Magnesium supplementation and the potential association with mortality rates among critically ill non-cardiac patients

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ABSTRACT

Objective: Recent literature showed that development of hypomagnesemia is associated with higher mortality. The objective of this study is to evaluate the impact of magnesium supplementation on mortality rates of critically ill patients.

Methods: All patients admitted to the Intensive Care Unit (ICU) of King Abdul-Aziz Medical City, Riyadh, Saudi Arabia since September 2003 were included. We recorded the demographics data, APACHE score, daily magnesium levels and magnesium supplementation. We collected the data for 30 days or until discharge from ICU. Statistical analysis was performed using the student t-test for continuous data and the Fischer's exact test for categorical data. Nothing was carried out to influence the behavior of intensivists in replacing magnesium.

Results: During the study period, 71 patients (45 males and 26 females) were admitted to the ICU, the mean age was 54 ± 18 years for males and 56 ± 19.2 years for females. The mean magnesium level on admission was 0.78 ± 0.2 mmol/L and the majority of the patients were medical admissions. Approximately 39.4% had hypomagnesemia on admission and the overall mortality rate was 31%. In able to standardize the supplementation of magnesium among groups, the daily magnesium supplementation index (DMSI = total magnesium supplement in grams/length of stay in days) was calculated. The mortality rates for DMSI with <1 grm/day (low groups) was statistically significant higher than that of DMSI with ≥1 grm/day (high group) (43.5% versus 17%, p=0.035). There was no statistically significant differences between magnesium levels of both groups of DMSI except at admission where DMSI group had higher magnesium levels (<1 grm/day).

Conclusions: Daily magnesium supplementation index higher than 1 grm/day is associated with lower mortality rates for critically ill patients. This effect was not found to be independent and may be related to severity of illness. Given that magnesium levels were similar between the 2 groups of DMSI at almost all points of the study, magnesium supplementation per se may be beneficial in lowering mortality rates. The exact cause of this effect is unknown. An aggressive magnesium supplementation protocol may be warranted. A larger scale randomized study is necessary to evaluate this effect.

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Magnesium (MG) is the second most abundant intracellular cation after potassium. It is pivotal in the transfer, storage, and utilization of energy as it regulates and catalyzes 300 enzyme systems and essential for life.[1-3] Magnesium as a co-factor plays a major role in the countless enzymatic processes in the body.[4] It plays an important role in numerous metabolic processes including cellular energy production, storage, and use in the form of adenosine triphosphate, as well as enzymatic reactions involved

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in protein synthesis.[5] Although magnesium levels are measured frequently in clinical practice, serum levels represent a very small percentage in the total magnesium stores in the body making them less reliable. In fact, serum levels constitute only 0.3% of all magnesium storage in the body.[6,7] Although the role of this electrolyte has not been clearly defined, many physicians use it regularly in critical care illnesses. The prevalence of hypomagnesemia among critically ill patients is not well defined but it ranges from 20-61%; more importantly, patients who develop hypomagnesemia in the intensive care unit have a mortality rate of 2-3 times higher and prolonged hospitalization compared with those who are not magnesium deficient.[3,8,9] Hypomagnesemia is a common finding in current clinical practice,[10] mainly in critically ill patients and postoperative patients. In the literature, the potential relationship between low magnesium levels and increased mortality has been suggested.[11,13] Magnesium has been directly implicated in hypokalemia, hypocalcemia and dysarrhythmia.[14-16] Magnesium affects the smooth muscle vasoconstriction, which is important to the underlying pathophysiology of several critical illnesses.[3] Clinical manifestations of hypomagnesemia include neuromuscular, neurological, psychiatric and cardiac disorders, which may considerably increase the morbidity of such patients.[11,13] The objective of this study is to evaluate the impact of magnesium supplementation on mortality rates of critically ill patients

Methods. In September 2003, we collected prospectively the data of all consecutive patients admitted in the Tertiary Medical and Surgical Intensive Care Unit of King Abdul-Aziz Medical City, Riyadh, Saudi Arabia. A database was created which included patient's age, gender, reason of admission, acute physiology and chronic health evaluation (APACHE) II scores, duration of mechanical ventilation (MV), length of stay (LOS) in ICU, development of arrhythmia (defined as atrial fibrillation, ventricular tachycardia or ventricular fibrillation), daily magnesium levels and magnesium supplementation. Data were collected for 30 days or until discharge from ICU whichever occurs first. This study was observational and no interference with routine patient management in the ICU was attempted. Magnesium was determined by analyzer based on the modified xylidyl blue reaction (ADVIA 1650® Chemistry system). Normal values range between 0.63 and 1 mmol/L. Patients were classified into 3 groups according to their initial magnesium level: Hypomagnesemia <0.63 mmol/L, normal magnesium 0.63- 1 mmol/L, and hypermagnesemia >1 mmol/L. All types of magnesium supplementation were recorded (intravenous or oral). Daily magnesium supplementation score was calculated starting at 7 am until the next day (7 am), which included the total of all types of magnesium supplementation in grams. In able to standardize the supplementation of magnesium among patients, a daily magnesium supplementation index (DMSI = total magnesium supplement in grams/length of stay in days) was calculated. Patients were stratified to 2 groups based on their DMSI: 1) high group if DMSI was ≥1gram/day and 2) low group if DSMI was <1 gm/day. Continuous data are expressed as mean ± standard deviation and compared using the student t- test. Categorical data are expressed as percentage and compared using the chi-square or Fischer's exact tests whichever is appropriate. Statistical significance was defined as alpha <0.05. Statistical analysis was performed using the Statistical Package for Social Sciences (Oklahoma USA 2001).

Result. During the study period, 71 patients were admitted to the ICU, the mean age was 54 ± 18 and 45 patients (64%) were males. The mean APACHE was 22.6 ± 9.1. The mean magnesium level on admission was 0.78 ± 0.2 mmol/L and the majority of the patients were medical admissions. Most medical admissions were due to acute renal failure, congestive heart failure, stroke and end stage renal failure (**Table 1**). On admission, 15 (22%) patients had normal magnesium, 41 (60%) had hypomagnesemia and 12 (18%) had hypomagnesemia. Twenty-nine (41%) patients were classified as high DMSI and 42 (59%) patients has a low DMSI. There were no significant difference between the 2 groups regarding the age, gender, admission type or use of diuretic but the low DSMI group had higher APACHE (25.1 versus 19.4, p=0.004) **Table 2**. There were no statistically significant differences between magnesium levels of both groups of DMSI except at admission where the low DMSI group had higher magnesium levels (0.82 versus 0.73 p=0.0045) **Figure 1**. The overall mortality rate was 31%. The mortality rates for low DMSI group were statistically higher than that of high DMSI group (43.5% versus 17%, p=0.035). Arrhythmia was encountered more often in the low DMSI group (7% versus 23%, p=0.001) and also intensive care unit length of stay (ICU LOS) and duration of mechanical ventilation (MV) were statistically significant, which is lesser in the high DMSI group (8.8 versus 21.2, p=0.036; 6.5 versus 19.5 p=0.026). Upon performing multivariate analysis using binary regression for predictors of hospital mortality only APACHE II score was found

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Table 1 - Demographic and outcome data (n=71).

Demographic data	n (%)
Mean age (year)	54 ± 18
Male/Female	45/26 (63.4/24)
Sepsis	34 (47.9)
Acute renal failure	17 (23.9)
Congestive heart failure	15 (21.1)
Pulmonary embolism	9 (12.7)
Acute myocardial infarction	4 (5.6)
End stage renal disease	8 (11.3)
Trauma	11 (15.5)
Medical admission	45 (63.4)
Cerebral vascular accident	14 (19.7)
APACHE II	22.61 ± 9.11
ICU LOS	15.8 ± 17.8
Admission magnesium	0.78 ± 0.2
Mechanical ventilation duration	14.12 ± 18
Vasopressor duration	6.8 ± 7.4
Admission heart rate	109.6 ± 25.4
Hospital mortality	22 (31)

APACHE II - acute physiology and chronic health evaluation, ICU LOS - intensive care unit length of stay,

as an independent risk factor for mortality (odd ratio 1.21; 95% confidence interval 1.09-1.34 $p<0.0001$) all other factors including serum magnesium and daily supplementation were associated with insignificant results. This indicates that the impact of magnesium supplementation on mortality may simply be related to severity of illness.

Discussion. Our results demonstrated that DMSI higher than 1 grm/day is associated with lower mortality rates as well as decreased ICU LOS and MV duration of critically ill patients. Magnesium deficiency has been linked to clinical outcomes in rather small trials with different designs mostly observational but the data is conflicting regarding the relationship between hypomagnesemia and clinical outcomes.[3] Although a study by Huijgen et al[17] showed no relationship between hypomagnesemia and clinical outcomes,[17] while a recent work by Soliman et al[18] demonstrated that the development of ionized hypomagnesemia is associated with higher mortality rates. This study was an observational prospective study over a 3-month period. Despite higher mortality rates for those who developed hypomagnesemia their APACHE II, sequential organ

Table 2 - Baseline and outcome characteristics of both DMSI groups.

Characteristics	High DMSI (N=29) ≥1 gram/d n (%)	Low DMSI (N=42) <1 gram/d n (%)	*P*-value
Age	56 ± 19.2	52 ± 16.2	0.34*
Gender			
Male	22 (75.9)	28 (66.7)	0.4*
Female	7 (24.1)	14 (33.3)	0.4
APACHE II	19.40 ± 6.7	25.10 ± 9.6	0.004
Underlying diseases			
Sepsis	9 (31)	18 (42.9)	0.003
Cirrhosis	5 (17.2)	12 (28.6)	0.5*
Renal failure	4 (13.8)	16 (38.1)	0.025
Diabetes mellitus	19 (65.5)	32 (76.2)	0.3*
Trauma	6 (20.7)	5 (11.9)	0.3*
Admission magnesium (mmol/l)	0.73 ± 0.2	0.82 ± 0.22	0.0045
Use of diuretics	21 (72.4)	27 (64.3)	0.5*
Use of steroid	5 (17.2)	20 (47.2)	0.009
Use of mechanical ventilation	22 (75.9)	34 (81)	0.6*
Clinical outcomes			
Hospital mortality	5 (17.2)	17 (40.5)	0.032
Arrhythmia	7 (24.1)	23 (54.7)	<0.0001
Intensive care unit length of stay (days)	8.8 ± 5.8	21.2 ± 20.9	0.036
Mechanical ventilation duration (days)	6.5 ± 5.6	19.5 ± 21.5	0.026

*not-significant, DMSI - daily magnesium supplementation index, APACHE II - Acute physiology and chronic health evaluation

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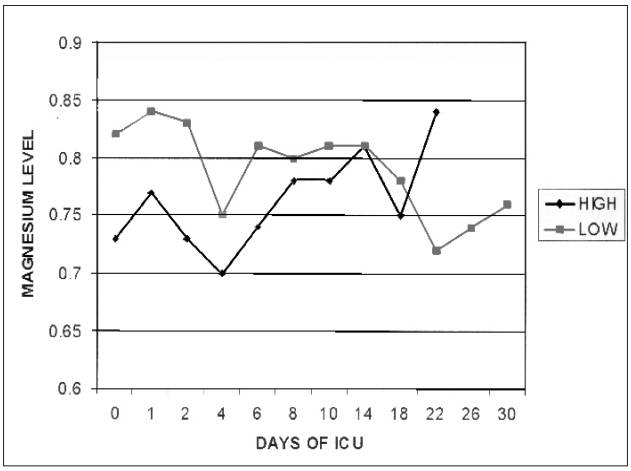

Figure 1 - Magnesium levels in intensive care unit patients per daily magnesium supplementation index.

failure assessment SOFA scores were higher as well as the percentage of sepsis and septic shock. This leads to an important question whether hypomagnesemia is really a risk factor per se or it is just a marker for severity of illness. To this end, Esen et al[19] embarked upon a very interesting research work wherein they postulated that magnesium could be a key player in the cascade of sepsis. This study was conducted on rats and demonstrated a potential therapeutic effect of magnesium especially in septic rats by attenuation of the increased blood brain barrier permeability defect, which may result in reduction of brain edema. These exciting and novel findings may explain why low magnesium patients had higher incidence of sepsis. Nevertheless, the results of this study remain subject to criticism due to the few existing clinical trial that implementing magnesium therapy in critical illness and there are no adequate guidance has been provided for the practicing clinician assign in the ICU.[3] Despite the significant morbidity related to hypomagnesium for patients in a critical care setting, such as cardiac arrhythmias, respiratory muscle weakness,[16,20] the most intriguing finding is that vigorous replacement of magnesium is significantly associated with lower mortality.[11] Caution should be taken with magnesium therapy in patients with severe degree of renal failure, the dose of magnesium should be halved, and the serum magnesium concentration must be monitored.[3] In our study, the incidence of renal failure was higher in the low DMSI group, which can simply be explained by the lack of need for aggressive replacement in this particular group. Although we found a strong association between survival and high DMSI in univariate analysis, this was not the case in multivariate analysis which could be explained by the severity of illness in those that do not require higher amounts of magnesium or simply by other associated illnesses mainly renal failure. We have to emphasize this finding that magnesium supplementation was only significant in univariate rather than multivariate analysis, therefore we cannot claim that it is an independent factor that influence the outcome favorably; nevertheless, we could suggest a potential association between magnesium supplementation and patients' outcomes. Our study has several limitations, the sample size is small and the study is observational and non-interventional as well we lack (as all of previous reports) a clear definition of hypomagnesemia; finally, no standard protocol for magnesium supplementation was implemented. We have used total magnesium in our study rather than ionized magnesium, which has been used in previous trials; nevertheless, there is no consensus in the literature on which type of magnesium should be used in clinical trials. As we elaborated previously, the lack of statistical significance in the regression analysis for hospital mortality may be explained by the severity of illness of those who received less magnesium. We believe that this small study may open new horizons into the existing but lacking evidence for the use of magnesium in non-cardiac critical care medicine. This is the first ever study that standardized magnesium replacement therapy in a quantifiable index (DMSI =average magnesium replacement per ICU day) that takes into account the ICU length of stay. In this way, the bias of longer ICU stays and hence the higher total magnesium supplementation can be avoided. Due to the observational nature of the study, we cannot claim to have controlled the aggressiveness of magnesium supplementation, which was left totally to the treating intensivist. We could emphasize the homogenous practice of our intensive care physicians who are mostly trained in North America and hence the variability of practice may be less encountered. Daily magnesium supplementation index higher than 1 grm/day is potentially associated with lower mortality rates for critically ill patients. Knowing that magnesium levels were similar between the 2 groups of DMSI at almost all points of the study, magnesium supplementation per se may be beneficial in lowering mortality rates. The exact cause of this effect is unknown. We believe that the jury is still out on the exact relationship between magnesium and critical care clinical outcomes. There is more than ever need for a large-scale randomized trial to elaborate on such clinically important and potentially beneficial effect.

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