Comparison of oral and intravenous magnesium repletion in patients with hypomagnesemia: A randomized controlled trial Study Protocol

Contents

Background

Although magnesium is an often-overlooked trace element, it is involved in numerous biochemical reactions of clinical significance. Its deficiency has been associated with a number of chronic diseases, including diabetes, hypertension and coronary artery disease, as well as acute disorders, such as cardiac arrhythmias and myocardial infarction [1-6]. Normal values are approximately 0.7–1 mmol/L (1.5–2 mEq/L; 1.7–2.4 mg/dL), though laboratory-specific variation exists [7,8]. The prevalence of magnesium deficiency ranges from 2.5-15% in the general population [9,10], to 6-11% in the inpatient population [11], to 65% in the intensive care unit [12]. Multiple methods have been used to identify magnesium deficiency, but the most common are serum magnesium and the magnesium loading test, in which intravenous magnesium is administered and urine subsequently collected to calculate the percentage of magnesium excreted.

This study aims to investigate the cost and efficacy of magnesium repletion in hospitalized patients at RCRMC with mild to moderate hypomagnesemia (1.2-1.7 mg/dL). Presently, correction of asymptomatic, moderate hypomagnesemia is accomplished with either oral magnesium (typically magnesium oxide) or an intravenous formulation (magnesium sulfate), the selection determined by clinician experience. Although there is a significant cost difference between the two routes, and the superiority of intravenous to oral supplementation in such circumstances has not been proven [13], no major study has ever compared them in general inpatients.

Two historical studies warrant mention. The first is a 1991 investigation by Gullestad et al. in which the magnesium loading test was used to demonstrate that a 6-week regimen of oral magnesium-lactate-citrate was equivalent to a 7-day regimen of intravenous magnesium sulfate [14]. However, the cohorts compared were not matched for comorbidities known to predispose to magnesium deficiency, creating a major confounding variable. The second study is a retrospective case review comparing oral magnesium oxide to intravenous magnesium sulfate in raising serum magnesium in cardiovascular care unit patients [15]. While it had the advantage of a fairly large sample size and propensity matching by stratifying the patients by initial serum magnesium levels, the patient population was not representative of general inpatients.

The benefit of this study will be the provision of information for evidence-based decision-making by hospitalists in the treatment of hypomagnesemia. Given that electrolyte disturbances are a common problem in the hospital setting, this study has significant clinical relevance.

References:

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Methods

Trial design

Randomized controlled trial. Three patients groups, divided evenly.

Participants

- Subject recruitment was achieved by contacting Medicine and Surgery teams at (Riverside County Regional Medical Center / Riverside University Medical Center; henceforth “RCRMC”). Each team was requested to agree to participate in the study. If a team agreed, it was stipulated that it would not initiate repletion of mild to moderate hypomagnesemia (defined below). Instead, the lab abnormality would be referred to the study investigators who would screen the potential subject against the study inclusion / exclusion criteria. If the criteria were met, the study investigators would consent the patient. If the patient agreed to be a subject in the study, the subject was considered enrolled and referred to the hospital pharmacist who initiate repletion based on after randomization. Randomization was based on 1-to-1 allocation of pre-numbered (1, 2, or 3) sheets of paper (120) concealed in envelopes specifying the group number.
- The magnesium study took place between July 2015 and September 2017 at RCRMC.
- Inclusion criteria: age over 18 years, serum magnesium 1.2-1.7 mg / dL
- Exclusion criteria:
    - Proton pump inhibitor (PPI) administration within 24 hours of initial serum magnesium level

    - Diuretic use,
    - Decompensated heart failure,
    - Acute or chronic kidney disease,
    - Active myocardial infarction,
    - Eclampsia, preeclampsia
    - Pregnancy
    - Incarceration
    - Inability to tolerate oral intake
    - History of bowel surgery,
    - Active inflammatory bowel disease/diarrhea
    - Chemotherapy
    - Severe sepsis
    - Prior enrollment in this study

- Institutional Review Board approval will be obtained.
- Written informed consent was obtained from each subject. (See consent form for details.) Benefits: no individual benefits and benefits to society of determining most efficacious and cost-effective methods of treating moderate hypomagnesemia. Risk is minimal, with potential for diarrhea with oral repletion and infusion site reactions with intravenous repletion.
- Confidentiality: Date collected will include medical record numbers, gender, age, any significant comorbidities, and the admission diagnosis. Prior to data analysis, the data will be de-identified by removing the medical record numbers and replacing them with subject numbers (there will be no relationship between the medical record numbers and the study numbers). The data will be stored on a secure computer drive that will be password protected. In addition, both the computer drive and any paper documents will be stored in a locked desk in the locked office of Dr Ali Motabar. The data will not be transmitted via unsecure modalities such as email, unless it has been completely de-identified.

Interventions

Group 1: magnesium oxide (MgOx) 400 mg PO x 5 [1200mg, then 800mg 4 hours later, for total of 2000mg PO] (with measurement of serum Mg at 24 hours)
Group 2: magnesium sulfate (MgSO4) 2 g IV infused over 2 hours with measurement of serum Mg 24 hours
Group 3: magnesium sulfate (MgSO4) 2 g IV infused over 6 hours with measurement of serum Mg 24 hours.

Stool softeners and motility agents, such as docusate and Senna will not be administered to patients enrolled in the study.

Outcomes

The primary outcome will be the serum magnesium level at the above-mentioned time periods. The pre- and post-intervention serum magnesium levels for each subject will be compared using paired t tests, and inter-group analysis will be performed using Wilcoxon [?] signed rank tests. Secondary outcomes [potential]: need for repeat administration of magnesium, side effects, and safety endpoints (adverse events) as below.

Sample Size

Sample size was calculated based on the following paired t test formula:

The estimated sample size n was calculated as the solution of:

$$n = \frac{(t_{n-1,\alpha/2} + t_{n-1,\beta})^2}{d^2}$$

- where d = delta/sd, a = alpha = 0.05, b = 1 – power = 0.8 and tv,p is a Student t quantile with v degrees of freedom and probability p. n was rounded up to the closest integer.

Randomization

Subjects who met inclusion / exclusion criteria will be randomized using random number generated cards that will be concealed in envelopes. They will be numbered 1, 2, 3, in concordance with the group allocation. Pharmacists participating in the study will be provided with the numbers in sealed envelopes which will be opened at the time of patient enrollment. Prior to each repletion the ordering pharmacist will open an envelope designated the group allocation of that particular patient. After placing the repletion orders, an order for serum magnesium will be placed for a lab check 24 hours after initiation of repletion.

Sequence Generation

We used blocked randomization to form the allocation list for the three comparison groups. We used a computer random number generator to select random permuted blocks with a block size of ten and an equal allocation ratio.

Allocation Concealment

The above mentioned numbers will be concealed in envelopes until the time of randomization.

Implementation

We the research team generated the random allocation sequence; the enrollment of the participants was made every patient that matched the inclusion criteria and also were

hospitalized during the time frame described above. The assignment of participants to each intervention was randomized according to our sequence generation.

Blinding

All patients both included/excluded and those in the control group were blinded. The care providers were blinded at time of randomization regarding route and dosage used to treat hypomagnesemia.

Statistical Methods

We are planning a study of a continuous response variable from matched pairs of study subjects. Prior data indicate that the difference in the response of matched pairs is normally distributed with standard deviation 0.25. If the true difference in the mean response of matched pairs is 0.12, we will need to study 36 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Therefore, we will enroll 40 patients in each group (accounting for 10% drop out of patients). Intergroup comparisons will be performed using Analysis of Variance (ANOVA). This means there will be 120 patients total.

Results

Participant Flow

A report of the participant flow was generated from the CONSORT (Consolidated Standards of Reporting Trials) flow diagrams guidelines.

Recruitment

Follow-up will conclude 48 hours after administration of magnesium.

Baseline Data

The following demographic information will be recorded for each patient: sex, age, race. The following clinical information will be recorded for each patient: past medical and surgical history, pre-hospital and in-hospital medication regimen, admitting diagnosis, use of histamine 2 antagonists, use of stool softeners / bowel motility agents / laxatives, time of magnesium administration and times of magnesium measurement.

Numbers analyzed

Intention to treat basis.

Outcomes and Estimations

Serum magnesium level was measured in 120 adults at time of enrollment and 24 hours +/- 6 hours (between 18 and 30 hours) after initiation of repletion.

Harms (Adverse Events)

The following potential adverse events will be recorded: diarrhea, infusion site reactions, hypermagnesemia. These will be treated in concordance with standards of care. Diarrhea will be treated with anti-diarrheal medications, as deemed appropriate by the primary team and/or ordering provider. Hypermagnesemia will be treated only if severe / symptomatic; this treatment will adhere to standards of care and may include calcium, diuretics, insulin+glucose, and hemodialysis.