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Comparative Clinical Efficacy between Standard and Extended Magnesium Sulfate Infusion Strategies In Hypomagnesemic Critically Ill Patients

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Abstract

Objectives Hypomagnesemia is commonly found in critically ill patients with a various consequences including neuromuscular and neurologic dysfunction and mortality.Approximately half of IV $MgSO_4$ is excreted in the urine due to Mg^{+2} slow uptake. The primary purpose of this study is to determine whether an extended infusion of 2 grams $MgSO_4$ over 12 hours twice daily for 5 days (Strategy I) compared to a standard infusion of 5 grams $MgSO_4$ over 4 hours once daily for 5 days (Strategy II) results in a greater sustainance of Mg^{+2} level ≥2 mg/dl after at least 2 days post $MgSO_4$ infusion end.

Methods A retrospective analysis was conducted in our adult ICU between April 2017 and Sep 2018. Patients were excluded if they were discharged or died before completing at least 1 week of ICU admission and if magnesium level exceeded 4 mg/dl. A chi-square test was conducted to evaluate the proportion of patients in both groups of study who had late magnesium level ≥2 mg/dl. An independent T-test was conducted to compare the Mean±SD of $\%\Delta Mg^{+2}$ between Strategy I and Strategy II.

Results There was a significant difference in the percentage of patients maintaining normal $Mg^{+2}\geq 2$ mg/dL during the late post-infusion phase favoring the group of patients receiving extended infusion, although there was no difference between the two groups in early achievement of $Mg^{+2}\geq 2$.

Conclusion The extended infusion of $MgSO_4$ was shown to significantly increase the percentage of patient achieving target Mg^{+2} levels, decrease the length of both ICU stay and overall hospital stay, in addition to lowering 28-days ICU overall mortality rates. further investigation is needed in order to rule out other confounders that may have affected the major clinical outcomes.

Keywords Critically ill patients, Extended infusion, Hypomagnesemia, Magnesium replacement, Mortality.

Introduction

Hypomagnesemia is a common electrolyte imbalance among critically ill patients with up to 60% of them reported to have Mg^{+2} deficiency, due to different etiologies including the use of loop diuretics, diarrhea, and/or malnutrition.[1,2,3] Strong clinical evidence has linked hypomagnesemia to poor clinical outcomes including the prolonged need for mechanical ventilation and ICU stay in addition to increased mortality rate 2 to 3 times compared to normo-magnesemic patients. Assessing and correcting magnesium abnormalities in critically ill patients is crucial to avoid poor clinical outcomes and other adverse sequelae, such as coma, convulsions, heart arrhythmias, and refractory hypokalemia and hypocalcemia. [2,3,4,5,6]

Due to poor oral intake in critically ill patients, intravenous magnesium repletion guided by serum Mg^{+2} level is often necessary. However, IV replacement can be challenging due to kidney handling of magnesium. In normal kidney function, IV Mg^{+2} is rapidly eliminated renally with only about half of the infused Mg^{+2} retained by the body, as the remainder is excreted in the urine.[6,7,8] Renal excretion of Mg^{+2} is dependent on the changes in serum Mg^{+2} levels via Ca^{+2}/Mg^{+2} sensing receptors on thick-ascending-limb cells. Given the slow distribution of Mg^{+2} into the intracellular compartment, administration via rapid infusion will result in high peak serum concentration, leading to a hypermagnesemic state that will inhibit Mg^{+2} tubular absorption and increase renal Mg^{+2} elimination.[8,9,10] According to these findings, It is reasonable to assume theoretically that Mg^{+2} retention could be increased by slowing the IV infusion rate to reduce magnesium wasting by kidneys.[7,8,9] The primary purpose of this study is to determine whether an extended infusion of 2 grams $MgSO_4$ over 12 hours twice daily for 5 days (Strategy I) compared to a standard infusion of 5 grams $MgSO_4$ over 4 hours once daily for 5 days (Strategy II) results in a greater sustaining in Mg^{+2} level ≥ 2 mg/dl after at least 2 days from $MgSO_4$ infusion ending (Late Mg^{+2} measurement). A secondary aim of our study is to evaluate the percentage changes in Mg^{+2} level (%ΔMg^{+2}) from baseline Mg^{+2} level and Mg^{+2} level after at least 4 hours from MgSO4 infusion ending (Early Mg^{+2} measurement).

Material and Methods

This was a single-center observational retrospective study conducted in the departments of King Hussein Medical Center (KHMC) at Royal Medical Services (RMS) in Jordan. This study was approved by our Institutional Review Board (IRB), and a requirement for consent was waived owing to its retrospective design. This study included 188 hypomagnesemic critically ill patients. Flow chart of our studied patient's selection and data collection process is fully illustrated in Figure 1.

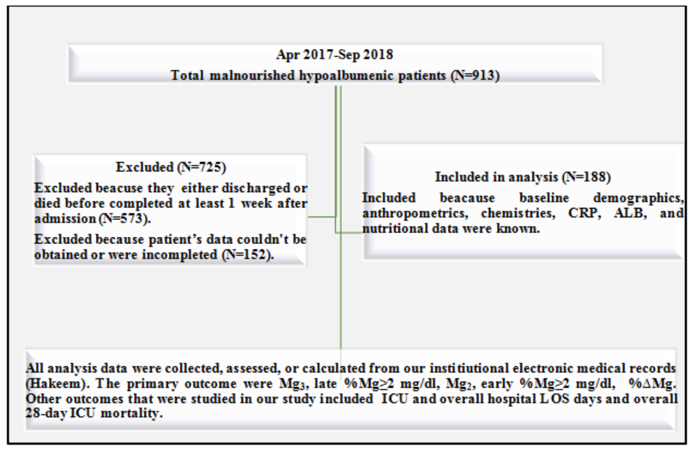

Fig 1. Flow chart of critically ill patient's selection and data collection process.

Apr: April.

CRP: C-reactive protein.

ICU: Intensive care unit.

Sep: September.

LOS: Length of stay

Results

The mean age of our 188 studied hypomagnesemic critically ill patients was 58.94±10.4 years in which 131 patients (69.7%) of the eligible sample were male and 57 patients (30.3%) were female. There were significant differences between Group I and Group II regarding Mg^{+2} before (Mg_1) and after (Mg_2) MgSO4 infusion commencing which was significantly lower in Group I compared with Group II in both cases with Mean difference ± SEM of -0.05±0.01 mg/dl and -0.01 ± 0.00

mg/dl, respectively. But if we assessed the %ΔMg between Mg_2 and Mg_1, hypomagnesemic patients in Group I had significantly higher %ΔMg than hypomagnesemic patients in Group II with Mean difference±SEM of 5.50%±0.79%. Either an extended infusion of 2 g MgSO4 for 12 hours twice daily (Strategy I) or a standard infusion of 5 g MgSO4 for 4 hours once daily (Strategy II), all hypomagnesemic critically ill patients in both tested groups were achieved the target Mg of 2 mg/dl and above when the Mg was measured after at least 4 hours of MgSO4 infusion ending (Early Mg measurement). In contrast when the Mg was measured after at least 48 hours of MgSO4 infusion ending (Late Mg measurement), hypomagnesemic patients in Group I had significantly higher Mg_3 and %Mg≥2 mg/dl (2.03±0.08 mg/dl and 50 (53.8%), respectively) than hypomagnesemic patients of Group II (1.78±0.21 mg/dl and 6 (6.3%), respectively) with Mean difference±SEM of 0.24±0.02 mg/dl. Regarding clinical outcomes of LOS and mortality, patients in Group I had significantly lower ICU LOS, overall hospital LOS, and 28-day ICU mortality (9.49±2.27 days, 11.94±3.74 days, and 4 (4.3%), respectively) than in patients of Group II (15.95±4.78 days, 22.11±5.62 days, and 72 (75.8%), respectively) with Mean differences±SEM in ICU and overall hospital LOS of -6.45±0.55 days and -10.17±0.69 days, respectively.

Discussion

What makes this study unique is that it compares two strategies of Mg^{+2} infusion; standard infusion versus extended infusion. In this study we were aiming to address the percentage of patients achieving normal Mg^{+2} blood levels above 2 mg/dL in two phases; phase 1 (early post-infusion phase) and phase 2 (late post-infusion phase), which are defined as at least 4 hours after the end of infusion and at least 48 hours after the end of infusion, respectively.

The baseline data of the patients included in the study were analyzed and appeared as shown in table 1. The average Mean Arterial Pressure (MAP) for the patients in both groups was (75.70±12.1 mmHg) and mean Total Calories Requirements (TCR) and Protein Density for the total number of patients were (9.49±0.75 Cal/kg/day) and (1.45±0.68 g/100 Cal), respectively.

There was no difference between the two groups of the study regarding the early achievement of Mg^{+2} levels above 2 mg/dL but on the other hand, there was a significant difference in the percentage of patients maintaining normal Mg^{+2} levels above 2 mg/dL during the late post-infusion phase favoring the patients in the first group. These outcomes strongly support the retention theory which states that only around 50% of the Mg^{+2} replaced intravenously will be retained by the body, due to slow cellular uptake of Mg^{+2} and replenishment of intracellular Mg^{+2} stores, leading to serum concentrations exceeding the renal threshold.[7,9]

The extended infusion of Mg^{+2} was shown to significantly decrease the length of both ICU stay and overall hospital stay, in addition to significantly lowering 28-days ICU overall mortality rates (4.3% vs. 75.8%). These major clinical outcomes, despite being significant, were not considered as part of the main outcomes investigated in this study because we did not address other confounders that may have affected the length of ICU or overall hospital stay, and/or overall mortality. This study is limited by its retrospective design, using single-center data. Nonetheless, our center is an experienced and high-volume unit, so our data may be useful in other centers. A larger, multisite, and prospective study is needed to control for multiple confounders.

Table 1. Baseline and follow-up comparison data of the study's hypomagnesemic critically ill patients.

Variables		Total (N=188)	Group I Extended MgSO4 infusion strategy (N=93)	Group II Standard MgSO4 infusion strategy (N=95)	Mean difference ± SEM	P-Value
Age (Yrs)		58.94±10.4	58.73±10.4	59.15±10.4	-0.42±1.52	0.784 (NS)
Gender	Female	57 (30.3%)	27 (29.0%)	30 (31.6%)		0.413 (NS)
	Male	131 (69.7%)	66 (71.0%)	65 (68.4%)		
BW (Kg)		74.05±10.2	75.04±9.81	73.07±10.59	1.96±1.49	0.188 (NS)
BMI (Kg/m^2)		25.90±3.97	26.48±3.83	25.33±4.05	1.15±0.58	0.047 (S)
CRP (mg/dl)		13.19±4.27	11.25±2.86	15.09±4.57	-3.84±0.56	0.001 (S)
ALB (g/dl)		2.37±0.18	2.46±0.14	2.29±0.17	0.17±0.02	0.000 (S)
H.ALB (g/day)		20.00±0.00	20.00±0.00	20.00±0.00	0.00±0.00	NS
CRP: ALB		5.73±2.45	4.66±1.59	6.77±2.69	-2.11±0.32	0.041 (S)
TCR (Cal/kg/day)		9.49±0.75	9.86±0.58	9.14±0.72	0.72±0.09	0.043 (S)
TCR (Cal/day)		651.7±79.6	676.3±74.9	627.6±76.9	48.7±11.1	0.282 (NS)
PD (g/100 Cal)		1.45±0.68	1.49±0.65	1.41±0.71	0.08±0.09	0.425 (NS)
SBP (mmHg)		105.6±12.9	111.2±7.37	100.1±14.77	11.1±1.71	0.000 (S)
DBP (mmHg)		60.34±13.2	66.1±7.47	54.7±15.08	11.3±1.74	0.000 (S)
MAP (mmHg)		75.70±12.1	81.2±7.37	70.3±13.45	10.8±1.59	0.000 (S)
BG (mg/dl)		188.7±6.72	185.7±3.87	191.7±7.55	-6.02±0.88	0.014 (S)
Ca (mg/dl)		6.77±0.33	6.99±0.16	6.57±0.33	0.43±0.04	0.000 (S)
cCa (mg/dl)		8.05±0.29	8.21±0.07	7.88±0.32	0.330.03	0.000 (S)

Mg_1		1.26±0.06	1.23±0.01	1.28±0.07	-0.05±0.01	0.000 (S)
Mg_2		2.31±0.01	2.31±0.00	2.32±0.02	-0.01±0.00	0.000 (S)
%ΔMg		84.6%±6.07%	87.4%±1.70%	81.9%±7.44%	5.50%±0.79%	0.000 (S)
Early %Mg≥2	**Not Achieved**	0 (0.00%)	0 (0.00%)	0 (0.00%)		0.000 (S)
	Achieved	188 (100.0%)	93 (100.0%)	95 (100.0%)		
Mg_3		1.90±0.20	2.03±0.08	1.78±0.21	0.24±0.02	0.000 (S)
Late %Mg≥2	**Not Achieved**	132 (70.2%)	43 (46.2%)	89 (93.7%)		0.000 (S)
	Achieved	56 (29.8%)	50 (53.8%)	6 (6.3%)		
Pre-ICU admission days		4.32±3.95	2.44±2.36	6.16±4.32	-3.72±0.51	0.000 (S)
ICU stay days		12.76±4.95	9.49±2.27	15.95±4.78	-6.45±0.55	0.000 (S)
Overall hospital stay days		17.07±6.98	11.94±3.74	22.11±5.62	-10.17±0.69	0.000 (S)
28-day ICU survival		112 (59.6%)	89 (95.7%)	23 (24.2%)		0.000 (S)
28-day ICU overall mortality		76 (40.4%)	4 (4.3%)	72 (75.8%)		

Values are presented as Mean±SD by using independent T-test and one sample T-test or as number (%)by using Chi-square test.

Group I: Patients who were on extended MgSO4 infusion strategy.	CRP: C-reactive protein.
Group II: Patients who were on standard MgSO4 infusion strategy.	CRP: ALB ratio: C-reactive protein to albumin level ratio.
Yrs: Years.	SBP: Systolic blood pressure.
Kg: Kilogram.	DBP: Diastolic blood pressure.
BW: Actual body weight.	MAP: Mean arterial pressure.
BMI: Body mass index.	BG: Blood glucose.
S: Significant (P-Value <0.05).	Ca: Total calcium level.
NS: Nonsignificant (P-Value >0.05).	cCa: Corrected total calcium level.
N: Number of study's patients.	Mg: Total magnesium level.
TCR: Total calories requirement.	Mg_1: Baseline total magnesium level.

PD: Protein density. Δ: Changes occurred after an intervention. ALB: Albumin level. H.ALB: Human albumin 20%.	Mg_2: Total magnesium level after at least 4 hours of infusion ends. Mg_3: Total magnesium level after at least 2 days of infusion ends. Early measurement: After at least 4 hours of infusion ends. Late measurement: After at least 2 days of infusion ends.

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