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A study to evaluate the efficacy of intravenous Magnesium Sulphate administration on lactate clearance in critically ill patients

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Abstract

Background: Magnesium (Mg) is crucial for normal mitochondrial function in human body. It functions as an important cofactor for numerous biological reactions involving ATP-generating enzymes such as mitochondrial ATP synthase and Na+/K+ ATPase.
Method: This prospective, randomized, interventional study involving two groups of critically ill patients in ICU with hypomagnesaemia. One group received intravenous administration of magnesium sulphate while the second group received intravenous administration of placebo.
Results: Comparison of serum lactate levels between cases and controls (n = 84) was statistically insignificant. Lactate clearance between cases and controls was comparable. Comparison of arterial blood gases between cases and controls was found to be statistically insignificant. Comparison of biochemical parameters between cases and controls. Hospital stay duration of cases and controls was found to be comparable. Mortality between cases and controls was comparable.
Conclusion: There was a significant proportion of critically ill patients with serum hypomagnesemia however intravenous magnesium sulphate administration did not significantly affect the lactate clearance, the days on mechanical ventilation, duration of ICU stay or the mortality.

Keywords: Magnesium sulphate, lactate clearance, critically ill patients

Introduction

Magnesium (Mg) is crucial for normal mitochondrial function in human body as it functions as an important cofactor for numerous biological reactions, many of them being ATP-generating enzymes such as mitochondrial ATP synthase and Na+ /K+ ATPase.[1] It is the fourth most abundant cation in the body. The major portion of magnesium about 53% is present in bone whereas 27% is in muscle, 19% in soft tissue, and 0.5% in erythrocytes and only 0.3% is found in serum. Total serum Mg levels are ranged from 0.7 to 1.0 mmol/L (1.7-2.4 mg/dL).[2]

Hypokalaemia in critically ill patients is found to be relatively refractory to potassium supplementation if associated with hypomagnesemia.[3,4] Hypomagnesemia is the commonest but underdiagnosed electrolyte abnormalities in sepsis patients, with an estimated prevalence as high as 20% to 65%.[5] Low level of magnesium is related to the longer ICU stay and increased mortality in critically ill sepsis patients by activating neuroendocrine pathways to induce a systemic stress response.6 A retrospective study done by Safavi M et al found an association between hypomagnesemia and an increase in the need and duration of mechanical ventilation in critically ill patients.[7] Hypomagnesemia causes a shift to anaerobic metabolism from oxidative phosphorylation in mitochondria leading to increase in lactic acid production. In a study by Moskowitz et al, magnesium deficiency was found

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as a risk factor for increased lactate production in critically ill patients.[8] Serum lactate levels more than 36 mg/dl is associated with high hospital mortality, hence hyperlactatemia has been described as a marker of impaired organ perfusion in critically ill patients.[9] Though anaerobic glycolysis is not the only causative factor for hyperlactatemia, Mg may decrease lactate production through attenuation of the anaerobic metabolism, by being a cofactor for enzymatic reactions of oxidative metabolism. It may also enhance liver and renal perfusion and metabolism, especially during the resuscitation phase, in addition to being an essential electrolyte for the proper functioning of the cardiovascular and respiratory systems. Thus, Mg may improve lactate clearance both by reduction in lactate synthesis and enhancement of its elimination.[10]

Materials and methods

This prospective, randomized, interventional study was conducted in the Department of Anaesthesiology & Critical Care, Pt. B. D. Sharma PGIMS, Rohtak (Haryana, India). Eighty-four critically ill patients of either sex with age >18years admitted in the ICU were enrolled in the study. Patients who did not consent to participate in the study, with pre-existing renal or liver disease, hypermagnesemia (serum Mg level > 3.5 mgdL-1). Diabetic ketoacidosis were excluded. Also, Pregnant patients, patients with Status epilepticus, MAP <65mmHg despite vasopressor therapy were not studied. Using computer generated randomization number table, the patients were divided into two groups of 42 each. Group I (n=42) received IV MgSO4 on the basis of serum magnesium levels to maintain it at around 3mg dL-1 for 3 days. Group II (n=42) received the same volume of normal saline. Blood samples to measure serum Mg and Lactate levels was collected for both groups at ICU admission and sent along with routine investigations. After obtaining serum Mg levels the patients in Group I received intravenous magnesium sulphate on the basis of rule of thumb (each 1 g intravenous magnesium sulphate raises 0.15 mEq.L-1 of serum magnesium) to maintain the targeted serum Mg level around 3 mgdL-1. Every 2 g of magnesium sulphate was diluted in 50 ml normal saline and infused over a 2-hour period. Group II patients received the same volume of normal saline. In patients in Group II, if serum magnesium level had dropped to less than 1.7 mgdL-1 at any time of the intervention course, it was corrected toward ≥1.7 mgdL-1. Blood levels for Mg and lactate was reassessed and recorded every day for 3 days.

Demographic data (age, sex and cause of ICU admission), physiologic and hemodynamic parameters, laboratory reports (including renal and liver function tests), ABG parameters, duration of mechanical ventilation, acute physiologic and chronic health evaluation (APACHE) II score, duration of ICU stay, and mortality were recorded.

Results

APACHE-II score at admission: comparison of APACHE – II score at admission between cases and controls was found to be statistically insignificant (table 2).

Comparison of serum magnesium levels between cases and controls(n = 84) was found to be statistically significant among two groups on day 2 and day 3.(table 3)

Table 1: Demographic profile of the patients

	Cases (n = 42)	Controls (n = 42)	p-value
Age(years) -Mean(SD)	45.16 (15.39)	39.45 (15.24)	0.091
Number of patients (%)			
Males	32 (76.19%)	38 (90.47%)	0.079
Females	10 (23.8%)	4 (9.52%)	

Both the groups were comparable

Table 2: APACHE-II score at admission

APACHE-II	Mean (SD)		p-value
	Cases (n = 42)	Controls (n = 42)	
Score on admission	14.28 (5)	14.23 (5.9)	0.968

Table 3: Serum magnesium levels

Serum Magnesium levels	Mean (SD)		p-value
	Cases (n = 42)	Controls (n = 42)	
Day 1	1.55 (0.32)	1.48 (0.31)	0.338
Day 2	2.96 (0.16)	1.89 (0.12)	<0.001
Day 3	2.99 (0.13)	1.84 (0.12)	<0.001
p-value (Intra-group)	<0.001	<0.001	

Table 4: Serum lactate levels between cases and controls

Serum Lactate levels	Mean (SD)		p-value
	Cases (n = 42)	Controls (n = 42)	
Day 1	3.3 (1.43)	3.25 (1.51)	0.889
Day 2	3.18 (1.66)	3.24 (1.66)	0.884
Day 3	3.16 (1.84)	3.03 (1.75)	0.756
p-valuc (Intra-group)	0.589	0.659	
Lactate clearance	6.86 (34.21)	5.72 (33.56)	0.882

Table 5: lactate clearance between cases and controls

Lactateclearanc	Mean(SD)		p-value
	Cases (n=42)	Controls (n=42)	
Negative(<0)	17 (40.47%)	18 (42.85%)	0.893
Nochange(0)	11(26.19%)	12 (28.57%)	
Positive(>0)	14 (33.33%)	12 (28.57%)	

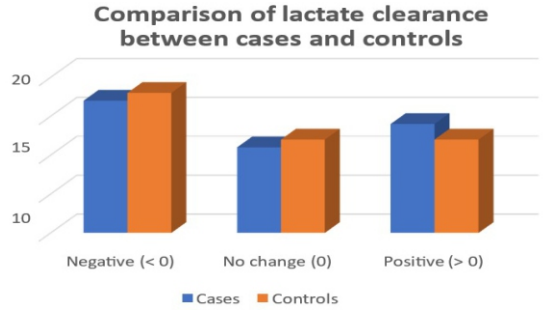

Figure 1: lactate clearance among two groups

Table 6: Arterial blood gases parameters

Arterial blood gases	Mean (SD)		p-value
	Cases (n = 42)	Controls (n = 42)	
Ph	7.36 (0.04)	7.36 (0.05)	0.853
PaO2 (mm Hg)	133.92 (48.1)	150.8 (66.93)	0.188
PaCO2 (mm Hg)	37.97 (4.22)	35.74 (5.17)	0.063
Serum HCO3	23.35 (2.5)	23.74 (2.61)	0.481
Sat O2 (%)	98.94 (0.95)	98.81 (1.22)	0.600

Table 7: Biochemical parameters

Biochemical parameters	Mean (SD)		p-value
	Cases (n = 42)	Controls (n = 42)	
Hemoglobin (g/dL)	10.49 (1.93)	10.3 (1.95)	0.655
TLC (cells/mm^3)	14500 (6131.92)	12430 (6172.43)	0.127
Platelet count	235476.19 (83569.52)	219357.14 (74054.3)	0.352
Blood Urea	17.09 (10.34)	17.4 (11.17)	0.895
Serum Creatinine	0.93 (0.2)	0.92 (0.21)	0.836
AST	20.92 (11.22)	24.76 (21.02)	0.300
ALT	19.85 (8.64)	23.83 (22)	0.279
ALP	88.83 (32.99)	92.42 (42.2)	0.665
T. Bilirubin	0.69 (0.32)	0.7 (0.33)	0.948
Sodium	139.16 (4.97)	140.26 (7.27)	0.423
Potassium	4.12 (0.83)	4.05 (0.75)	0.711

Table 8: Hospital stay duration

Hospital stay (in days)	Mean (SD)		p-value
	Cases (n = 42)	Controls (n = 42)	
No. of days on ventilator	3.87 (1.39)	3.64 (1.26)	0.439
No. of days in ICU	5.8 (1.58)	5.76 (1.28)	0.911

Table 9: Mortality in either group

Clinical outcome	Number of cases (%)		p-value
	Cases (n = 42)	Controls (n = 42)	
Mortality present	2 (4.76%)	3(7.14%)	0.645
Mortality absent	40 (95.23%)	39 (92.85%)	

Comparison of serum lactate levels between cases and controls (n = 84) was statistically insignificant. (Table 4)

Lactate clearance between cases and controls (n = 84) was comparable (Table 5, Fig 1)

Comparison of arterial blood gases between cases and controls (n = 84) was found to be statistically insignificant (table 6).

Comparison of biochemical parameters between cases and controls (n = 84) is shown in Table 7

Hospital stay duration of cases and controls (n = 84) was found to be comparable (Table 8).

Mortality between cases and controls (n = 84) was comparable (table 9).

Discussion

In our study age and sex composition of patients between study and control groups were comparable. This was similar to a study conducted by Noormandi et al.[11] In this study, the mean serum magnesium levels of patients on day 1 in control group and in study group were 1.55 ± 0.32 mgdL-1 and 1.48 ± 0.31 mgdL-1 respectively (p=0.338) which was statistically insignificant. This was comparable to a study by Noormandi et al11 in which the serum magnesium levels were 1.84 ± 0.31 mgdL-1 study group and 1.80 ± 0.31 mgdl-1 in the control group. In our study the mean serum lactate levels of patients on day 1 of cases group was 3.3 ±1.43 mmol-1 and in control group was 3.25 ± 1.51 mmoll-1 with p=0.889 showing insignificant differences between groups. Similarly in a study by Noormandi et al11 lactate levels 2.10 ± 0.61 in study group and 2.09 ± 0.57 in control group p =0.98 which was insignificant. In our study, mean APACHE II score on admission was14.28 ± 5.0 in study group and 14.23 ± 5.9 in control group with p=0.968 which was insignificant. This result was similar to a study done by Noormandi et al[11] where they found APACHE II score on admission was 17.23 ± 6.23 in study group and in control group 16.86 ± 6.18 with p=0.81 which was insignificant statistically. Additionally in study by Rubeize et al[12] similar results were observed. In our study, all biochemical parameters, Arterial blood gas values and complete haemogram results were found to be comparable in either group.

In our study the mean total days on ventilator was 3.87±1.39 in the study group and 3.64 ± 1.26 in control group with a p value of 0.439 which showed statistical insignificance. The mean number of days in ICU stay in our study was 5.8 ± 1.58 in the study group and 5.76 ± 1.28 in the control group with a p value 0.911 which showed no statistical significance between groups. Two of 42 patients in study group (4.76%) while 3 of 42 in control group (7.14%) expired during the course of the study with

p of 0.645 which was statistically insignificant between two groups. In our study correlation between serum magnesium on admission with duration of ICU stay in cases and control was found to be statistically not significant with p values of 0.071 in study group and 0.072 in control group, however correlation coefficient was -0.288 in study group and was 0.296 in control group. Similar result was observed in a study by Sunil Kumar et al[13] and Soliman et al.[14] These findings were in contrast to study done by Upala et al,[15] Assarian et al[1] and Noormandi et al.[11] This might be due to differences in socio demographic parameters between the` studies. Correlation of days on ventilator of patients with serum magnesium levels was found to be statistically significant with p=0.046 between study and control groups. This is similar to study by Assarian et al.[1] There was no statistically significant difference between study and control group in relation to mortality with a p value of 0.645 in our study. Similar result was observed by Sunil Kumar et al[13] and Soliman et al.[14] Results were in contrast to studies by Noormandi et al[11] and Rubeiz et al.[12] The mean APACHE II scores in both the study and control groups among the patients expired were 32.00 ± 4.24 and 33.00 ± 3.61 respectively as compared to the remaining patients whose APACHE II scores were 13.40 ± 3.00 and 12.79 ± 2.64 of study and control groups respectively. The p value was <0.001 in both the groups showing statistical significance with strong positive correlation between higher APACHE II scores and mortality. This is similar to the findings by Assarian et al,[1] Noormandi et al[11] and Soliman et al.[14]

In our study, the expired patients in both study and control groups had higher lactate levels of 6.50 ± 0.42mmolL-1 and 6.73 ± 0.42mmolL-1 respectively as compared to the remaining patients of study and control groups 3.14 ± 1.26 and 2.99 ± 1.20 respectively with p value of 0.001 which is statistically significant. Showing strong association between higher serum lactate levels and mortality. This is similar to the results observed by Shapiro et al who found a correlation between threshold lactate levels of 4mmol.L-1 and mortality.[16] In this study the correlation between lactate clearance and days on ventilator and duration of ICU stay showed no statistical significance between cases and control groups with p values of 0.988 and 0.520 respectively. In our study of the total 84 patients, 59 patients i.e., 67.81% were found to be hypomagnesemic of which 28 were in study group and 31 patients were in control group. Similar result was observed in studies by Sunil Kumar et al (59.3%)[13] and Dabbagh et al (60%).[17]

In this study the doses of magnesium sulphate administered to patients varied between study and control group as magnesium levels of patients in the study group were aimed for serum levels of 3mg. dL-1 while those in the control group were only aimed to correct serum magnesium levels ≥1.7 mg.dL-1. The dose of magnesium sulphate administered to the cases group was 7.9 ± 1.69g while that to the control group was 1.41 ± 1.25g showing statistically significant difference with p value of <0.001. In our study the calculated lactate clearance in the cases group was 6.86 ± 34.21 % and in control group was 5.72 ± 33.56 % with p value of 0.882 among the groups which is statistically insignificant. This was in contrast to a study by Noormandi et al[11] that showed lactate clearance of 49.83% vs 37.02% in the control group with a p value of 0.001. However, mortality was similar between both the groups similar to our study. In this study we found that lactate clearance in cases group showed 17 patients (40.47%) having negative lactate clearance, 11 patients (26.19%) having zero lactate clearance and 14 patients (33.33%) having positive lactate clearance. In the control group 18 patients (42.85%) having negative lactate clearance, 12 patients (28.57%) having zero lactate clearance and 12 patients (28.57%) having positive lactate clearance.

Limitations

The study was carried out in a single tertiary care centre, a small sample size, too broad an inclusion criterion including patients of numerous underlying etiologies resulting in varied outcomes and causing ambiguity and causing difficulty in drawing any significant association between serum magnesium levels and lactate clearance .

Conclusion

There was a significant proportion of critically ill patients with serum hypomagnesemia however intravenous magnesium sulphate administration did not significantly affect the lactate clearance, the

days on mechanical ventilation, duration of ICU stay or the mortality. This might be because hypomagnesemia in critically ill may depend on magnesium fraction measured and lack of correlation with clinical outcomes may suggest that hypomagnesemia to be merely an epiphenomenon.

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