A Survey on Dialysis-Related Muscle Cramping and a Hypothesis of Angiotensin II on Its Pathophysiology

Shweta Punj[1], Alsoufi Enaam[1], Alonso Marquez[1], Arthur J. Atkinson Jr[1] and Daniel Batlle[1]

[1]Division of Nephrology and Hypertension, Northwestern University Feinberg Medical School, Chicago, Illinois, United States

Correspondence: Daniel Batlle, Division of Nephrology and Hypertension, Northwestern University Feinberg School of Medicine, 320 E Superior Street, Chicago, Illinois 60611, USA. E-mail: d-batlle@northwestern.edu

Received 4 December 2019; revised 6 February 2020; accepted 2 March 2020; published online 12 March 2020

Kidney Int Rep (2020) **5,** 924–926; http://dx.doi.org/10.1016/j.ekir.2020.03.003

© 2020 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The increasing emphasis on patient-centered care has refocused research interests, and hemodialysis patients have identified symptom management as a top research priority.[1,2] A recent study analyzed the top 3 prioritized physical symptoms of insomnia, muscle cramps, and fatigue from the standpoint of their current state, barriers, and knowledge gaps impeding progress and a possible path forward.[3] In keeping with the importance of this topic, a survey of our dialysis center patients was conducted to characterize the frequency, severity, and timing of dialysis-related cramps. Dialysis-related cramps can be extremely painful and can compromise the efficacy of hemodialysis therapy, but their pathophysiology is unclear.[4,5] The central role of volume removal as the trigger for susceptible patients seems evident from the fact that intradialytic cramps are usually associated with hypotension and that prompt correction of hypotension by saline administration and discontinuation of ultrafiltration often improve the cramping. Here we propose a central role of relative angiotensin II deficiency as the cause of decreased muscle blood flow during dialysis and therefore a key contributor to this painful complication of dialysis.

Of the 149 participants surveyed, 79 (53%) self-identified as diabetic. In all, 79% of the participants (117 of 149) reported having experienced cramps at least once during dialysis (Table 1). Of these 117 patients, 63 (54%) stated that cramps occurred during only dialysis days, whereas 54 (46%) reported cramps during both dialysis and nondialysis days. None of the patients reported cramps on nondialysis days only. A total of 73% (85 of 117) reported cramps during the last hour and 26% (30 of 117) in the middle of dialysis (Table 1). Severity of cramps was rated using a scale from 1 to 10 and then classified in 3 categories: minor (1−3), moderate (4−6), and severe (7−10). Two patients were not able to estimate the severity of their cramps. Among the 117 participants who experienced cramps, 14% (n = 16) rated the pain as minor and 38% (n = 44) as moderate, whereas almost half (47%, n = 55) reported severe cramps (Table 2). Patients who reported severe pain were subcategorized for the analysis into moderately severe (pain scale rating of 7−8) and extremely severe (pain scale rating of 9−10). In all, 41 of the 55 patients (75%) reporting severe pain scored the pain as moderately severe, and 14 of 55 patients (25%) scored the pain as extremely severe.

Most patients surveyed (76%) reported that fluid removal by dialysis was decreased, was stopped, and/or fluid was given back as the main intervention used to alleviate their cramps (Table 2). Half of the patients stated that "bringing the toes up" was tried as a way to ameliorate the cramps. When asked about all interventions to alleviate dialysis cramps, the most frequent response (29%) was a combination of decreasing fluid removal, raising the lower extremities, and massaging the extremities. Stopping dialysis prematurely was 1 of the measures reported by some (22 of 117), either alone or in combination with other measures (19%). Pain from intradialytic cramps was frequently reported as severe and a cause for premature termination of dialysis in 19% of the cramping patients we surveyed, a percentage similar to the 17.9% termination rate previously reported.[4]

Among the 117 patients with cramps, 15 (12.8%) were receiving angiotensin II receptor blockers (ARBs), and 21 (17.9%) were receiving angiotensin-converting enzyme (ACE) inhibitors (Figure 1). In total, the 2 classes of renin−angiotensin system (RAS) blockers

Table 1. Reported muscle cramps frequency and characteristics

Survey question	Response, n (%)	Response, n (%)	Response, n (%)
Have you ever had muscle cramps during dialysis?	Yes 117 of 149 (79)	No 32 of 149 (21)	
Which days do you usually experience muscle cramps?	Dialysis days only 63 of 117 (54)	Nondialysis days 0 of 117 (0)	Both 54 of 117 (46)
When you have cramps during dialysis, when do they usually occur?	Initiation (first h) 1 of 117 (1)	Middle 30 of 117 (26)	End (last h) 85 of 117 (73)
Has the dialysis session sometimes been interrupted because of the cramps?	Yes 92 of 117 (79)	No 24 of 117 (21)	
How often does dialysis interruption occur?	More than 50%[a] 15 of 92 (16)	Less than 50%[b] 77 of 92 (84)	

[a]As many of 10% of the patients (9 of 92) reported that they almost always had the session interrupted because of cramps.
[b]The majority (64%) of the patients (59 of 92) reported that interruptions in the dialysis session happened rarely.

were used by 36 of the 117 patients with cramps (30.7%) and only 4 of the 32 patients without cramps (12.5%). This difference was statistically significant by the Fisher exact test ($P = 0.028$). There were no significant differences in the percentage of cramping and noncramping patients receiving β-blockers or calcium channel blockers (Figure 1).

Attempts to develop a rational approach for treating muscle cramps are clearly hampered by an incomplete understanding of its pathophysiology. The efficacy of fluid replacement as a palliative measure supports the key role of fluid removal as the initiating event. Yet, for similar degrees of fluid removal, some patients experience severe cramps whereas others do not. This suggests that an abnormal response to fluid removal is involved in those patients who experience cramps. Our survey also revealed that some patients experience cramps on nondialysis days, which may suggest a predisposition unrelated to fluid removal. A delayed effect of fluid removal during dialysis, however, may be responsible for their cramping much in the same way that some patients

Table 2. Reported muscle cramps frequency and characteristics

Survey question	Response, n (%)	Response, n (%)	Response, n (%)	Response, n (%)
How severe are the cramps?	Mild 16 of 117 (14)	Moderate 44 of 117 (38)	Severe 55 of 117 (47)	Unable to estimate 2 of 117 (2)
What treatment is usually being done for dialysis cramps?	Decrease fluid removal/infuse fluid back 89 of 117 (76)	Bring toes up 60 of 117 (51)	Massage or squeeze the extremities 56 of 117 (48)	Stop dialysis prematurely 22 of 117 (19)

experience a delayed hypotensive response after hemodialysis.[5]

Mechanisms that have been proposed to be responsible for dialysis-related cramps include hypoxia caused by hypotension and vasoconstriction, osmotic shifts, hyponatremia, hypomagnesemia, and carnitine deficiency.[4] A clue to the nature of the pathogenesis of cramps was provided by using a tilt table to study the hemodynamic response of cramping and noncramping dialysis patients to postural change.[6] From this study, it was concluded that intradialytic skeletal muscle cramps result at least in part from a sympathetic nervous system response to dialysis-induced volume stress.

We now propose a key role of angiotensin II as a main contributor to muscle cramping during dialysis. Specifically, we hypothesize that the lack of an appropriate increase in angiotensin II activity during fluid removal by hemodialysis results in decreased muscle blood flow, which in turn causes cramps. Normally, within seconds of changing from a recumbent to a standing position, hemorrhage, or other stress that causes a perceived reduction in intravascular volume, such as fluid removal during dialysis, there is release into the circulation of renin secreted by the kidney juxtaglomerular apparatus.[7] This leads to the rapid formation of angiotensin I by cleavage of angiotensinogen by renin and concurrent angiotensin II formation. When appropriately regulated during volume removal by hemodialysis, angiotensin II may ensure adequate muscle blood flow and helps to prevent cramping. In support of the proposed angiotensin II hypothesis of cramping during dialysis is the key finding of Fliser *et al.*[8] that infusions of angiotensin II caused a marked increase in skeletal muscle blood in normal volunteers, which has been confirmed by others. The action of angiotensin II on muscle blood flow is in contrast to the vasoconstrictive properties of this peptide and the decreased renal blood flow consistently reported after infusions of this peptide.

Why would a blunted angiotensin II response be involved in dialysis cramping? An appropriate response of angiotensin II to fluid removal is dependent on several factors: namely, renin secretion, which is often decreased in patients with end-stage kidney disease as a result of chronic volume overload and sclerosis of the juxtaglomerular apparatus in some cases.[7] What we are hypothesizing is that the more impaired the RAS response is, the more likely it is that cramping occurs as a result of inappropriately low angiotensin II levels. When dogs with intact kidneys were dialyzed, they exhibited a normal RAS response to fluid removal as shown by an increase in plasma renin activity and did not exhibit capillary

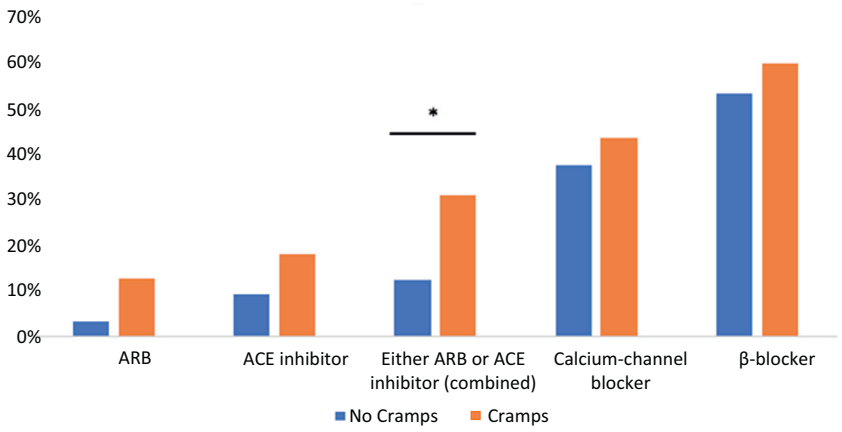

Figure 1. Antihypertensive medications in patients with and without cramps. *$P = 0.028$, one-way Fisher's exact test, otherwise not significant. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

derecruitment.[9] Peripheral vasoconstriction from sympathetic activation is likely to occur in all patients during hemodialysis, leading to derecruitment of skeletal muscle capillaries. Muscle cramping is more likely in patients whose sympathetic system activation during hemodialysis is not accompanied by an appropriate activation of the RAS during fluid removal and the attendant increase in renin and therefore plasma angiotensin II. Our survey findings moreover are consistent with the angiotensin II hypothesis of dialysis cramping proposed here, as patients treated with RAS blockers experienced cramps more often than those who were not treated with these agents (Figure 1).

Weaknesses of our survey that should be noted include an open recall period (from initiation of dialysis to the survey period), which creates variability in the intervals being surveyed. Another weakness is the lack of data on blood pressure during dialysis. Lack of validation of our questionnaire and our use of the Stanford Pain Scale, which is not specific to dialysis-related cramps pain, are additional limitations. Further studies are needed to confirm our observations from larger databases before it can be recommended that RAS blockers be avoided in patients with cramps. Now that angiotensin II is commercially available for treating patients with shock that is refractory to norepinephrine infusions, it may be possible to study whether infusions of this natural peptide or novel agonists may be effective in preventing intradialytic skeletal muscle cramps.

DISCLOSURE

AJA holds U.S. patent number 9,919,022 relating to the use of AII receptor agonists to prevent or reduce hemodialysis-associated skeletal muscle cramps. DB is a co-inventor of U.S. patent number 10,443,049 relating to the use of ACE2 truncates and also the founder of Angiotensin II therapeutics Inc. All the other authors declared no completing interests.

ACKNOWLEDGMENTS

This work was supported in part by National Institute of Diabetes and Digestive and Kidney Diseases grant R01DK104785. We wish to thank all the dialysis patients at the Northwestern/Fresinius Dialysis Unit who participated in our surveys to evaluate cramping during dialysis.

REFERENCES

1. Manns B, Hemmelgarn B, Lillie E, et al. Setting research priorities for patients on or nearing dialysis. *Clin J Am Soc Nephrol*. 2014;9:1813–1821.
2. Palmer SC, de Berardis G, Craig JC, et al. Patient satisfaction with in-centre haemodialysis care: an international survey. *BMJ Open*. 2014;4:e005020.
3. Flythe JE, Hilliard T, Lumby E, et al. Fostering innovation in symptom management among hemodialysis patients: paths forward for insomnia, muscle cramps, and fatigue. *Clin J Am Soc Nephrol*. 2019;14:150–160.
4. Rocco MV, Burkart JM. Prevalence of missed treatments and early sign-offs in hemodialysis patients. *J Am Soc Nephrol*. 1993;4:1178–1183.
5. Batlle DC, von Riotte A, Lang G. Delayed hypotensive response to dialysis in hypertensive patients with end-stage renal disease. *Am J Nephrol*. 1986;6:14–20.
6. Kaplan B, Wang T, Rammohan M, et al. Response to head-up tilt in cramping and noncramping hemodialysis patients. *Int J Clin Pharmacol Ther Toxicol*. 1992;30:173–180.
7. Tang J, Wysocki J, Ye M, et al. Urinary renin in patients and mice with diabetic kidney disease. *Hypertension*. 2019;74:83–94.
8. Fliser D, Dikow R, Demukaj S, Ritz E. Opposing effects of angiotensin II on muscle and renal blood flow under euglycemic conditions. *J Am Soc Nephrol*. 2000;11:2001–2006.
9. Bowsher DJ, Krejcie TC, Avram MJ, et al. Reduction in slow intercompartmental clearance of urea during dialysis. *J Lab Clin Med*. 1985;105:489–497.