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Total and ionized magnesium testing in the surgical intensive care unit – Opportunities for improved laboratory and pharmacy utilization☆,☆☆

Daniel Dante Yeh, MD [a,*], Nalin Chokengarmwong, MD [a], Yuchiao Chang, PhD [b], Liyang Yu, MS [b], Colleen Arsenault, RN [c], Joseph Rudolf, MD [d], Elizabeth Lee-Lewandrowski, MPH, PhD [d], Kent Lewandrowski, MD [d]

[a] Massachusetts General Hospital, Department of Surgery, Division of Trauma, Emergency Surgery, and Surgical Critical Care, United States
[b] Massachusetts General Hospital, Department of Medicine, United States
[c] Massachusetts General Hospital, Surgical Intensive Care Unit, United States
[d] Massachusetts General Hospital, Department of Pathology, United States

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ABSTRACT

Purpose: Ionized fraction (iMg) is the physiologically active form of magnesium (Mg); total Mg may not accurately reflect iMg status. Erroneously "low" Mg levels may result in unnecessary repetitive testing.
Materials and methods: From 11/2015 to 01/2016, patients ordered for Mg from a pilot ICU also had iMg tested. Weighted kappa statistic was used to assess agreement between Mg categories (low, normal, high). Predictors of unnecessary repeated Mg testing and repletion using data were explored through logistic regression models using GEE techniques to account for repeated measurements in both bivariate and multivariable analyses.
Results: There were 470 Mg/iMg paired measurements from 173 patients. The weighted kappa statistic was 0.35 (95%CI 0.27–0.43) indicating poor agreement in assessment of magnesium status. Of the 34 Mg samples reported as "low", only 6 (18%) were considered "low" using concurrent iMg testing. In the multivariable models, history of atrial fibrillation (aOR = 1.61, 95%CI 1.16–2.21, p = 0.004) and concomitant metoclopramide (aOR = 1.71, 95%CI 1.03–2.81, p = 0.036) were significant predictors of unnecessary repeat Mg testing.
Conclusions: In the surgical ICU, categorical agreement (low, normal, high) was poor between Mg and iMg. Over 80% of "low" total Mg values are erroneous and may result in unnecessary additional measurements and repletion.

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1. Introduction

Magnesium (Mg) is the second most prevalent intracellular cation and is considered an important cofactor in many enzymatic reactions, including protein synthesis, DNA replication, mRNA transcription, mitochondrial function, and energy production through adenosine triphophatase [1]. Derangements in measured magnesium levels in the critically ill are more common than for any other electrolyte [2] and much attention is paid towards maintaining normal Mg homeostasis in these patients, as hypomagnesemia has been associated with neuromuscular symptoms (weakness, delirium, convulsions, etc.) cardiac arrhythmias (premature contractions, atrial fibrillation, torsades de pointes, etc.), metabolic derangements (refractory hypokalemia, hypocalcemia), and increased mortality [1,3]. Most intensive care units (ICUs) routinely measure total plasma Mg and have developed protocols for Mg administration.

Nearly 99% of the total body magnesium is confined to the intracellular compartment [1,4]. Extracellular plasma magnesium exists in three states: bound to protein (particularly albumin, 25% of total plasma magnesium), complexed with anions such as phosphate bicarbonate, and citrate (8%), and in ionized form (65%) [5]. Measurement of intracellular magnesium is not possible in routine clinical practice and total plasma magnesium is poorly reflective of intracellular levels [6]. Within the extracellular compartment, the ionized magnesium (iMg) fraction is acknowledged to be the physiologically active form of Mg [7]. Thus, it follows that clinical decisions should be based on the ionized fraction rather than the total Mg level. However, because the total Mg and iMg concentrations are independent of albumin concentration within the normal range, it is not possible to accurately correct for hypoalbuminemia or calculate an iMg; it must be measured directly [8-11]. Additionally, the correlation between total magnesium and ionized magnesium

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* Corresponding author at: 1800 NW 10th Ave., T-215, Miami, FL 33136, United States.
E-mail address: dxy154@miami.edu (D.D. Yeh).

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has been shown to be poor in critically ill patients [12]. While the measurement of iMg has been commercially available since 1994 [13], routine iMg measurement has not become widespread, in part because the iMg assay is only offered by one device manufacturer in the United States. For this reason, most ICUs continue to measure total Mg levels and provide Mg supplementation based on the total plasma Mg.

The primary purpose of this study was to assess the feasibility of implementing iMg into clinical practice and to estimate the potential impact on utilization and laboratory charges. We hypothesized that a large proportion of "low" total magnesium levels would actually be normal on ionized magnesium testing and that substitution of iMg for Mg would lead to significant decreases in repetitive testing and unnecessary magnesium replacement therapy. A secondary objective of this study was to explore potential reasons for why patients received additional magnesium monitoring and replacement outside the bounds of standard protocol.

2. Material and methods

This prospective study was approved by our Institutional Review Board. We enrolled patients admitted to the surgical ICU of an academic hospital. The surgical ICU admits post-traumatic and post-surgical patients from the following specialties: general surgery, surgical oncology, hepatobiliary, vascular, thoracic, orthopedic, obstetrics and gynecology, and neurosurgery. Medical patients are occasionally admitted secondary to medical ICU bed shortages. There are two 18-bed surgical ICUs in our hospital, but only one participated in this pilot project. However, we collected total Mg and patient demographic information and concomitant medications from both ICUs during the study period. Each ICU admits approximately 100 patients per month and orders approximately 1000 plasma magnesium tests per month. Both ICUs follow the same magnesium replacement protocol (described below).

It is routine practice in our ICU to obtain "daily morning labs", including plasma magnesium, in most critically ill patients. These labs are drawn shortly after midnight. From November 2015 to January 2016, all surgical ICU patients were screened from Monday through Friday (convenience sample). If the clinical team in the pilot ICU ordered a plasma magnesium test to be drawn the following morning, a separate iMg test order was also completed.

Ionized magnesium was measured on anaerobically collected heparinized whole blood samples on the Nova Biomedical Stat Profile® pHOx Ultra analyzer (Nova Biomedical, Waltham, MA, USA). All analyses were performed within 30 min of sample collection. The residual sample was then centrifuged and the plasma component decanted followed by measurement of the total Mg on the Roche Diagnostics Cobas C50® automated chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA). The results of the ionized magnesium testing were not made available to the clinical team and no clinical decisions were made based on ionized magnesium values.

We defined a plasma Mg value 1.8 to 2.4 mg/dL as normal. For Mg values between 1.6 and 1.8, our existing protocol recommends a 4 g magnesium sulfate ($MgSO_4$) injection over 2 h. For Mg values <1.6 mg/dL, the protocol recommends a 6 g $MgSO_4$ injection over 3 h. For plasma Mg values above the normal range, there is no specific treatment recommended. An ionized Mg value of 0.45 to 0.60 mmol/L was considered normal based on published literature and manufacturer's guidelines [14]. For subjects in both the pilot and control ICU, all subsequent Mg testing and $MgSO_4$injections performed for the next 24 h were recorded. A repeated Mg test was considered unnecessary when the iMg (pilot ICU) or Mg (control ICU) earlier that day was within normal limits or higher than normal. A $MgSO_4$ injection was considered unnecessary when the iMg (pilot ICU) or Mg (control ICU) earlier that day was within normal limits or higher than normal.

Daily chart review was performed to assess for clinical factors that may influence the decision to provide supplemental magnesium above normal values. It has been our observation that supplemental $MgSO_4$ injections in the ICU are often given because of concerns about actual or potential cardiac arrhythmias. Many patients are also taking concomitant medications that may result in QT interval prolongation. Therefore, subjects were assessed for the presence of atrial fibrillation (AF), history of AF, or concomitant administration of common QT interval-prolonging medications: metoclopramide, erythromycin, ondansetron, fluconazole, haloperidol, or quetiapine. All patients in both ICUs receive daily electrocardiogram (ECG) and QT interval is measured from the ECG.

2.1. Statistical analysis

We examined the agreement between Mg and iMg measurements using data from the pilot ICU and iMg was considered the more accurate "gold standard" measurement. The correlation between Mg and iMg values was summarized using a Pearson correlation coefficient. A linear regression model using the Generalizing Estimating Equations (GEE) techniques was used to account for the repeated measurements from the same individual. We created low, normal, and high categories based on the normal range values for Mg and iMg. A weighted kappa statistic was used to assess the agreement between the categories. We explored the predictors of unnecessary repeated Mg testing and unnecessary $MgSO_4$ injection using data from both surgical ICUs, where unnecessary repeated testing or injection was defined by the earlier Mg results. Logistic regression models using the GEE techniques were used to account for the repeated measurements from the same individual in both bivariate and the multivariable analyses. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary NC). A two-sided p value of 0.05 or less was considered as statistically significant.

3. Results

3.1. Agreement between Mg and iMg

There were 470 pairs of Mg and iMg measurements from 173 patients in the pilot ICU. The Pearson Correlation Coefficient between Mg and iMg was 0.70 ($p < 0.0001$), showing a moderate correlation (Fig. 1).

Among 470 pairs, 34 (7%) were classified as low, 364 (78%) were normal (1.8–2.4 mg/dL), and 72 (15%) were high (>2.4 mg/dL) based on the normal range for Mg, while 19 (4%) were classified as low (< 1.8 mg/dL), 325 (69%) were normal (0.45–0.60 mmol/L), and 126 (27%) were high (>0.60 mmol/L) based on the normal range for iMg (Table 1). Overall, the Mg value was more likely to present a lower category of assessment than the iMg value ($p < 0.0001$). The weighted kappa statistic was 0.35 (95%CI 0.27–0.43) indicating poor agreement between the two measurements in the category assessment.

3.2. Categorized as low based on total Mg

Of 34 Mg samples reported as "low", only 6 (18%) were also considered "low" using concurrent iMg testing (Fig. 1, "True Low"). Among the 28 assessed with low Mg but normal iMg (Fig. 1, "False Low"), the erroneously low Mg levels resulted in 27 additional repeat (i.e. unnecessary) Mg measurements and 60 unnecessary grams of $MgSO_4$ given (Table 2).

3.3. Categorized as normal based on total Mg

Of 364 "normal" Mg values, 12 (3%) were low and 75 (21%) were high on iMg testing (Fig. 1, "False Normal"). Despite a normal Mg value, there were 301 additional repeat (i.e. unnecessary) Mg measurements and 138 additional grams of $MgSO_4$ given. Excluding the 12 that were deemed low based on the iMg measurement, there were 282 unnecessary repeat Mg measurements and 116 unnecessary grams of $MgSO_4$ given (Table 2).

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