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Research Article

Magnesium and Muscle Cramps in End Stage Renal Disease Patients on Chronic Hemodialysis

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We evaluated the frequency and severity of muscle cramps, and the effect of dialysate magnesium on muscle cramps in 62 stable ESRD patients on chronic hemodialysis. Each subject was surveyed twice within a 6-month period. A single nephrology fellow conducted all in-person surveys. During the first survey, the patients were dialyzed with dialysate magnesium of 0.75 meq/L (0.375 mmol/L). Prior to the second survey, the dialysate magnesium was increased to 1.0 meq/L (0.50 mmol/L). The severity of cramps was scored on a 1–10 scale, with 10 indicating maximal severity. The number of patients with muscle cramps was significantly lower with dialysate magnesium of 1.0 meq/L (0.50 mmol/L) (56% versus 77%, $P = 0.02$). No significant difference was observed in interdialytic weight gain, intradialytic ultrafiltration, dry weight, or intradialytic hypotension. The mean ± SD severity score of muscle cramps decreased from 5.34 ± 3.61 to 3.89 ± 3.94 ($P = 0.003$). Seven of 31 (23%) patients in the group with low dialysate magnesium while 0/20 (0%) patients receiving high magnesium dialysate terminated hemodialysis early due to cramps ($P = 0.02$). Both the number of patients reporting muscle cramps and the severity score decreased with higher dialysate magnesium which contributed to better adherence to hemodialysis treatments.

1. Introduction

Painful muscle cramps, usually in the lower extremities are common in patients receiving chronic hemodialysis (HD) [1]. These cramps frequently occur toward the end of the dialysis sessions, sometimes precede hypotension, and are associated with higher fluid removal during HD [1]. Recurrent muscle cramps frequently lead to noncompliance with the prescribed HD treatment [2] and impact patients' quality of life [3]. Varying the magnesium (MG) concentration to a low or no MG containing dialysate has been shown to increase the incidence of muscle cramps [4]. Intravenous MG given during an episode of severe muscle cramping while on HD was shown to ameliorate the symptom [5]. Previous therapies including quinine, vitamins C and E [6], L-carnitine [4], MG [7–9], and the use of sequential compression devices [10] have been investigated to ameliorate the frequency and intensity of muscle cramps with mixed efficacy. MG functions as a cofactor in the energy metabolism, nucleotide and protein synthesis, and as a regulator of sodium, potassium, and calcium channels [11]. Severe hypomagnesaemia can cause muscle cramps, tremors, tetany, and cardiac arrhythmia [11]. In patients on HD, the serum MG concentration parallels the dialysate MG level. MG readily crosses the dialysis membrane with its movement determined by the gradient between the concentration of diffusible MG in the blood and the level of MG in the dialysate [12]. We hypothesized that a change in dialysate MG concentrations will alter the frequency and severity of muscle cramps in HD patients. This is the first study comparing low and high dialysate MG concentration on the frequency and severity of muscle cramps in stable ESRD patients receiving HD treatments.

2. Materials and Methods

2.1. Participants. The initial survey was performed at a single outpatient dialysis center to evaluate frequency and severity of muscle cramps in stable end stage renal disease (ESRD) patients receiving maintenance HD for more than 3 months. At that time, the patients were receiving HD

with a dialysate containing MG concentration of 0.75 meq/L (0.375 mmol/L). Two months after the completion of the survey, the dialysis center changed the dialysate concentrate because of nonavailability from the vendor. The new dialysate concentrate provided the dialysate MG concentration of 1.0 meq/L (0.5 mmol/L). The rest of the constituents in the dialysate remained the same and the patients were not aware of the change. We used this opportunity to evaluate the effect of dialysate MG on the frequency and severity of muscle cramps. We repeated the same survey among the stable ESRD patients receiving HD with the new dialysate containing MG of 1.0 meq/L (0.5 mmol/L). Each survey consisted of an in-person questionnaire that was conducted by the same nephrology fellow. The study was approved by the Stony Brook University IRB and was administratively approved by Dialysis Clinic Inc. (DCI). Informed written consent was obtained from each patient prior to their participation in the survey.

2.2. Materials. We developed a questionnaire to evaluate patient's perception of frequency, severity, quality, and the impact that muscle cramps had on their prescribed treatment. The questionnaire was administered by the same nephrology fellow at the in-center hemodialysis unit. The severity of the cramps was scored on a 1–10 scale with the rating of 1 reflecting least severity of cramps and 10 reflecting cramps of the maximal severity. All patients that participated in the survey received thrice weekly maintenance HD on the respective dialysate MG concentration for a minimum period of three months.

2.3. Clinical Demographics and Measurements. Data on patient's age, gender, and race, etiology of ESRD, and initiation date of chronic HD were obtained from the DCI dialysis center database. Routine monthly dialysis lab data were used to compare electrolytes and HD adequacy. Blood pressure (BP) measurements, interdialytic weight gain, intradialytic ultrafiltration (UF), and dry weight were obtained from three consecutive dialysis sessions with each dialysate magnesium concentration at the time of the surveys. Mean values of the BP measurements were taken for analysis. To identify patients with intradialytic hypotension (IDH), we utilized KDOQI guideline which defines IDH as a decrease in systolic blood pressure (SBP) by ≥20 mmHg or a decrease in mean arterial blood pressure (MAP) by 10 mmHg.

2.4. Statistical Analysis. Paired t-test for interval variables, and McNemar's test for dichotomous variables, was used to compare differences in the matched pairs. Pearson correlation was performed to assess the relationship between interval variables and logistic regression was performed to evaluate predictors of muscle cramps.

3. Results

The first survey enrolled 85 patients with a mean age of 59.8 ± 16.7 years. The second survey enrolled 79 patients with a mean age of 61.9 ± 15.4 years. A cohort of 62 patients with a mean age of 60.0 ± 15.9 years participated in both surveys and had laboratory data available for paired analysis. Demographic data are summarized in Table 1. The KT/V was 1.79 ± 0.68 during the first survey and 1.69 ± 0.31 during the second survey ($P = 0.25$). Similarly, pre-HD serum potassium, PTH, phosphorus, calcium, and albumin were not significantly different between both surveys. Interdialytic weight gain, intradialytic UF, dry weight, and dialysate temperature are summarized in Table 2. No significant difference was observed in interdialytic weight gain, intradialytic (UF), and dry weight during the two surveys. The MAP using dialysate magnesium concentration of 0.75 mEq/L was 95.3 ± 12.2 mmHg while the MAP using dialysate magnesium concentration of 1.00 mEq/L was 93.6 ± 12.5 mmHg. There was no statistically significant difference between the two groups ($P = 0.36$).

Forty-eight (77%) of the patients during the first survey and 35 (56%) during the second survey reported having muscle cramps within the previous month ($P = 0.02$). The cramp severity scores decreased significantly from a mean of 5.34 ± 3.6 in the first survey to 3.89 ± 3.9 ($P = 0.003$) during the second survey. Figure 1 showed the severity scores in an individual patient during the first and second surveys. Fifteen patients with muscle cramps during the first survey with a mean severity score of 6.2 ± 2.6 reported no cramps during the second survey. Ten of these 15 patients had an increase

Table 1: Demographics.

Demographics	Total	Survey 1 Cramps N (%)	Survey 2 Cramps N (%)	P value
	62	48 (77)	35 (56)	0.01
Gender				
Male	36	29 (81)	19 (53)	0.01
Female	26	19 (73)	16 (62)	0.10
ESRD cause				
Diabetes mellitus	26	21 (81)	14 (54)	0.03
Hypertension	10	7 (70)	3 (30)	0.07
Glomerular nephritis	7	6 (86)	5 (71)	0.51
Race				
White	23	14 (61)	9 (39)	0.14
Black	19	16 (84)	15 (47)	0.67
Hispanic	13	12 (92)	7 (54)	0.02

Table 2: Factors affecting hemodynamic stability during HD.

Variable	MG 0.75 mEq/L	MG 1.00 mEq/L	P value
Interdialytic weight gain (Kg)	2.8 ± 1.03	2.6 ± 1.15	NS
Intradialytic UF (Kg)	2.99 ± 0.91	2.92 ± 0.97	NS
Dialysate temperature (Centigrade)	36.74 ± 0.37	36.72 ± 0.39	NS
Dry weight (Kg)	77 ± 21.0	76 ± 20.1	NS

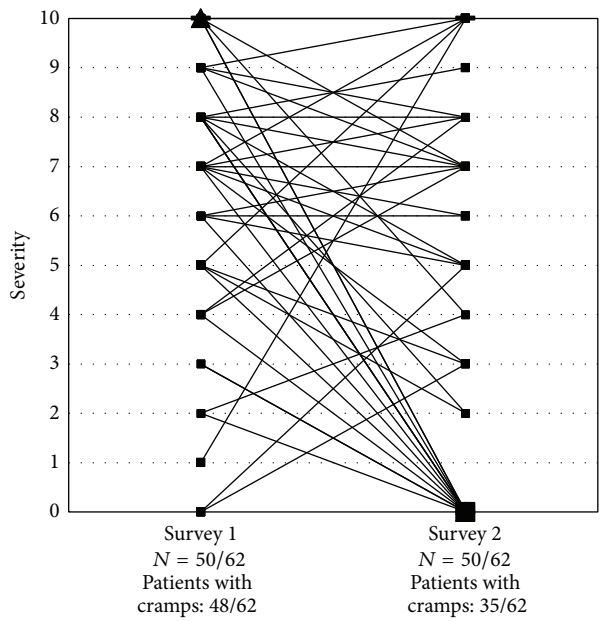

Figure 1: Muscle cramp severity in the 50 patients that had cramps during either survey.

in the serum MG level and 4 had the same serum MG level. The mean serum MG level in these 15 patients increased from 1.9 ± 0.39 to 2.1 ± 0.32 mg/dL. However, 2 patients that did not report muscle cramps during the first survey subsequently reported muscle cramps during the second survey with a severity score of 3 and 5. Both had an increase in serum MG level from 1.7 to 2.2 mg/dL and 1.5 to 2.5 mg/dL.

The predialysis serum MG levels were influenced by the dialysate MG concentration with an increase from a mean of 1.88 ± 0.29 to 2.16 ± 0.31 mg/dL ($P < 0.001$). There was a significant decrease in the number of patients with hypomagnesemia (serum MG < 1.6 mg/dL) from 9 during the first survey to 1 during the second survey ($P = 0.008$). Two patients developed asymptomatic hypermagnesemia (serum MG > 2.6 mg/dL) with serum MG concentration of 2.7 and 3.0 mg/dL, respectively. However, predialysis serum MG level was not a significant predictor for muscle cramps in either survey.

Forty-three of 48 (90%) patients with muscle cramps in the first survey and all 35 patients with cramps in the second survey reported that muscle cramps occurred on their HD days. During the first survey, 21/31 (68%) of patients with muscle cramps during the hemodialysis treatment requested that fluid removal be decreased. During the second survey, 18/20 (90%) of patients with muscle cramps during their treatment session requested fluid removal to be decreased. Seven of 31 (23%) patients with cramps in the first survey terminated HD treatment early while none of 20 in the second survey terminated HD early ($P = 0.02$). The reason for termination of HD treatment was due to cramps. Sixteen (33%) patients during the first survey and 11 (31%) during the second survey reported having cramps to their nephrologist. Surprisingly, 12 (25%) patients during the first survey and 8 (23%) during the second survey did not tell any healthcare provider about their cramps.

4. Discussion

We found that muscle cramps are common among patients undergoing chronic HD and interfere with the delivery of the HD treatment. Our two surveys of HD patients revealed that 77% of the patients during the first survey and 56% during the second survey reported having muscle cramps within the previous month. In fact, our results are consistent with a recent survey of 623 HD patients that found 74.3% of the patients reported having muscle cramps [13]. Despite the high prevalence of muscle cramps in our surveys, only 31–33% of the patients with muscle cramps reported this to their nephrologist. Surprisingly 23–25% of the patients with cramps during both surveys did not inform any healthcare provider in the HD unit.

MG deficiency has been reported to be linked with muscle cramps and contributes to the morbidity related to muscle cramps [14]. Hypomagnesaemia in HD patients has been significantly associated with an increased risk of mortality [15]. Kelber et al. reported that 8/15 (53%) patients developed muscle cramps during HD treatment with MG-free dialysate. In all patients, muscle cramps completely resolved after changing to a dialysate with MG of 1.5 meq/L (0.75 mmol/L) [4]. In our study among patients receiving chronic HD, the number of patients with muscle cramps was significantly higher while receiving HD with a lower dialysate MG of 0.75 meq/L (0.375 mmol/L) in comparison to a higher dialysate MG of 1.0 meq/L (0.5 mmol/L). Seventy-seven percent of patients had cramps with the lower MG dialysate while 56% of patients had cramps with the higher dialysate MG concentration. A significant decrease was observed in male gender from 81% to 53% ($P = 0.01$), in patients with diabetic nephropathy as the cause of ESRD from 81% to 54% ($P = 0.03$) and in Hispanics from 92% to 54% ($P = 0.02$). Similarly, the severity score was significantly greater when patients received HD with the lower dialysate MG.

MG stabilizes neuromuscular excitation and skeletal metabolism, and optimization of MG ameliorates muscle cramps [16]. MG supplementation has been used in muscle cramps during pregnancy and nocturnal leg cramps [7, 8]. The utilization of MG containing phosphate binders is an alternative method of achieving an increase in the predialysis serum MG level [17]. However, this study did not address the effect of increased serum MG levels on muscle cramps in HD patients [17]. Triger and Joekes reported a case with severe muscle cramps related to acute hypomagnesaemia during HD. Muscle cramps improved when treated with an intravenous infusion of 4 meq of MG in the form of 10% MG sulphate [5]. Subsequent change to a dialysate with MG of 1.5 meq/L (0.75 mmol/L) in the same patient resulted in a complete resolution of muscle cramps [5]. Kelber et al. similarly described a complete resolution of muscle cramps during HD in 8 (53%) of 15 patients after changing zero MG dialysate to dialysate MG of 1.5 meq/L (0.75 mmol/L) [4]. In this study, muscle cramps resulted

in these patients independent of intradialytic hypotension or fluid removal [4]. Similarly, we found no difference in intradialytic hypotension or UF. In the present study, both the number of patients and the severity score of muscle cramps decreased significantly in ESRD patients receiving HD treatment with the higher dialysate MG concentrations. Both serum and erythrocytes MG has been shown to be elevated with a dialysate MG concentration of 1.5 meq/L (0.75 mmol/L) while only erythrocytes potassium remained higher than normal with both 1.5 meq/L (0.75 mmol/L) and <0.2 meq/L (<0.1 mmol/L) dialysate concentration [18]. However, Stewart and Fleming reported normal skeletal muscle and lymphocyte MG levels with either 1.5 meq/L (0.75 mmol/L) or 0.4 meq/L (0.2 mmol/L) dialysate concentrations in 12 HD patients [19]. It is believed that a sudden decrease in serum MG during HD may result in intracellular shifts of MG to extracellular compartment [20] which may be responsible for muscle cramps when patients are receiving HD with a low MG dialysate. The higher dialysate MG concentration may decrease acute MG outward flux from blood to dialysate, thereby keeping intracellular MG and potassium optimal. This in turn may prevent or decrease the intensity of muscle cramps.

Muscle cramps associated with HD can be debilitating and often affect the patient's compliance with the HD treatment. In the first and second survey, respectively, 68% and 90% of the patients with cramps during the HD session refused to comply with the prescribe rate and amount of fluid removal. Previous studies have reported that 17.9% of patients had early sign-offs of HD treatment because of muscle cramps [2]. In Kelber et al.'s study, 2 of 8 (25%) patients with muscle cramps during HD with MG-free dialysate refused to continue participation in the study due to severe muscle cramps [4]. In our study, 7 of 31 (23%) patients that had cramps during HD treatment in the first survey and none in the second survey terminated their treatment early. We believe that this decrease in early sign-offs was probably related to a decrease in the severity of muscle cramps.

The strengths of our study include the following: we have paired data within a 6-month period before and after the change in dialysate MG concentration and the questionnaire was administered by the same physician who was able to clarify questions and keep responses consistent. We recognize a number of limitations to our study including the following: a validated visual analog scale was not used to score the severity of muscle cramps and the survey used needs to be validated in future studies, the study is subject to recall bias, and the study was not intentionally designed to evaluate the effect of dialysate MG concentration on muscle cramps or serum MG level. Instead we took advantage of the change in dialysate magnesium concentration to study the relationship between magnesium and muscle cramps.

In conclusion, muscle cramps in stable ESRD patient on HD are very common and lead to nonadherence to HD treatment. The number of patients and severity of muscle cramps both decreased while the predialysis serum magnesium levels increased when dialyzed with a higher dialysate MG concentration. This may have contributed to better compliance with HD treatments. Further studies are needed to evaluate the efficacy and safety of higher dialysate MG concentrations in ESRD patients on HD with muscle cramps.

5. Questionnaire

We are conducting a survey of our patients with end stage renal disease that are receiving chronic renal replacement therapy. We are attempting to determine the frequency of muscle cramps in this population and to understand what our patients do when they have muscle cramps.

Participation in this survey is voluntary and will not affect your treatment

(1) Do you get muscle cramps?

(a) Yes
(b) No

(2) When did you last get a muscle cramp?

(a) Within the last day
(b) Within the last week
(c) Within the last two weeks
(d) Within the last month
(e) Greater than a month ago

(3) How often do you get muscle cramps?

(a) Greater than 5 times a day
(b) Twice a day
(c) Daily
(d) Every other day
(e) Twice a week
(f) Once a week
(g) Twice a month
(h) Once a month
(i) Less than once a month

(4) What time of day do you get muscle cramps?

(a) Morning
(b) Afternoon
(c) Evening
(d) Night

(5) Which days do you get muscle cramps?

(a) Dialysis days
(b) Non-Dialysis days
(c) Both

(6) When you get cramps on your dialysis day, when do they occur?

(a) Before dialysis
(b) During dialysis

(c) After dialysis
(d) Not applicable

(7) How severe are the muscle cramps?

(a) Scale 1–10. . .

(8) Where do you get muscle cramps?

(a) Leg
(b) Arm
(c) Chest
(d) Abdomen
(e) Neck
(f) Head
(g) Back
(h) Shoulder

(9) Which health care providers have you discussed your muscle cramps with?

(a) Nephrologist
(b) Primary care provider
(c) Nurse
(d) Social Worker
(e) Dietician
(f) Family
(g) Hemodialysis Technician
(h) Have not discussed it with a health care provider

(10) What do you do when you get muscle cramps?

(a) Decrease fluid removal/Put fluid back
(b) Walk or move around
(c) Heating pad or hot compress
(d) Move the extremity or stretch
(e) Stand up
(f) Massage or squeeze the extremity
(g) Bring toes up
(h) Stay still
(i) Drink plenty of fluids
(j) Drink ice water
(k) Drink milk
(l) Stop Hemodialysis
(m) Do nothing
(n) Take Medication:

(i) Pain medication
(ii) Quinine
(iii) Requip
(iv) CoEnzyme q10
(v) Chicken Broth
(vi) Other: . . .

Conflict of Interests

None of the authors has any conflict of interests.

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