory cytokines, impaired immunological functions and susceptibility of Hypothalamic-Pituitary-Adrenal (HPA) axis and sympathetic nervous system to physical stress [32]. In addition to increased cytokine concentration, impaired immune system functions due to hypomagnesemia was important in sepsis. Also, previous studies found an association between reactive oxygen species (ROS) production rate and magnesium deficiency [33]. On the other hand, increased extracellular magnesium concentration can reduce inflammatory events [32].

In animal models, magnesium deficiency and increase in serum magnesium level was associated with increased mortality and protective effects against endotoxin [34]. Also, the relationship between hypomagnesemia and mortality in critically ill patients was investigated in previous studies. In an observational study, Rubeiz et al. concluded that hypomagnesemia increase mortality rate in medical ICU

patients [35]. A cohort study on 144 patients admitted to ICU, a higher mortality rate in hypomagnesemic patients was found [36]. A systematic review and meta-analysis conducted by Jiang et al. found the association of hypomagnesemia and higher mortality rate [37]. Our findings showed a significant difference in mortality of patients with hypomagnesemia compared to patients with normal magnesium level that indicated greater risk of mortality in hypomagnesemic patients.

Similar to previous researches, our findings indicate that hypomagnesemia is a risk factor for a shift from aerobic metabolism to anaerobic metabolism and an increase in lactate production [26]. As mentioned previously, magnesium deficiency can increase inflammation and impair aerobic metabolism of glucose which may be an explanation for increase in lactate production. Hypomagnesemia by increasing lactate production, impairing ATP production and utilization, increasing inflammatory cytokines and impairing immunological functions, reducing respiratory and cardiac functions and inducing electrolyte abnormalities caused higher mortality in critically septic patients. Many clinical studies show that hypomagnesemia correlates with sepsis, however sepsis is recognized as independent factor for development of hypomagnesemia [38].

Conclusion

We concluded that admission hypomagnesemia might lead to an increase in morbidity and mortality of sepsis patients, duration of ventilation and serum lactate level. Our study has limitations such as small sample size, difference in source of sepsis. Further investigation needs to clarify any causality between hypomagnesemia and lactate concentration in sepsis patients. Also the role of magnesium therapy for improving outcomes in critically ill patients with sepsis should be evaluated through well-designed clinical trials.

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