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Serum and erythrocyte magnesium in critically ill patients

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Abstract *Objectives:* To evaluate the prevalence of serum and erythrocyte magnesium (Mg) abnormalities in patients on admission to the intensive care unit (ICU) and to test the hypothesis that low levels of Mg are associated with a higher mortality.
Design: Prospective study.
Setting: 14-bed ICU in a 1000-bed teaching hospital.
Patients: 179 consecutive patients admitted over a 4-month period.
Measurements: Total serum Mg (Mgs) and erythrocyte Mg (Mge) were determined on admission by atomic absorption spectrophotometry. Severity of illness was assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II and the number of organ system failures (OSF) during the first 24 h. The patients were followed up until discharge from hospital.
Main results: On admission, 79 patients (44%) were hypomagnesemic and 10 (6%) were hypermagnesemic. A low level of Mge was observed in 119 patients (66%). In patients with similar APACHE II scores and OSF numbers, more of those with hyperMgs died during their ICU stay. However, the Mge value on admission did not correlate with patient outcome.
Conclusions: We confirm the high prevalence of Mgs abnormalities as well as Mg deficiency on admission to a medical ICU. Low levels of Mgs and Mge are not associated with higher fatality. HyperMgs was associated with patient death.

Key words Intracellular magnesium · Magnesium · Magnesium deficiency · Prognosis in intensive care unit

Introduction

The prevalence of hypomagnesemia in patients on admission to the intensive care unit (ICU) ranges between 20 and 61% [1–4]. In patients who are admitted to the ICU, several factors may be associated with magnesium (Mg) deficiency, like excess Mg loss, prolonged intravenous therapy, malnutrition, diabetic ketoacidosis, and blood transfusions. Mg depletion can result in cardiac arrhythmias, neuromuscular derangement, respiratory muscle weakness, and various metabolic abnormalities such as hypocalcemia and refractory hypokalima [5]. Some recent reports of critically ill patients have suggested a link between hypomagnesemia on admission and mortality in hospital [4]. Mg is mainly located in the intracellular fluid. In addition, total serum Mg (Mgs) levels are a combination of ionized (55%), chelated (12%), and protein-bound (33%) fractions. Accordingly, the Mgs level does not mirror adequately tissue Mg levels. Reports in critically ill patients are mostly based upon Mgs levels. Therefore, we assessed intracellular Mg concentration in

erythrocytes (Mge) together with Mgs. We aimed to measure the prevalence of these alterations in Mg and their relationships to outcomes in the ICU and in hospital. Our working hypothesis was that low Mgs and low Mge levels were associated with a higher ICU or in-hospital mortality.

Patients and methods

Patients

Over a 4-month period, all the adults admitted to our 14-bed, mostly medically-oriented ICU (part of a 1000-bed teaching hospital) were eligible for this study. Our institutional ethics committee stated that informed consent was not necessary. During the observation period, 191 patients entered our ICU, but 12 were excluded because of lack of data. The remaining 179 are reported on here.

Methods

Erythrocyte magnesium measurement

A 5-ml blood sample, drawn a few minutes after the patient was admitted, was centrifuged. After centrifugation, erythrocytes were whased and then lysed by freezing at −20 °C for 3 h. The 50-µl hemolysate was diluted in lanthanum chloride (1/60) and Mg was measured by atomic absorption spectrophotometry (AAS) using a Perkin–Elmer 2360 analyzer. Normal values in the laboratory ranged from 2.05 to 2.60 mmol/l; the limits were taken from Toitou et al. [6]. Accordingly, the patients were classified into three subgroups: hypo- (Mge < 2.05 mmol/l), normo- (2.05–2.60 mmol/l), and hypermagnesemic (Mge > 2.60 mmol/l).

Serum magnesium measurement

Total Mgs was measured by AAS on the same sample as that used for Mge determination. In the laboratory, normal Mgs values range from 0.75 to 1 mmol/l. Patients were classified into three subgroups: hypo-(Mgs < 0.75 mmol/l), normo-(Mgs < 0.75 – 1 mmol/l), and hypermagnesemic (Mgs > 1 mmol/l). On the same sample, routine blood variables were also measured (normal range in the laboratory): sodium (135–145 mmol/l), potassium (3.5–4.5 mmol/l), chloride (98–108 mmol/l), total calcium (2.25–2.60 mmol/l), phosphate (0.90–1.40 mmol/l), CO_2 content (23–30 mmol/l), urea nitrogen (2.5–7.5 mmol/l), creatinine (60–120 µmol/l), protein (60–80 g/l) and glucose (3.9–5.3 mmol/l). Patients with hypoMgs were supplemented parenterally with magnesium sulfate; those with normo- or hyperMgs were not. Values for Mgs and other metabolic variables were determined daily.

Clinical assessment

The following clinical data were prospectively recorded: age, sex, medical or postoperative reason for admission Acute Physiology and Chronic Health Evaluation (APACHE) II score [7], number of organ system failures (OSF) during the first 24 h [8], origin of admission (emergency room, other wards, or home), and major diagnosis categories [9].

ICU and in-hospital outcome

Patients were followed up during their ICU and hospital stays. At the time of ICU or hospital discharge, patients were either alive or dead, therefore we computed ICU and in-hospital mortality rates.

Statistical analysis

Values are mean ± SD. Univariate comparisons of means between groups were done by ANOVA. Scheffé's test was used to compare one of the means and each of the others when multiple comparison was significant. Category variables were compared by chi-square. A p level of < 0.05 was considered significant.

Results

Clinical characteristics of the patients on admission

Among the 179 patients (112 males), the mean age was 62 ± 12 years, APACHE II score 18 ± 10, and number of OSFs 0.75 ± 1. Seventy-five patients (42%) entered the ICU from other wards, 59 (33%) from the emergency room, and 45 (25%) from home. The primary diagnoses in the 169 medical patients admitted were the following: cardiovascular (51), drug overdose and poisoning (31), respiratory (42), central nervous system (21), gastrointestinal (10), infection (9), and renal and metabolic disorders (5). The 10 postoperative patients were admitted after emergency abdominal surgery (3), non-emergency surgical procedure (neck surgery 3, hiatal hernia repair 1, femoral–popliteal bypass graft 1, neurosurgery 1), and trauma (1).

Serum and erythrocyte magnesium and other electrolytes disturbances

Seventy-nine patients were hypoMgs (44%), 90 (50%) were normoMgs, and 10 (6%) were hyperMgs on admission. The three Mgs subgroups were comparable (Table 1). Elevated serum creatinine concentrations and hyperkalemia were more prevalent in the hyperMgs group. In the 179 patients, Mgs correlated with phosphate ($r = 0.36$, $p < 0.001$), serum creatinine ($r = 0.37$, $p < 0.001$), and blood urea nitrogen ($r = 0.39$, $p < 0.001$). On admission, 119 patients (66%) were hypoMge, 54 (30%) normoMge, and 6 (4%) hyperMge. The three Mge subgroups did not differ. Mge did not correlate with any serum metabolic variable. Mge and Mgs correlated weakly over the 179 patients (Mge = 1.42 + 0.76 Mgs; $r = 0.40$, $p < 0.001$).

Table 1 Comparisons of the three groups according to the serum magnesium level on admission to the ICU. Values are mean ± SD (*OSF* organ system failure)

	Hypo magnesemic ($n = 79$)	Normo magnesemic ($n = 90$)	Hyper magnesemic ($n = 10$)
Age (years)	62 ± 17	63 ± 18	60 ± 20
Number of OSFs	0.94 ± 0.12	1.00 ± 0.11	1.80 ± 0.43
APACHE II score	18 ± 9	16 ± 10	22 ± 7
Medical admission (n)	75	85	9
Postoperative admission (n)	4	5	1
ICU death (n)	14 (18%)	15 (17%)	5 (50%)*
In-hospital death (n)	21 (27%)	22 (24%)	5 (50%)

*$p < 0.05$ between hyperMgs and both normoMgs and hypoMgs subgroups

ICU and in-hospital outcome

ICU and in-hospital mortalities were 19 and 27%, respectively. The ICU, but not the in-hospital, mortality was significantly higher in the hyperMgs group (Table 1). ICU and in-hospital mortality did not differ between Mge subgroups. Among the medical patients who were hypoMgs, normoMgs, and hyperMgs, ICU mortality was 17, 15, and 56% ($p < 0.01$), respectively, and was 27, 24, and 56%, respectively, during the hospital stay (NS). Both ICU mortality and in-hospital mortality were similar among medical and postoperative Mge patients. In the cardiovascular category, the ICU and in-hospital mortality for hypo-, normo- and hyperMgs patients was 14, 7, and 100% ($p < 0.05$) and 29, 18, and 100% ($p < 0.05$), respectively. The same analysis done for Mge in the cardiovascular category showed no difference. Among the other diagnostic categories, Mgs and Mge did not correlate with outcome.

Discussion

In our study, the 44% prevalence of hypomagnesemia on admission falls in the middle of the reported rates [1–4]. The definition of hypomagnesemia could explain this wide range. Rubeiz et al. [4] found a 20% prevalence of hypomagnesemia on admission, with a threshold of 0.62 mmol/l. With such a level, our prevalence of hypomagnesemia would have gone down to 11%.

Hypomagnesemia was the second most frequent electrolyte abnormality in our study, after hypocalcemia (59% of the patients). Hyperkalemia and elevated serum creatinine levels were more prevalent among hypermagnesemic patients. This result is not surprising since one-third of Mg is eliminated through the kidneys.

Rubeiz et al. [4] have recently found that, for similar APACHE II scores, the in-hospital mortality (46%) of hypomagnesemic patients was almost twice that (25%) of normomagnesemic patients. We did not observe this (Table 1). As discussed, the range used to define normal Mgs was not the same in the two studies. In addition, although APACHE II scores were similar for the hypomagnesemic subgroup in the two studies, the mortality rates were statistically different. Since our patients were 10 years older, similar APACHE II scores suggested less severity in our patients. Chernow et al. [3] reported a 13% in-hospital mortality in hypomagnesemic versus 11% in normomagnesemic patients (NS). They found, however, a higher mortality (41%) in 17 patients with severe hypomagnesemia (Mgs ≤ 0.50 mmol/l) than in the re-

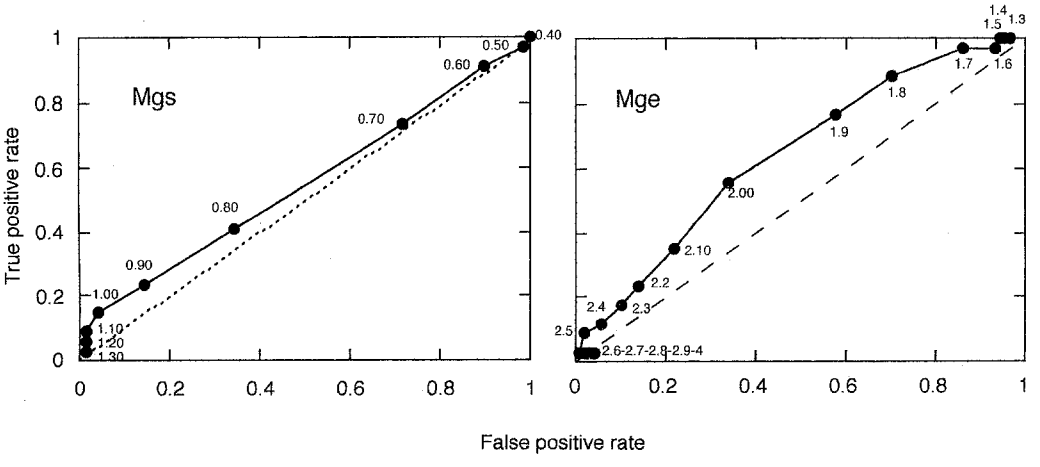

Fig. 1 The receiver operating characteristics curve describing performance of different thresholds of serum (*Mgs, left panel*) and erythrocyte magnesium (*Mge, right panel*) to predict ICU outcome. The small numbers are the different thresholds (in mmol/l). The dotted diagonals are the lines for which true-positive rate = false-positive rate

maining population [3]. In our study, in the 4 severely hypomagnesemic medical patients, according to Chernow, the hospital mortality was 50% – not statistically different from that of the remaining patients, which is probably due to the small number of patients.

In our study, more hypermagnesemic patients died during their ICU stay than hypomagnesemic or normomagnesemic patients, whereas the in-hospital mortality was not significantly different (Table 1). Similar results were obtained in adult [3] and in pediatric critically ill patients [10]. Hypermagnesemia can lead to hypotension, neuromuscular blockade, respiratory depression, and cardiac conduction abnormalities [11–14]. To determine the critical value of Mgs for predicting ICU death, we constructed receiver operating characteristics (ROC) curves at different Mgs and Mge thresholds (Fig. 1). The ROC curve of Mgs exhibited an inflexion point at 1.00 mmol/l, for which the sensitivity is 0.15 and the specificity 0.96. Below this level, the thresholds are on a linear curve which parallels and is very close to the line of identity. The same was true for the ROC curve of Mge (Fig. 1). Accordingly, Mgs and Mge are not able to predict ICU mortality in the patients in this study. Our results suggested that a number of patients might have had Mg deficiency, according to Mge, that was not predicted by Mgs levels. However, there are few data from ICU patients to compare with ours. Fifty-three percent of 104 consecutive cardiac ICU patients had a low Mg content in blood mononuclear cells, whereas only 7.7% had hypomagnesemia [15]. In our study, Mgs correlated with Mge. Mgs did not correlate with mononuclear cell Mg in cardiac patients but did correlate with mononuclear Mg in hypomagnesemic and normal control subjects [15].

In summary, our study confirms the high prevalence of Mg disorders in patients on admission to a medical ICU. We could not confirm the link between hypoMgs and outcome. Mge determination may detect more patients with Mg deficiency, but it is not correlated with outcome.

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