ARTICLE

Intradialytic massage for leg cramps among hemodialysis patients: A single-center, randomized crossover trial

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ABSTRACT

ackground: Leg cramps are commonly experienced by hemodialysis patients, and its persistence may lead to treatment noncompliance. Limited studies are available examining the efficacy of intradialytic massage on reducing leg cramps.

Objectives: To determine the efficacy of intradialytic leg massage on reducing leg cramps among patients undergoing maintenance hemodialysis at the East Avenue Medical Center.

Methodology: This is a single-center, randomized crossover trial. A total of 44 adult patients were randomized in a 1:1 ratio into two groups—Group A (intradialytic massage followed by control) and Group B (control followed by intradialytic massage). Each patient underwent the first assigned intervention for 2 weeks, followed by a washout period of 4 weeks, then the second intervention was performed for another 2 weeks. The primary outcomes were the change in frequency, duration, and intensity of cramps. The secondary outcome was patient quality of life.

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Results: A higher proportion of patients during the intervention period did not experience cramps post-intervention than during the control period; however, the results were not statistically significant (p=0.2059). The median change in frequency, duration, and intensity of leg cramps did not significantly differ between intervention and control (p>0.05). Moreover, quality of life measures were not significantly different between the two groups (p>0.05).

Conclusion: Intradialytic massage alone is not efficacious in reducing leg cramp frequency, duration, and intensity. Moreover, intradialytic massage failed to improve the quality of life of patients undergoing hemodialysis treatment. Underlying factors that lead to leg cramps should be addressed through comprehensive and individualized interventions.

INTRODUCTION

Chronic kidney disease (CKD) and hemodialysis (HD) therapy are tightly associated with extrarenal symptoms that heavily affect a patient's quality of life (QOL). Among these symptoms are restless leg syndrome, insomnia, sadness, anxiety, cramping, and exhaustion (Hung et al. 2009). Leg cramps are a common

KEYWORDS

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problem affecting 33 to 86% of HD patients during or after their sessions (Oguma et al. 2012). Leg cramps are characterized as an abrupt onset of severe, and protracted involuntary muscle spasm that may be felt or seen (Oguma et al. 2012). Cramps may be attributed to vasoconstriction and reduced oxygen delivery to muscle in the presence of hypotension, as well as osmotic and fluid alterations in muscle cells during HD (Ulu and Ahsen 2015).

Interdialytic muscular cramps may be caused by an accumulation of uremic solutes as well as a lack of various dietary components (Ulu and Ahsen 2015). When this becomes chronic, noncompliance may become a critical problem as they may lead to early hemodialysis termination, chronic fluid overload, hypertension, and cardiovascular disease (Hung et al. 2009). Also, cramps are highly uncomfortable, thus, impairing the functional status and QOL of HD patients (Hargrove et al. 2021).

Over the past ten years, the usage of massage in healthcare has increased. When done properly, massage has been found in research studies to reduce pain, enhance energy, reduce inflammation, and reduce feelings of worry in cancer patients (Yeh and Yeh 2007). To date, there is only one published study supporting its utility during HD. These preliminary studies stress that to be generalizable, the effects of interdialytic massage should be demonstrated in broader and more diverse populations with an evaluation of the skills of the therapists, optimal massage dosage, and an evaluation of the treatment duration, dialysis adequacy, morbidity, mortality, QOL, and healthcare costs (Mastnardo et al. 2016).

We aimed to determine the efficacy of intradialytic leg massage in reducing leg cramps among Filipino patients undergoing maintenance HD at East Avenue Medical Center (EAMC). As muscle cramps are a common occurrence among these patients, we hypothesized that intradialytic massage may help minimize patient symptoms (reduce frequency, duration, and intensity of cramps), improve their QOL, and enhance their compliance to HD therapy.

MATERIALS AND METHODS

We employed a single-center, open-label, randomized crossover trial. Patients were randomized in a 1:1 ratio into two groups— Group A (intradialytic massage followed by control) and Group B (control followed by intradialytic massage). Each patient underwent the first assigned intervention for two weeks, followed by a washout period of 4 weeks, then the second intervention was performed for another two weeks. Patient participation was up to 8 weeks from the time of recruitment. We performed the study at the EAMC HD Unit from June to August 2023 where there were approximately 74 patients on maintenance HD twice or thrice a week. Depending on the severity and duration of the cramps and on the patient's status, the ultrafiltration volume, ultrafiltration profile and dialysis temperature are adjusted by the fellow-on-duty in the dialysis unit.

Inclusion and exclusion criteria

Patients included in the study were those aged 19 to 60 years old, both private and service, who only underwent outpatient treatment and HD for at least 2 months and had at least 1 cramp episode in the past year during and/or after HD quantified severity. Ultrafiltration volume was allowed at 10 to 13 mL/kg/hour for at least 1 month. We excluded and/or withdrew patients with the following conditions:

• Admitted patients or initially eligible but hospitalized due to any cause during the course of the study

- History of deep vein thrombosis (DVT) or peripheral vascular disease (PVD) at any point in time
- Sensory deficits in lower extremity
- Open wounds, infections and fracture on lower extremities
- Vascular access in a lower extremity
- Fluctuating dry weight
- Refusal to participate or continue participation
- Mortality during the study period

The researcher sought approval from the EAMC Institutional Ethics Review Board before the conduct of the study. Privacy and confidentiality were kept at all times in accordance with the Data Privacy Act of 2012 and the National Ethical Guidelines for Research Involving Human Participants (NEGRIHP) 2022. Patient details were anonymized in the data collection forms using assigned unique study codes. Completed data collection forms were kept in a locked cabinet and all encoded data were stored in a password-protected computer and were only shared with the biostatistician for data analysis. All data will be discarded securely 5 years from study completion.

Convenience sampling was employed. PASS15 software was used to calculate the minimum sample size required. Parameters were based from a published study (Mastnardo et al. 2016). Specifying a 0.7 difference in the change in number of cramping episodes per week between the massage and control group, and alpha set at 0.05, a minimum of 35 patients were needed to achieve 80% power in detecting a significant difference. Sample size was increased to 44 to account for 20% potential dropout.

An independent researcher generated an allocation schedule. A list of patient numbers was randomly assigned in a 1:1 ratio into two groups—Group A and Group B—using sealedenvelope.com. Block randomization technique was employed with random block sizes of 2 and 4. The independent researcher prepared sequentially numbered sealed opaque envelopes containing the treatment allocation written in a piece of paper. The allocation schedule was concealed from other study investigators and patients until the end of the study. Patient blinding was not feasible due to the nature of control used.

The researcher explained the study objectives, procedures, risks, and benefits to each invited patient. Patients were encouraged to ask any question related to the study. To affirm voluntary participation, patients were asked to sign a written consent form. Patients assigned to Group A received the intradialytic massage intervention on top of the standard care for 2 weeks followed by control treatment for another 2 weeks. Group B underwent control treatment for another 2 weeks. There was a washout period for 4 weeks (Figure 1).

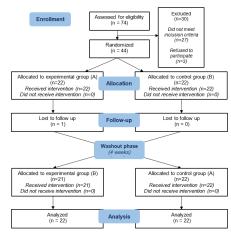


Figure 1: Flow diagram of the study

The massage protocol by Mastnardo et al was used as defined by their study's lead massage therapist based on the recognized physiological effects of manual therapy (Mastnardo et al. 2016). The intervention was provided by a duly licensed physical therapist. To further validate the technique, volunteer fellows were asked to evaluate the accuracy of the massage. Baby oil was used. The product contained no substances that were considered hazardous to health at their given concentration (Singh and Vinayadev 2021). Control treatment comprised standard care by the dialysis center staff. Cramps that occur during hemodialysis were assessed by the first-year fellow on duty and addressed by correcting any hypotension, stopping further fluid removal, stretching the affected muscle, and, if cramps continued, normal saline was used.

Outcomes were assessed at weeks 2 and 8. Each patient was asked about the frequency and intensity of leg cramp in the past week during and 24 hours post HD. Duration was patientmeasured during HD treatment and at home until 24 hours post HD using their own smartphone timer. A monitoring sheet was provided. Patients were also asked to answer the validated 36item Kidney Disease Quality of Life Short Form (KDQOL-SFTM) translated in Filipino for the assessment of their QOL (Bataclan and Dial 2009). Permission to use the tool was obtained from the author. The primary outcomes measured were the change in frequency, duration, and intensity of cramps. The secondary outcomes measured QOL and individual components of the KDQOL-SFTM questionnaire.

Data gathering and statistical analysis

The investigators obtained baseline data via face-to-face interview and these included QOL, and the frequency, duration, and intensity of cramps in the past 2 weeks. Other variables were obtained from the patient charts: age, sex, dry weight, average interdialytic weight gain, average blood pressure, body mass index (BMI), duration and frequency of dialysis. Baseline laboratory values were also collected, namely serum sodium, potassium, magnesium, calcium, phosphorus, blood urea

Table 1: Baseline patient characteristic: Group A vs. Group B (n=44)

nitrogen, creatinine, index of the removal efficiency per dialysis session (Kt/V), and urea reduction ratio.

Data were encoded in MS Excel and Stata MP version 17 software was used for data processing and analysis. Continuous variables were presented as mean (standard deviation/SD) and median/interquartile range (IQR) depending on the data distribution. Shapiro Wilk's test was used to assess normality of data. Categorical variables were presented as frequencies and percentages.

Continuous data were compared using the independent t-test and Mann Whitney U test, while categorical variables were compared using Chi square test and Fisher's exact test. The change in frequency, duration, and severity of leg cramps and the QOL were compared between intervention and control using Wilcoxon signed rank rest, while McNemar-Bowker were used to compare categorical variables. Period and carryover effects were examined by using the independent t-test and Mann Whitney U test. P values ≤ 0.05 were considered statistically significant. Both the intention-to-treat (ITT) and per-protocol (PP) analyses were analyzed. For ITT, missing data were imputed using the last observation carried forward approach.

Results and discussion

A total of 44 patients were included in the study. One patient from Group A dropped out from the study at week 1 due to hospitalization for pneumonia. No carryover or period effect was observed.

Table 1 compares the baseline characteristics between Group A (intradialytic massage followed by control) and Group B (control followed by intradialytic massage). All demographic, clinical and laboratory profiles were not significantly different between the two groups (p>0.05). For QOL, all scales were comparable between the two groups except for symptom/burden list, role-emotional, and mental component summary scales.

	GROUP A	GROUP B	p-value
	(n=22)	(n=22)	-
	n (%)	n (%)	
Age (in years), median	40	39	0.9954ª
	[IQR: 33-52]	[IQR: 29-55]	
Age category: ≥ 60 years old, %yes	3 (14)	5 (23)	0.698 ^b
Males, %yes	14 (64)	13 (59)	0.757°
Dry weight (in kg), mean	54.6 ± 13.1	54.0 ± 8.5	0.8553 ^d
Interdialytic weight gain (in kg), mean	1.7 ± 0.6	1.9 ± 0.6	0.2573 ^d
Systolic blood pressure (in mmHg), median	120	130	0.1232ª
	[IQR: 120-130]	[IQR: 120-130]	
Diastolic blood pressure (in mmHg), median	85	90	0.7087^{a}
	[IQR: 80-90]	[IQR: 80-90]	
BMI (in kg/m ²), median	28.5	28.5	0.8113ª
	[IQR: 24-31]	[IQR: 26-33]	
Duration of dialysis (in hours), mean	4.0 ± 0	4.0 ± 0	-
Frequency of dialysis			
2x/week	4 (18)	2 (9)	0.664 ^b
3x/week	18 (82)	20 (91)	
Hemoglobin (in g/L), median	99.5	105.5	0.5647ª
	[IQR: 88-117]	[IQR: 93-117]	
Normal	5 (23)	7 (32)	0.925°
Low	11 (50)	9 (41)	
High	6 (27)	6 (27)	
Sodium (in mmol/L), median	137.9	136.4	0.0623ª
	[IQR: 135.4-140.8]	[IQR: 133.7-138.3]	
Normal	14 (64)	13 (59)	0.755 ^b
Low	7 (32)	9 (41)	
High	1 (5)	0	

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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Sexual function	75		0.5714 ^a
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	[n=8]	[IQR: 50-87.5]	[IQR: 75-100]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Sleep	46.3	53.8	0.1676 ^a
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	5 6			
KUK-DIYSIVAI I U I Z.) I U 1497"		IQK: 13-031	1QK: 23-031	

	[IQR: 0-50]	[IQR:0-50]	
Pain	66.3	56.3	0.4079ª
	[IQR: 45-90]	[IQR: 55-70]	
General health	52.5	45	0.1053ª
	[IQR: 40-65]	[IQR: 35-55]	
Emotional well-being	72	68	0.8108ª
	[IQR: 52-80]	[IQR: 56-84]	
Role-emotional	0	50	0.0201*a
	[IQR: 0-33.3]	[IQR: 33.3-100]	
Social function	62.5	62.5	0.5903 ^a
	[IQR: 50-75]	[IQR: 50-75]	
Energy/ Fatigue	55	62.5	0.3034ª
	[IQR: 50-75]	[IQR: 55-75]	
Physical component summary	38.6	32.5	0.2578ª
	[IQR: 31.5-43.3]	[IQR: 30-41.3]	
Mental component summary	43.2	51.7	0.0369*a
	[IQR: 37.9-51.4]	[IQR: 44.7-57.5]	

^aMann Whitney U test; ^bFisher's Exact test; ^cChi Square test; ^dIndependent t-test;*statistically significant

IQR, interquartile range; QOL, quality of life; URR, urea reduction ratio

Results of the ITT analysis are presented in Table 2. A higher proportion of patients during the intervention period did not experience cramps post-intervention than during the control period; however, results were not statistically significant. The median change in frequency of leg cramps also did not significantly differ between intervention and control. Twenty percent of patients during the control period had an increased frequency in cramps versus only 14% during intervention period but the difference in proportion was not statistically significant. Duration and intensity of cramps did not significantly differ between intervention and control (p>0.05). Results were comparable with the per-protocol analysis.

Table 2: Primary outcomes: intervention versus control (n=44)

	INTERVENTION (n=44) Median [IQR]	CONTROL (n=44) Median [IQR]	p-value
Cramps post-intervention, %yes	8 (18)	12 (27)	0.2059ª
Change in frequency of leg cramps, median	0 [IQR: 0-0]	0 [IQR: 0-0]	0.5010 ^b
No change	32 (73)	28 (64)	0.4180ª
Increased	6 (14)	9 (20)	
Decreased	6 (14)	7 (16)	
Change in duration of cramps, median	0 [IQR: 0-0]	0 [IQR: 0-0]	0.8877 ^b
Duration of cramps post-intervention			
None	36 (82)	32 (73)	0.4779ª
<1 minute	1 (2)	1 (2)	
1 to 5 minutes	6 (14)	9 (20)	
6 to 10 minutes	1 (2)	0	
>10 minutes	0	2 (5)	
Change in severity of cramps, median	0 [IQR: 0-0]	0 [IQR: 0-0]	0.7745 ^b
Severity of cramps post-intervention			
None	36 (82)	32 (73)	0.2822ª
Mild	1 (2)	3 (7)	
Moderate	3 (7)	7 (16)	
Severe	4 (9)	2 (5)	

^aMcNemar-Bowker test ; ^bWilcoxon signed-rank test

IQR, interquartile range

Table 3 compares the QOL subscales between the intervention and control groups. None of the KDQOL scales were significantly different between the two groups (p > 0.05). Similar results were obtained in the per-protocol analysis.

able 3: Secondary outcomes (QOL): inter	INTERVENTION (n=44) Median [IQR]	CONTROL (n=44) Median [IQR]	p-value ^a
Symptom/problem list	79.6	79.6	0.8872
Effects of kidney disease	[IQR: 72.7-93.2] 54.5 [IQR: 42.2-71.9]	[IQR: 72.7-87.5] 59.4 [IQR: 50-68.8]	0.3925
Burden of kidney disease	25 [IQR: 6.3-37.5]	18.9 [IQR: 0-31.3]	0.4782
Work status	0 [IQR: 0-50]	0 [IQR: 0-50]	1.0000
Cognitive function	33.3 [IQR: 20-53.3]	33.3 [IQR: 20-46.7]	0.9786
Quality of social interaction	33.3 [IQR: 20-50]	33.3 [IQR: 20-46.7]	0.8366
Sexual function [n=15]	75 [IQR: 50-100]	81.3 [IQR: 50-100]	0.2500
Sleep	48.8 [IQR: 38.8-57.5]	51.3 [IQR: 40-58.8]	0.5631
Social support	66.7 [IQR: 33.3-100]	83.3 [IQR: 41.7-100]	0.4333
Dialysis staff encouragement	87.5 [IQR: 75-100]	75 [IQR: 68.8-100]	0.1534
Overall health	55 [IQR: 50-70]	60 [IQR: 50-70]	0.4561
Patient satisfaction	50 [IQR: 50-83.3]	58.3 [IQR: 50-83.3]	0.9564
Physical functioning	50 [IQR: 35-65]	47.5 [IQR: 32.5-60]	0.5603
Role-physical	25 [IQR: 0-37.5]	0 [IQR: 0-25]	0.3276
Pain	58.8 [IQR: 45-77.5]	55 [IQR: 45-71.3]	0.1122
General health	45 [IQR: 35-55]	50 [IQR: 37.5-55]	0.3376
Emotional well-being	66 [IQR: 56-80]	62 [IQR: 52-80]	0.0827
Role-emotional	33.3 [IQR: 0-66.7]	33.3 [IQR: 0-66.7]	0.4334
Social function	62.5 [IQR: 50-68.8]	56.3 [IQR: 50-75]	0.6876
Energy/ Fatigue	57.5 [IQR: 50-75]	62.5 [IQR: 50-75]	0.7198
Physical component summary	37.4 [IQR: 32.3-41.0]	35.3 [IQR: 32.6-39.5]	0.2913
Mental component summary	44.2 [IQR: 41.4-54.2]	45.1 [IQR: 39.8-50.2]	0.6879

^aWilcoxon signed-rank test

IQR, interquartile range; QOL, quality of life

The prevalence of late-stage CKD (stages 3 to 5) in Southeast Asia is 13.1%. The rate is astoundingly higher in the Philippines at 35.9% (Suriyong et al. 2022) indicating a substantial burden of disease. There has been a steep rise in the prevalence of HD patients in the country with about an 800% jump in only 10 years (2018). Muscle cramps are the second most common complication during HD occurring in around 5% to 20% of patients (Shahgholian et al. 2016) often characterized as sustained, involuntary, and perceived as painful (Ozdemir et al. 2013). Factors like plasma volume contraction, hypertension, hyponatremia, hypomagnesemia, and carnitine deficiencyinduced muscle energy metabolism impairment are responsible for the cramps in dialysis treatment (Ozdemir et al. 2013). The painful muscle cramps experienced by HD patients are attributed to tissue ischemia, rapid ultrafiltration, and most importantly volume contraction (Shahgholian et al. 2016). Because muscle

cramps are unpleasant, debilitating, and challenging to manage, HD patients become hesitant to comply with prescribed therapies (Cox et al. 2017; Lynch et al. 2014).

Manipulative and body-based approaches are recently explored areas for the control or reduction of the physical symptoms in CKD patients (Chu et al. 2022). Massage therapy or reflexology is an age-old modality done by the direct application pressure to soft tissue and muscles and is believed to contribute to the physiological alleviation, improved blood flow, and enhanced comfort of patients (Bullen et al. 2018). Reflexology before HD treatment reduced the severity of fatigue, pain, and cramps and was suggested as a complementary method in improving the patients' QOL (Ozdemir et al. 2013). In a pilot study conducted on 32 patients in the US, HD patients were subjected to intradialytic massage for the treatment of leg cramps (Mastnardo et al. 2016). Patients in this trial reported 1.3 fewer cramping bouts at home in the intervention group compared to 0.2 in the control group (p=0.005). In the intervention group, subjects reported a decrease in cramping episodes at dialysis of 0.8 compared to 0.4 in the control group (Mastnardo et al. 2016). Acupressure was also shown to significantly reduce fatigue (F(1,54)=9.05, p=0.004) and depression (F(1,54)=4.20, p=0.045) among HD patients vs. those without acupressure therapy (Cho and Tsay 2004). Likewise, massage with glycerin and lavender oil had a positive effect in reducing the severity of restless legs syndrome among HD patients (Mirbagher Ajorpaz et al. 2020). Other manipulative therapies described in literature that are useful in addressing physical symptoms in HD patients include chiropractic and osteopathic manipulation, acupuncture, and yoga (Chu et al. 2022).

In this study, intradialytic massage was not seen to significantly reduce leg cramps and improve QOL among the study participants. Although the same massage protocol used by Mastnardo and colleagues was implemented by the researchers in the present study, the results did not replicate the original study findings. The difference in the outcome measurement could explain the differences in the results. The present study did not separately analyze cramping episodes occurring during dialysis and at home.

Nonetheless, it can be argued that based on the mechanism of leg cramps, episodes mainly occur during or near the end of each HD session (Nurfitriani et al. 2020; Punj et al. 2020; Ulu and Ahsen 2015). During HD, hypotension, osmotic and fluid alterations may occur, leading to cramping (Ulu and Ahsen 2015). On average, leg cramps mainly occur 4 hours after HD initiation (Howe et al. 1978). Although leg cramps may also happen after HD while the patient is at home, cramping episodes most likely occur during HD. In a study by Punj, all participants who experienced cramping during non-dialysis days also had an episode during dialysis day (Punj et al. 2020). The authors argued that cramping during non-dialysis days may be caused by delayed hypotensive reactions (Punj et al. 2020). However, it is also possible that cramping at home may be unrelated to HD treatment. According to a recent study, muscle cramping may be due to the inactivity of patients receiving dialysis and/or inadequate physical activity (Grandinetti et al. 2023). Therefore, the effect of massage in reducing cramping at home may not be generalizable to cramps due to HD treatment. Moreover, intradialytic massage does not directly address the underlying causes of cramps; thus, more mechanisms and supplementary treatment options should be explored. Other biological mechanisms that may explain leg cramping during HD include electrolyte derangement, elevated plasma intact parathyroid hormone, vitamin C deficiency, and increased serum leptin (Ozdemir et al. 2013; Ulu and Ahsen 2015).

Using a crossover trial instead of a parallel group design (Mastnardo et al. 2016) may also explain the variation in results. Crossover trials are more advantageous in controlling confounding bias since patients serve as their own controls. Potential confounding variables that may be potentially difficult to control in a parallel group design may be minimized in a crossover trial.

The lack of statistically significant findings regarding cramp frequency, duration, and intensity may also be caused by the low proportion of patients with cramp episodes in the present study compared with the Mastnardo study. At baseline, most (80%) participants had no leg cramp episode in the past 2 weeks. Thus, a reduction in cramp measures among these patients is no longer expected. Surprisingly, 14% of patients had an increased frequency of cramps after receiving intradialytic massage in the present study. Variations in outcome measures could have occurred based on the slightly different inclusion criteria. Based on these findings, it can be hypothesized that intradialytic massage may not be efficacious for all HD patients and may only benefit patients who experienced at least one leg cramp episode in the past 2 weeks.

The present study also failed to show a significant improvement in the QOL measures. A leg cramp is only one factor that may influence QOL. Other patient factors, more serious HD complications, and other significant life events may substantially affect QOL more than leg cramps. Moreover, intradialytic massage only offers transient relief and relaxation but does not address all other aspects that may influence QOL. Our study has several limitations. First, the intervention was only performed for 2 weeks, which may be insufficient to provide favorable results. Second, blinding patients is not feasible in the present study due to the nature of the intervention; thus, this could have led to information bias. Results could have been influenced by the patient's expectations regarding the effect of the intradialytic massage. Nonetheless, no crossover or period effect was observed in this trial, and this denotes that the treatment effect is constant over time, and the washout period is sufficient.

CONCLUSION

In conclusion, this crossover study provides evidence that intradialytic massage alone is not efficacious in reducing leg cramp frequency, duration, and intensity. Moreover, there is insufficient data supporting intradialytic massage to improve the QOL of patients undergoing HD treatment. Underlying factors that lead to leg cramps should be addressed through a comprehensive and individualized intervention. Given the multifactorial nature and differences in the etiology of leg cramps among HD patients, studies exploring interventions that directly address the underlying causes of cramps are needed.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

The authors confirm their contribution to the paper as follows: Study conception and design: Krizia Mari Anne R. Daguman; Vince Bryan B. Viscayno; Monalisa L. Dungca. Data collection: Ed Jico B. Conde; Henry Angelo S. Go. Analysis and interpretation of results: Krizia Mari Anne R. Daguman; Marissa Elizabeth L. Lim. Draft manuscript preparation: Krizia Mari Anne R. Daguman; Marissa Elizabeth L. Lim. All authors have reviewed the results and approved the final version of the manuscript.

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