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Impact of an Intravenous Magnesium Shortage on Potassium Doses in Adult Surgical Patients Receiving Parenteral Nutrition

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Abstract

Background: Shortages of parenteral nutrition (PN) components have been common in recent years. Effects on patient management and outcomes have not been well documented. This study aimed to determine the effect of a parenteral magnesium shortage, and an institutional decision to omit magnesium from adult PN, on magnesium and potassium doses and serum concentrations. *Materials and Methods:* This was a retrospective cohort study of adult surgical patients during two 6-month periods: prior to the magnesium shortage (2011) and during the shortage (2012). The relation between study period and electrolyte doses was evaluated by unadjusted and adjusted mixed models, while the relation between study period and hypokalemia and hypomagnesemia exposure was evaluated by Student's *t* tests and multiple linear regression. *Results:* During the shortage, patients received more supplemental magnesium (0.11–0.12 mEq/kg/d, $P < .0001$) but received less total daily magnesium (0.08–0.09 mEq/kg/d, $P < .0001$) and had greater exposure to hypomagnesemia (9.6–14.2 h·mcg/dL/h, $P < .05$ for all comparisons except multivariate analysis in a matched subpopulation). Patients received similar amounts of potassium in PN (0.06–0.08 mEq/kg/d less, $P < .05$ for full cohort but $P > .05$ for matched cohort), in supplemental doses (0.01–0.05 mEq/kg/d less, $P > .05$), and in total (0.07–0.14 mEq/kg/d less, $P > .05$), and they had similar exposure to hypokalemia. *Conclusion:* Daily magnesium doses were lower and hypomagnesemia exposure was greater during the shortage, but the differences were numerically small and their clinical significance was questionable. Potassium doses and hypokalemia exposure were not higher during the shortage. This supports the strategy of omitting magnesium from PN of select patients and supplementing as clinically necessary. (*JPEN J Parenter Enteral Nutr*. 2016;40:688-692)

Keywords

parenteral nutrition; parenteral formulas/compounding

Clinical Relevancy Statement

Drug shortages can affect the ability to optimize parenteral nutrition (PN) by forcing reduction or omission of certain components and/or increasing reliance on premixed solutions. However, clinical consequences of PN-related shortages and the institutional strategies implemented to minimize their impact are not well documented. This study found that the omission of magnesium sulfate from PN during a drug shortage resulted in slightly greater supplemental intravenous magnesium doses and hypomagnesemia but did not increase total daily potassium doses or hypokalemia. Further studies are needed to ascertain the best strategies for managing drug shortages related to PN.

Introduction

Shortages of parenteral nutrition (PN) components have become common in recent years, forcing providers to choose between reducing or omitting PN components, or substituting individualized PN admixtures with multichamber, standardized, commercially available PN solutions, also referred to as "premixed" PN.[1-3] Premixed PN may contain the component in short supply but may not have an optimal balance of other components.

A recent shortage of magnesium sulfate prompted the authors' institution to remove magnesium from PN admixtures for adults weighing >30 kg. Premixed PN solutions were not used during the shortage period. Rather, all PN admixtures

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were compounded individually, with contents managed by multidisciplinary care teams including physicians, mid-level providers (nurse practitioners and physician assistants), pharmacists, dieticians, and trainees, per normal institutional practice. Magnesium omission from PN admixtures was the sole systematic change in PN processes during this time. This strategy was thought to be viable only because of the ability to closely monitor patients receiving PN as well as the ability to give supplemental intravenous (IV) magnesium if indicated.

Omission of PN magnesium, if not adequately compensated, could have both direct and indirect clinical consequences. Hypomagnesemia may result if patients do not receive adequate supplemental magnesium. Further, because magnesium distributes slowly into the intracellular compartment and is excreted in urine following an IV dose of magnesium, magnesium supplemental requirements may not be exactly the same when given as a typically faster-infused supplemental dose (over 1–4 hours) compared with a PN dose administered over a longer period of time (over 12–24 hours).[4,5] It is unclear whether supplemental IV doses of magnesium are adequate to maintain normomagnesemia in PN-dependent patients when magnesium is omitted from PN admixtures.

Magnesium homeostasis is also closely related to potassium homeostasis. Hypomagnesemia and hypokalemia often occur together.[6,7] A deficiency in magnesium can lead to inhibition of Na-K-ATPase, which results in decreased uptake of potassium into cells.[8] This mechanism may contribute to the clinical findings that hypokalemia may be refractory to potassium supplementation without first repleting magnesium and that IV magnesium given in addition to potassium supplementation may improve potassium balance.[9-11]

Given the potentially serious clinical implications of hypokalemia, this study aimed primarily to assess any changes in potassium doses or hypokalemia during the parenteral magnesium shortage. We also assessed any changes in magnesium doses or hypomagnesemia during the same period.

Materials and Methods

Study Design

This was a retrospective, single-center cohort study at the University of Michigan Health System. Eligible patients were 18 years of age or older, were admitted to surgical hospital services, and received PN between January 1, 2011, and May 31, 2011, or between January 1, 2012, and May 31, 2012 (this latter period during the magnesium shortage). Patients weighing <30 kg were excluded because they would have been eligible to receive PN magnesium during the shortage. The study also excluded patients with a calculated creatinine clearance <40 mL/min at baseline (by Cockcroft-Gault equation, using a serum creatinine of 1 mg/dL for patients >65 years of age with measured serum creatinine <1 mg/dL) and those patients who received renal replacement therapy, received tube feeds at rates >20 mL/h, or received continuous infusion diuretics on any PN day. The study protocol was approved by a University of Michigan institutional review board.

Data Collection

Medical record data were collected for all patients including age, sex, weight, PN indication, baseline serum creatinine, daily PN potassium and magnesium, daily IV and oral supplemental potassium chloride, daily IV supplemental magnesium sulfate, daily oral supplemental magnesium oxide, serum potassium and magnesium concentrations on days PN was ordered, and any intermittent diuretic doses given on days PN was ordered. Indications for PN were categorized as obstruction (mechanical or pharmacological ileus, small bowel obstruction), intestinal defect (fistula, leak, discontinuity), or other (inability to tolerate enteral feeds, peritoneal adhesions, severe *Clostridium difficile*–associated diarrhea).

Outcomes

The primary endpoint was the total daily potassium dose. Secondary endpoints included the daily PN potassium dose, the daily supplemental (ie, not in PN) potassium dose, the total daily magnesium dose, the daily supplemental magnesium dose, and exposure to hypokalemia and hypomagnesemia. For exposure to hypomagnesemia and hypokalemia, areas under the curve (AUCs) corresponding to any periods of hypokalemia (serum potassium concentration <3.5 mM or <4.0 mM [both comparisons made]) or hypomagnesaemia (serum magnesium concentration <1.5 mg/dL) were calculated for each patient and normalized for total time of observation. These were calculated as AUC/Time = Sum(Amount Below Cutoff × Time Below Cutoff)/Total Observation Time.

Statistical Methods

The relation between data collection period and weight-adjusted electrolyte daily doses was assessed with linear multilevel mixed models fit by maximization of restricted log-likelihood. In the base (unadjusted) model, data collection period was included as a fixed effect whereas day of PN administration was included as a random effect grouped by subject to account for the expected correlation of multiple data points for an individual patient over time. In the adjusted model, demographic variables (age, sex, and weight) and baseline clinical variables (indication group, estimated creatinine clearance group [40–60 or > 60], and intermittent diuretic treatment) were included as additional fixed effects. AUC/time values were compared between study periods by Student's *t* tests. Multiple linear regression was used to compare AUC/time values between study periods controlling for the same demographic and clinical variables included in the adjusted mixed models.

All analyses were performed for the entire study population (full cohort) as well as for a matched subset (matched cohort). To determine inclusion in the matched cohort, patients were matched on the basis of sex, age (±3 years), weight (±5 kg), and PN indication.

All statistical comparisons were made using R (v 3.0.2, Vienna, Austria) and were interpreted relative to a prespecified significance level of .05. It was initially estimated that 75 patients per group would be needed to detect a clinically significant difference in total daily potassium dose (70 ± 40 mEq vs 100 ± 40 mEq,) using a 2-tailed repeated-measures analysis of variance with an α of 0.05, power of 0.85, within-subject variability of 0.9, and decay rate of 0.1.

Results

A total of 316 patients met the study criteria and were included in the analysis, including 166 during the nonshortage period and 150 during the shortage period. The matched cohort included 52 patients from each group. Baseline demographic and clinical characteristics were similar between groups (Table 1). The most common indication for PN was obstruction, and most patients had a creatinine clearance >60 mL/min.

Electrolyte dosing is summarized in Tables 2 and 3. In the shortage and nonshortage periods, average serum potassium concentrations were 4.1 mM (range, 2.7–6.0 mM) and 4.1 mM (range, 3.0–5.8 mM), respectively; average serum magnesium concentrations were 1.8 mg/dL (range, 1.0–5.4 mg/dL) and 2.0 mg/dL (range, 1.3–3.4 mg/dL), respectively; serum potassium concentrations were <3.5 mM in 5% and 6% of samples, respectively; serum potassium concentrations were <4.0 mM in 39% and 38% of samples, respectively; and serum magnesium concentrations were <1.5 mg/dL in 9% and 1% of samples, respectively. In the unadjusted mixed models, patients in the full cohort received less PN potassium (0.08 mEq/kg/d less, $P < .05$), more supplemental magnesium (0.12 mEq/kg/d more, $P < .0001$), and less total daily magnesium (0.09 mEq/kg/d less, $P < .001$) during the magnesium shortage period. Other variables were similar between study periods.

As shown in Table 4, hypokalemia exposure was similar during the shortage and nonshortage periods, while hypomagnesemia was more common during the shortage (9.6–14.2 h·mcg/dL/h, $P < .05$ for all comparisons except matched cohort multivariate analysis).

Findings were generally very similar between the matched and full cohorts and between analyses controlling for and not controlling for demographic and clinical variables.

Table 1. Characteristics of Study Sample.[a]

Characteristic	Magnesium in PN	No Magnesium in PN
No. of patients		
Full cohort	166	150
Matched cohort	52	52
Age, y		
Full cohort	56 ± 16	60 ± 14[b]
Matched cohort	59 ± 14	59 ± 14
Female sex		
Full cohort	74 (45)	67 (45)
Matched cohort	20 (38)	20 (38)[c]
Weight, kg		
Full cohort	79 ± 21	81 ± 22
Matched cohort	78 ± 17	77 ± 17[c]
Height, cm		
Full cohort	169 ± 17	170 ± 17
Matched cohort	172 ± 9	172 ± 10
Creatinine clearance 40–60 mL/min		
Full cohort	32 (19)	40 (27)
Matched cohort	12 (23)	11 (21)
PN days (total)		
Full cohort	1113	1133
Matched cohort	392	434
PN days per patient		
Full cohort	7 ± 7	8 ± 9
Matched cohort	8 ± 10	8 ± 7
Intermittent diuretics		
Full cohort	17 (10)	11 (7)
Matched cohort	6 (12)	2 (4)[c]
Diagnosis		
Obstruction		
Full cohort	78 (47)	83 (55)
Matched cohort	31 (60)	31 (60)
Defect		
Full cohort	41 (25)	29 (19)
Matched cohort	9 (17)	9 (17)
Other		
Full cohort	47 (28)	38 (25)
Matched cohort	12 (23)	12 (23)

[a]Data other than patient and parenteral nutrition (PN) day counts are presented as frequency (%) or mean ± standard deviation.
[b]$P < .05$.
[c]Statistical test not performed for matched cohort.

Discussion

In this study, removal of magnesium sulfate from PN due to a shortage was associated with an increase in supplemental magnesium doses but lower total daily IV magnesium and greater hypomagnesemia exposure, both in base analyses and in analyses controlling for age, sex, weight, creatinine clearance, and use of intermittent diuretics. Potassium doses and hypokalemia exposure were similar during the shortage and nonshortage periods.

Although daily magnesium doses were lower during the magnesium shortage, patients received a total of around 6–7 mEq/72 kg/d less. While some studies have suggested that low dietary magnesium or hypomagnesemia correlate with cardiac arrhythmias, there are not clear intake levels or serum magnesium levels that correspond to risk for arrhythmias or other

Table 2. Electrolyte-Related Variables in the Full Cohort.

Variable	Nonshortage	Shortage
Potassium, mEq/d		
PN	62	58
Supplemental	11	10
Total	72	68
Magnesium, mEq/d		
PN	18	0
Supplemental	6	19
Total	24	19
Hypokalemia AUC, h·μM/h		
3.5-mM cutoff	12	17
4.0-mM cutoff	152	149
Hypomagnesemia AUC, h·mcg/dL/h	3	13

AUC, area under the curve; PN, parenteral nutrition.

Table 3. Effect of Magnesium Shortage on Magnesium and Potassium Doses.[a]

	Unadjusted		Adjusted	
Electrolyte Dose	Per kg	Per 72 kg	Per kg	Per 72 kg
Potassium (PN; mEq/d)				
Full cohort	–0.08	–5.6[b]	–0.06	–4.7[b]
Matched cohort	–0.07	–5.1	–0.08	–5.6
Potassium (supplemental; mEq/d)				
Full cohort	–0.01	–0.5	–0.01	–0.5
Matched cohort	–0.04	–2.7	–0.05	–3.9
Potassium (total; mEq/d)				
Full cohort	–0.08	–6.0	–0.07	–5.1
Matched cohort	–0.13	–9.1	–0.14	–9.8
Magnesium (supplemental; mEq/d)				
Full cohort	0.12	8.5[c]	0.12	8.5[c]
Matched cohort	0.11	8.1[c]	0.11	7.8[c]
Magnesium (total; mEq/d)				
Full cohort	–0.09	–6.4[c]	–0.08	–5.9[c]
Matched cohort	–0.09	–6.3[b]	–0.09	–6.7[c]

[a]Data collection period included as a fixed effect, while day of parenteral nutrition (PN) administration included as a random effect grouped by subject in both models. Adjusted models also included age, sex, weight, indication group, estimated creatinine clearance group (40–60 or >60 mL/min), and intermittent diuretic treatment as fixed effects.
[b]$P < .05$.
[c]$P < .001$.

Table 4. Effect of Magnesium Shortage on Hypokalemia and Hypomagnesemia Exposure.[a]

Electrolyte Abnormality	Univariate Analysis, ΔAUC	Multivariate Analysis, ΔAUC
Hypokalemia (3.5-mM cutoff)		
Full cohort	5.1	3.1
Matched cohort	2.3	2.2
Hypokalemia (4.0-mM cutoff)		
Full cohort	–2.8	–12.3
Matched cohort	–37.0	–36.2
Hypomagnesemia		
Full cohort	10.3[b]	9.6[b]
Matched cohort	14.2[b]	12.3 ($P = .054$)

[a]Multivariate analysis included age, sex, weight, indication group, estimated creatinine clearance group (40–60 or >60 mL/min), and intermittent diuretic treatment as covariates. ΔAUC (change in area under the curve) represents the difference in exposure for the no-magnesium group compared with the magnesium group. Units are h·μM/h for potassium comparisons and h·mcg/dL/h for magnesium comparisons.
[b]$P < .05$; Student's *t* test (univariate) and multiple linear regression (multivariate) results presented.

adverse effects.[12,13] Due to the limitations of retrospective chart review, data regarding the incidence of arrhythmias were not collected. In this way, the clinical impact of the difference in daily magnesium doses seen in this study is unclear. The differences in hypomagnesemia exposure between study periods were also considered statistically significant but were numerically small and of questionable clinical importance. While it is possible that a subgroup of patients required higher potassium doses or experienced more hypokalemia during the magnesium shortage than they would have receiving PN magnesium, these effects were not seen in the broader population. Because of the relatively mild exposure to hypomagnesemia in the study population, conclusions cannot be drawn regarding hypokalemia or need for higher potassium doses in patients experiencing more severe hypomagnesemia.

Total daily potassium doses in both the nonshortage and shortage groups were lower than expected, around 60 mEq/d. This corresponds to a dose <1 mEq/kg/d, which is below the typical range for daily adult potassium requirements.[14] While patients with renal dysfunction have lower potassium requirements, patients with estimated baseline creatinine clearance <40 mL/min were excluded from this study. The patients in this study instead commonly had high output fistulas and other conditions leading to significant fluid losses, and many received diuretics, all factors likely to increase potassium requirements. Despite the seemingly low total daily doses of potassium, patients in general did not have low serum potassium concentrations.

In this study, an institutional decision to omit magnesium from PN in response to a shortage was not associated with any apparent clinically significant changes in potassium or magnesium doses or requirements. Of particular concern initially was the potential for increases in IV potassium supplementation or hypokalemia, given the close interrelation of potassium and magnesium homeostasis. If another IV magnesium shortage were to occur, these data support the decision to remove magnesium and supplement as needed, without other systematic changes to patient management, in certain adult patients at this institution.

Several limitations of this study should be noted. First, it was a retrospective study subject to several inherent design limitations,

particularly the potential for patient selection bias. While attempts were made to control for relevant clinical variables and to confirm findings in both full and matched cohorts, these strategies give no guarantee of perfect comparability between the two study populations. Second, while the study site has guidelines for electrolyte replacement in the intensive care setting, electrolyte goals and management strategies are expected to vary by provider and patient. Providers may target a serum potassium concentration of 4 mmol/L and a magnesium concentration of 2 mg/dL in some surgical patients, but these goals are not used for every patient and are subject to change. Furthermore, a patient's goal may change depending upon his or her clinical course. While patients in this study were very similar in terms of renal function and diagnosis, and these factors were included in multivariate analyses, it is possible that patient- and provider-specific differences affected doses, monitoring, or both in some way that could have influenced results. The fact that serum concentrations of magnesium were used in this study is also a limitation, as serum concentrations may not be an accurate reflection of total body magnesium. Third, while data on all IV and oral potassium and magnesium doses were accounted for in analyses, patients may have received some limited enteral potassium and magnesium through tube feeds or oral diets. While the exclusion of patients receiving tube feeds given at a rate of >20 mL/h aimed to minimize the potential contribution of tube feeds to total daily potassium and magnesium doses, this is nonetheless a potential source that was not accounted for in analysis. Next, our institution's PN is compounded at an outside facility. Because of this, data could not be collected regarding the amount of IV magnesium that was wasted as a result of the decision to omit from PN for adults >30 kg. Given the centralized nature of compounding, however, there is anticipated to be minimal impact on magnesium waste during the shortage period. Finally, although some recent studies examining the impact of drug shortages in PN have reported cost data, no such data were included in this analysis.[15,16] While costs clearly pose an institutional concern whenever strategies need to be implemented in response to a shortage, the primary aim of this study was to assess the impact of the implemented strategy on clinical care rather than on institutional costs. The results suggest that the main difference in resource use during the IV magnesium shortage was an increase in IV magnesium sulfate supplementation, but additional costs could potentially be identified through further studies.

In conclusion, this study adds to a limited collection of evidence on the clinical impact of PN-related shortages. It also describes a strategy for management of an IV magnesium shortage that minimized the impact on nonmagnesium PN components and was not associated with any clear, clinically significant changes in patient management. With product shortages likely to be an ongoing challenge, it will be increasingly important to document the downstream effects of shortages and any effective strategies that minimize the impact on patient care and resource utilization.

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Statement of Authorship

M. R. Pleva, M. D. Kraft, and M. P. Dorsch contributed to the conception and design of the research; L. A. Scherkenbach, S. M. Stout, X. Chen, and H.-D. Tran contributed to the design of the research. All authors contributed to the acquisition, analysis, or interpretation of the data; L. A. Scherkenbach drafted the manuscript; and all authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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