Kidney Medicine

Patient-Reported Outcomes in Kidney Trials: Magnesium, Muscle Cramps, and PROMising Better Care for Kidney Patients

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There has been and continues to be great interest in magnesium and dialysis. The results of a simple MEDLINE search showed the earliest listing assessing the ultrafiltration of magnesium in children to be in 1954,

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with the earliest clinical trials in hemodialysis starting in the early 1970s.[1-3] This interest in magnesium and hemodialysis continues to the present day.

Although reports in the literature vary, muscle cramping in patients treated with dialysis is common, with the reported prevalence ranging from 12% to 80%.[4-6] Muscle cramps are painful, occur suddenly, vary in duration, and can occur at any time. This common symptom in patients receiving dialysis results in poor quality of life, negatively affects sleep, and contributes to anxiety and depression.[7] Patients may shorten or miss dialysis treatment sessions because of cramping.[4]

Despite being a common symptom with significant negative effects on patients, the pathophysiology of muscle cramping in patients receiving dialysis is poorly understood. Many therapeutic strategies have been unsuccessful in alleviating muscle cramping.[8] Patients have reported using remedies such as pickle juice or yellow mustard.[9] The gaps in understanding the pathophysiology of muscle cramping in patients receiving dialysis likely hinder innovation in preventing or treating muscle cramping in patients treated with dialysis.

In this issue of *Kidney Medicine*, Srisuwarn et al[10] report the results of the MIRACAL study, a study with a quasiexperimental design conducted at 6 centers in Bangkok, Thailand. The study examined the effect of a high dialysate magnesium concentration, defined as 1.75 mEq/L, on coronary artery calcification and bone mineral density. The predefined primary outcomes were changes in the coronary artery calcification score and bone mineral density from those at baseline. The predefined secondary outcomes were changes in laboratory data and the rate of coronary artery calcification progression. Adult in-center hemodialysis patients with a life expectancy of >6 months and an Agaston score of ≥300 were eligible. Of 48 eligible patients, the first 20 patients, all treated at 1 of 2 centers, received a high magnesium dialysate concentration. The remaining patients were matched 1:1 on the Agaston score. The study lasted 26 weeks.

All the patients were monitored for signs and symptoms of hypermagnesemia by hemodialysis nurses for the first month and then by patient self-report for the remainder of the study. Muscle cramping was not specifically queried; however, the number of muscle cramping episodes was extracted from the medical record.

For the primary outcomes, the authors found a significant increase in the coronary artery calcification score from the baseline in both the groups and a nonsignificant tendency for a decline in bone mineral density at several sites. As would be expected, the serum magnesium and ionized magnesium concentrations in the high magnesium dialysate concentration group were significantly higher than those in the standard dialysate magnesium concentration group. There were no statistically significant differences in the secondary outcomes between the groups.

Although not a predefined primary or secondary outcome, the authors report a remarkable difference in the number of episodes of muscle cramps reported in the medical record between the 2 groups. Only 2 episodes were reported in the group that received a high magnesium dialysate concentration, and 285 episodes were reported in the standard magnesium dialysate group. The most compelling sentence in the discussion is as follows: "Most patients who were on high magnesium dialysate requested this treatment be continued after study completion largely due to the alleviation of muscle cramps."

As mentioned earlier, no therapeutic strategies to prevent or treat muscle cramping in patients receiving dialysis have shown a benefit, making the above statement even more compelling. At the end of the MIRACAL study, the "patients who were on high magnesium dialysate were switched back to standard dialysate magnesium concentrations. They then experienced muscle cramps and 15 of 20 patients requested to be back on high magnesium dialysate" (S. Disthabanchong, personal communication, October 2021). This is a remarkable finding; to my knowledge, this level of treatment success has not been shown with any other therapeutic strategy.

On the surface, this result suggests that a high magnesium dialysate concentration may be an effective approach to preventing or reducing muscle cramping in patients receiving hemodialysis. However, assessing the effect of a high magnesium dialysate concentration on muscle cramping in hemodialysis patients was not a predefined aim of this study, and the data were not collected in a standardized manner. "Hemodialysis nurses did not receive any special training … for assessment of muscle cramps prior to the study. Intradialytic symptoms including muscle cramps

were routinely monitored (observed and confirmed by HD nurses or volunteered by the patients) during each HD session and the presence of any intradialytic symptoms were routinely recorded" (S. Disthabanchong, personal communication, October 2021). Although study resources were spent on collecting these interesting data, these results, at best, can be considered anecdotal. This unexpected and potentially important result is of great interest but will require going back to the drawing board to plan additional studies to assess and verify.

The study participants' enthusiasm toward the use of a higher magnesium dialysate concentration, specifically that they connected this intervention with reducing their muscle cramping, aligns with the increasing interest in the field of preventing or treating muscle cramping in patients treated with dialysis. Randomized clinical trials are being planned, and at least 2 Kidney Health Initiative workgroups have focused on this problem.[8] The results of the first workgroup demonstrated that patients ranked muscle cramping in the top 3 symptoms to be prioritized for treatment innovation, and the second workgroup will soon publish its recommendations on using patient-reported outcome measures (PROMs) for skeletal muscle cramping in patients treated with dialysis.[11,12]

This study is an example of a missed opportunity when research solely focuses on traditional "hard" clinical outcomes and does not incorporate PROMs. Symptoms are experienced by patients and, to be accurately recorded, must be documented by the patient in a reliable and valid manner. Research has suggested that symptom reporting is highly variable and often plagued by underreporting, and there are many factors that influence the likelihood of patients reporting their symptoms.[7,13] Health care providers are known to underrecognize and undertreat symptoms.[14–16] Assessing symptoms, particularly in a clinical trial, needs to be standardized to avoid bias in reporting, inquiring, and documenting. Psychometrically sound PROMs (ie, surveys or questionnaires) are reproducible and minimize bias in questioning, reporting, and documenting.[17,18]

The findings of this study would have been much stronger if a PROM was used to assess the effect of a higher magnesium dialysate concentration on the occurrence of muscle cramping instead of relying on clinician documentation and the patients' self-reports. The authors could have not only systematically and reproducibly assessed the number of cramping episodes but also collected other items of interest, including the timing, location, duration, and severity of muscle cramping. Having reproducible, reliable, and valid data on muscle cramping in the setting of a high magnesium dialysate concentration, compared with those in a setting of a standard magnesium dialysate concentration, would be a giant step forward.

In general, there is increasing recognition that PROMs should be considered as key endpoints to be included in clinical trials. The Food and Drug Administration (FDA) Guidance on Supporting Medical Labeling Claims[19] and the Recommendations for Interventional Trials (SPIRIT) Patient-Reported Outcomes (PRO) Extension both emphasize that PROMs be included as trial endpoints.[19-21] There are many initiatives in nephrology that are working to elevate the importance of PROMs in clinical research and clinical care. Recent examples include extensive work being done by the Standardised Outcomes in Nephrology (SONG) initiative, Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference, which recommended that PROMs be incorporated into clinical trials and kidney disease care registries, and the American Society of Nephrology Kidney Health Initiative Workgroups.[22,23] Using PROMs requires expertise and planning, and this call to action does not suggest that integrating PROMs in clinical trials is easy or that they should always be a primary endpoint.

Especially while assessing symptoms, PROMs must have, at a minimum, equal footing with traditional clinical outcomes. Many patients value improved quality of life and symptom improvement more than survival.[24] Now is the time to routinely think out of the traditional box for clinical trials, do things differently, and place patients' input higher up on the scale of importance. As is suggested by this study's findings, in doing so, we might just be pleasantly surprised by what we find.

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