*Seminars in Dialysis*

WILEY

Seminars in Dialysis

REVIEW ARTICLE

# Pharmacological Treatment for Dialysis-Related Muscle Cramps: A Systematic Review

Nidia Mantilla-Manosalva[1,2] | Santiago Guadarrama[1,2] | Lennis Jazmin Bedoya-Muñoz[1,2] | Sara Giraldo-Moreno[3] | Laura Cuellar-Valencia[1,2] | María Fernanda Iriarte-Aristizábal[1,2] | Marta Ximena León[1] | Fernan Alejandro Mendoza-Montenegro[1] | Juan Esteban Correa-Morales[1,2]

[1]Palliative Care Program, Universidad de La Sabana, Bogotá, Colombia | [2]Palliative Care Department, Instituto Nacional de Cancerología, Bogotá, Colombia | [3]Medicine Department, Universidad CES, Medellín, Colombia

**Correspondence:** Juan Esteban Correa-Morales (jecorreamorales1@gmail.com)

**Received:** 22 May 2024 | **Accepted:** 6 August 2024

**Funding:** The authors received no specific funding for this work.

## ABSTRACT

**Background:** Patients with end-stage renal disease undergoing dialysis suffer from muscle cramps, a prevalent and burdensome symptom for which there is a paucity of efficient and safe treatments.

**Aim:** What is the efficacy and safety of pharmacological interventions for the treatment of dialysis-related muscle cramps?

**Design:** A systematic review was conducted in OVID, CINAHL, PubMed, Web of Science, and Central Cochrane databases up to August 25, 2023.

**Data Sources:** Experimental studies reporting on a pharmacological intervention for the treatment of dialysis-related muscle cramps were included. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis, and the studies quality was assessed with the RoB2 tool.

**Results:** A total of 4660 studies were retrieved, and 13 articles were included. The studies reported on nine interventions: vitamin C, vitamin E, vitamin K2, vitamin B7, dextrose solutions, gabapentin, sodium chloride, creatine monohydrate, and L-carnitine. The studies testing L-carnitine and creatine monohydrate were the only ones deemed to have a low risk of bias. Side effects were reported in only two trials, consisting primarily of gastrointestinal discomfort and hyperglycemia. Vitamins C and E are the two most studied interventions that showed positive results in reducing the frequency, severity, and duration of dialysis-related muscle cramps. L-carnitine is a promising intervention that warrants further investigation.

**Conclusion:** Our review consolidates the existing evidence, elucidating the range of treatments along with their potential benefits and limitations. Future studies should uphold high-quality standards, incorporate patient-reported outcomes, and utilize well-defined, robust samples to improve patient care.

## 1 | Introduction

People living with end-stage renal disease experience a significant and often overwhelming symptom burden [1]. Specifically, patients undergoing dialysis therapy, whether as a bridge to renal transplantation or as a definitive treatment, contend with an additional cluster of symptoms associated with the treatment itself [2]. Dialysis-related symptoms have been categorized into eight clusters: gastrointestinal, musculoskeletal and fluid volume, neurological, irritation of the mucous membranes and skin, depression, sleep disturbance, sexual, and anemic [3, 4]. Evaluating their occurrence is crucial because they are correlated with overall mortality, quality of life, and functional status [5–7]. Nevertheless, there are limited available assessment instruments [8]; the current ones are burdensome and time consuming [9], and, worst of all, even after recognizing the occurrence of some symptoms, such as fatigue, depression, and muscle cramps, treatment options remain limited [10].

Muscle cramps, for instance, are considered as an orphan symptom [11], despite being encountered by 42% of dialysis-dependent patients [12]. At present, only two guidelines have reviewed and provided recommendations for managing muscle cramps [11, 13]. However, neither of these guidelines considers the particularities of patients undergoing dialysis or addresses dialysis-related muscle cramps (DMCs) specifically. Modest research regarding dialysis-related muscle cramp prevention has been carried out [14]. Still, a significant number of patients continue to present and endure muscle cramp pain stemming from dialysis treatment, and there is currently no established standard treatment [15]. The scarcity of data contrasts with the perspectives of patients, who have emphasized the importance of addressing this symptom due to its debilitating nature, impacting motor function, sleep, and mood and changing the way patients act, feel, and what they do [16]. Thus, we conducted a comprehensive systematic literature review on the efficacy and safety profile of pharmacological interventions used to treat DMCs, so nephrologists and palliative care physicians can offer patients options to alleviate this orphan symptom.

## 2 | Methodology

### 2.1 | Search Strategy

We conducted a comprehensive search strategy using Medical Subject Headings (MeSH) related to patients undergoing dialysis and experiencing muscle cramps. We conducted searches on five databases (OVID, CINAHL, PubMed, Web of Science, and Central Cochrane) employing the following search string: *(((((cramp*) OR (muscle cramp*)) OR (leg cramp*)) OR (spasm*)) OR (muscle spasm*)) AND (((((((chronic kidney failure) OR (End-Stage Kidney Disease)) OR (End-Stage Renal Disease)) OR (Chronic Renal Failure)) OR (Renal Dialysis)) OR (Hemodialysis)) OR (Peritoneal Dialysis))*. The systematic review protocol was registered with the International Prospective Register of Systematic Reviews PROSPERO (CRD42023464297). The search results were imported into EndNote software for deduplication. The refined search was then uploaded to Rayyan, where two reviewers (JEC and NM) screened abstracts and selected relevant titles, with an inter-rater agreement of 0.84. In cases of differing opinions, consensus was reached through discussion. The review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria.

### 2.2 | Study Selection

The inclusion criteria to meet by eligible studies were as follows: (1) original investigation with an experimental design published in a peer-reviewed journal before August 25, 2023; (2) report on the efficacy and safety of a pharmacological intervention for the treatment of DMCs; (3) include at least 10 participants 18 years and older; and (4) be published in English or Spanish. The review excluded quasi-experimental studies, gray literature, editorials, commentaries, case series with fewer than 10 patients, case studies, and protocols.

### 2.3 | Data Extraction

Two reviewers (NM and LB) independently extracted data into a Microsoft Excel spreadsheet. Extracted data included the country and year of publication, study design, number of participants, patients characteristics, type of dialysis, time receiving dialysis, scales used to assess symptom improvement, details of the intervention (dose and administration interval), comparators, primary and secondary outcomes assessed, results reported, adverse reactions, follow-up time, number of patients lost to follow-up, and trial limitations. To ensure consistency, extracted data were cross-checked between reviewers, and any discrepancies were resolved through discussion and consensus.

### 2.4 | Quality Appraisal

Five reviewers (SGV, SGM, LC, MXL, and MFI) independently assessed studies risk of bias. Randomized controlled trials (RCTs) were evaluated using the Cochrane Collaboration's Risk-of-Bias Tool 2 [17]. No study was excluded based on its quality appraisal. The information was uploaded to the *robvis* online tool and is presented in a traffic light plot with the judgment on each evaluated domain for the reader's convenience.

### 2.5 | Data Synthesis and Analysis

The synthesis of results was conducted in accordance with the guidance on the Conduct of Narrative Synthesis in Systematic Reviews [18]. A meta-analytic analysis was not explored due to the low number of studies per intervention and their heterogeneity. Efficacy and safety outcomes related to the pharmacological management of DMCs were reported using means (or differences in means), standard deviations with confidence intervals (CIs), and *p*-values, as reported by the original articles. All authors were involved in the data synthesis and interpretation of the results, and they vouched for the completeness and accuracy of the findings.

## 3 | Results

### 3.1 | Search Strategy

A total of 4660 studies were retrieved. After excluding duplicates and irrelevant articles, the 25 remaining articles were screened as full texts. Of these studies, 13 articles were included. Figure 1 depicts the complete screening process and the reasons for exclusion.

### 3.2 | Study and Subject Characteristics

The included studies were published between 1973 and 2021, from 6 different countries: United States ($n=7$), Iran ($n=2$), United Kingdom ($n=1$), Taiwan ($n=1$), Japan ($n=1$), and China ($n=1$). The median number of patients per study was 31.53 (range: 10–82). The mean follow-up and goal assessment time was 13.75 weeks (range: 6–28 weeks). The studies excluded patients with concomitant cardiovascular disease, other underlying causes of cramps, hemodynamic instability, hypotensive episodes, or electrolyte

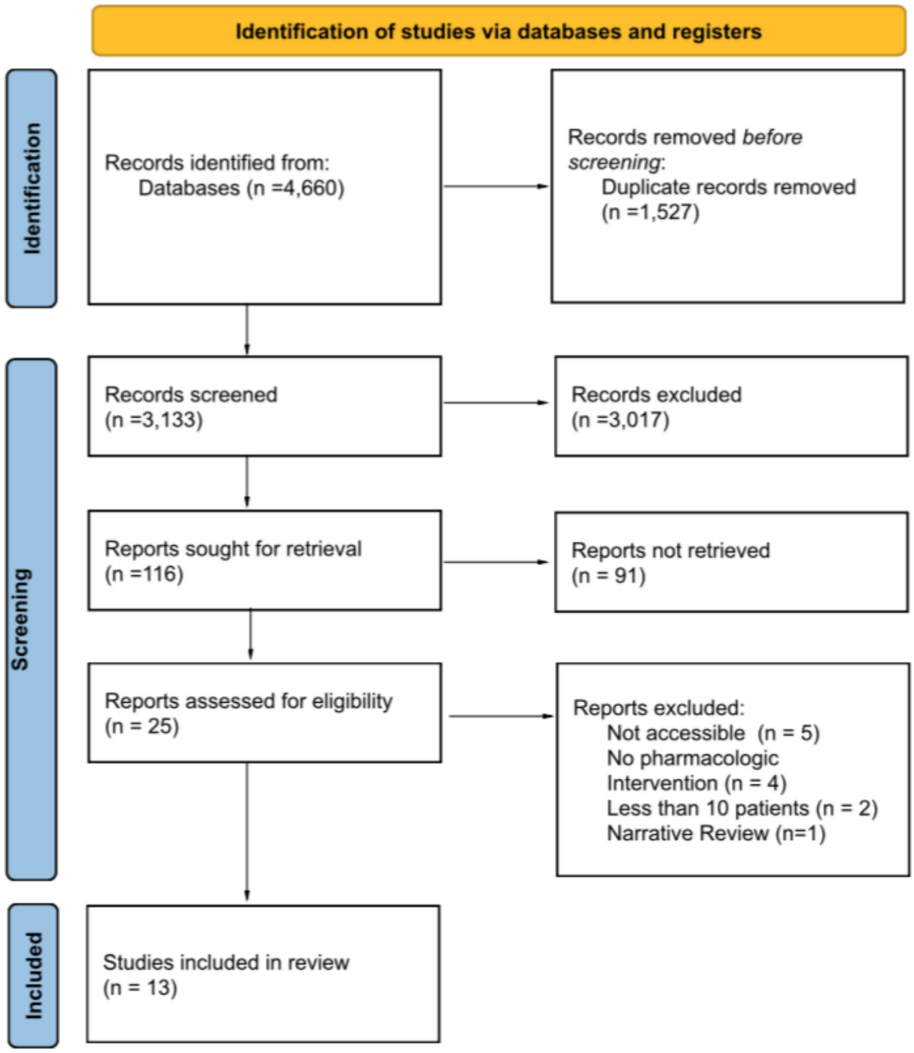


**FIGURE 1** | PRISMA diagram.

abnormalities or those who were simultaneously taking supplements or medications for muscle cramps. Side effects related to interventions were reported in only two trials, consisting primarily of gastrointestinal discomfort while taking vitamin K2 and hyperglycemia during dextrose infusion. Most studies lacked information on patient continuity and had unclear reasons for dropouts.

### 3.3 | Quality Appraisal

The methodological quality of the included studies is summarized in Figure 2. The trials exhibited several quality deficiencies, particularly in terms of randomization process and measurement of outcome. As a result, two trials were judged to have a low risk of bias, three some concern, and eight high risk of bias.

### 3.4 | Treatments for Dialysis-Related Muscle Cramps

This section presents the results of trial studies examining different pharmacological treatments for DMCs. The characteristics and outcomes of the studies are summarized in Table 1.

### 3.5 | Vitamins

Roca et al. conducted a controlled, randomized, double-blind clinical trial that aimed to assess the frequency and severity of leg cramps in 40 patients under dialysis. Following a 2-month placebo washout, participants were randomly assigned to receive either vitamin E 400 IU or quinine 325 mg at bedtime for a period of 2 months, followed by a 16-week follow-up. Both groups experienced a significant reduction in leg cramps, with mean values dropping from approximately 10 cramps per month to 3.3 and 3.6 cramps for vitamin E and quinine, respectively. Initially, the pain rating stood at 3.5, experiencing a reduction of about 1.4 points in both groups ($p < 0.0005$). After 1 month of treatment, the pain ratings were 2.2 and 2.0 for the vitamin E and quinine groups, respectively. The study indicated that both quinine and vitamin E are effective treatments for leg cramps in dialysis patients but recommended vitamin E over quinine, as the initial treatment choice, to avoid potential quinine toxicity [25]. El-Hennawy and Zaib conducted an evaluation of vitamin E for muscle cramps induced by hemodialysis in a cohort of 19 patients. These individuals experienced a minimum of 60 cramp episodes during and between hemodialysis sessions over a duration

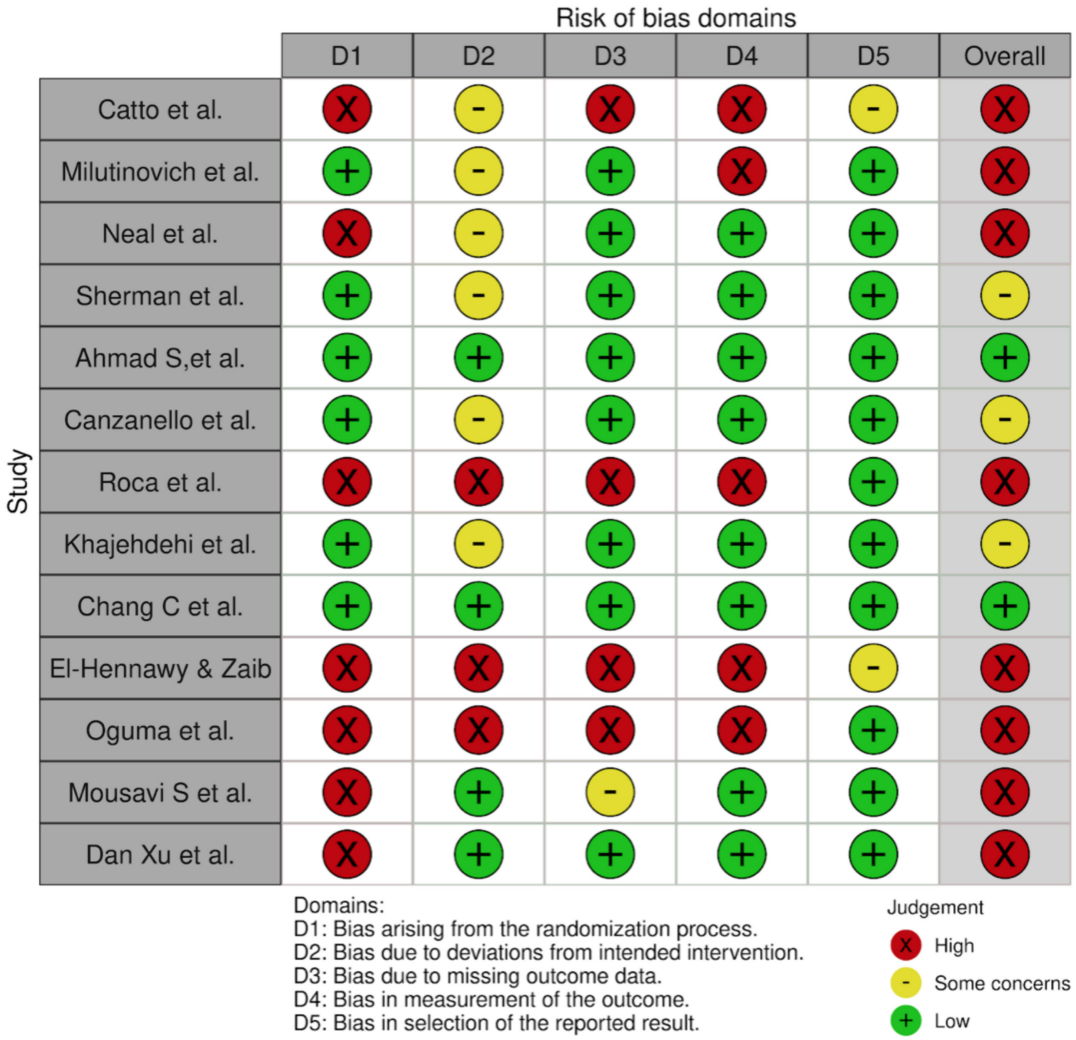


**FIGURE 2** | Trial's risk of bias assessment.

of 12 weeks. Patients received 400 international units of vitamin E daily for a period of 12 weeks. At the end of the trial, patients experienced a 68.3% reduction in the frequency of muscle cramps, compared to the patient's baseline showing a positive correlation with the type of therapy ($p = 0.0001$). No side effects were encountered. They concluded that short-term vitamin E treatment is safe and effective in reducing patients' DMCs [28]. In another placebo-controlled, double-blind study conducted by Khajehdehi et al., 60 hemodialysis patients experiencing a minimum of two muscle cramps per week were enrolled. These patients were randomly assigned to receive daily treatment for 8 weeks, consisting of either 400 mg of vitamin E, 250 mg of vitamin C, a combination of both, or a placebo. They evaluated the change in the frequency and severity of the pain, finding a significant reduction in both variables in all vitamin groups compared to the pretreatment values and the placebo group ($r = 0.33$, $p = 0.01$). At the end of the trial, vitamins E, C, their combination, and placebo produced cramp reductions of 54%, 61%, 97%, and 7%, respectively. The cramp related pain severity changed in the vitamin E group from $3.5 \pm 1.6$ to $2.1 \pm 1.2$ ($p = 0.02$), in the vitamin C group $2.8 \pm 1.4$ to $2.0 \pm 0.76$ ($p = 0.04$), vitamin E plus vitamin C group $3.5 \pm 1.6$ to $1.1 \pm 0.35$ ($p = 0.00003$), and placebo group $3.1 \pm 1.6$ to $3.1 \pm 1.9$. No adverse effects were reported during the trial, concluding the safety and efficacy of the therapy and the enhanced effect of short-term combination therapy for DMCs [26].

Vitamin K was also evaluated in one study conducted by Xu et al. This multicenter, randomized, placebo-controlled, crossover clinical trial aimed to investigate the efficacy of vitamin K2 (360 mg/d) in reducing the frequency and severity of muscle cramps in 41 patients under hemodialysis with muscle cramps refractory to conventional interventions. Participants received vitamin K2 or placebo for two 4-week phases, crossing over after a 2-week washout. The frequency of muscle cramps in the vitamin K2-initial group decreased significantly from $7.4 \pm 2.5$ to $2.5 \pm 1.9$ in Phase 2 ($p < 0.001$). The frequency of attacks did not change in the placebo-initial group. As participants crossed over, they experienced the opposite result. Muscle cramp attacks increased from $2.5 \pm 1.90$ to $5.7 \pm 1.9$ ($p < 0.001$) in the vitamin K2-initial group and decreased from $7.0 \pm 1.7$ to $2.7 \pm 1.4$ in the placebo-initial group. Secondary outcomes also showed a significant reduction in the duration and severity of muscle cramps in the vitamin K2 group compared to placebo (all $p < 0.05$). No serious adverse events occurred. This pilot trial suggests that vitamin K2 supplementation may effectively alleviate DMCs [31].

**TABLE 1** | Characteristics of studies of pharmacological treatment for dialysis-related muscle cramps.

| Author and year | No. of patients | Intervention | Outcome | Result |
|---|---|---|---|---|
| Catto et al. 1973 [19] | 19 | 600 mg sodium chloride | Frequency and severity of DMCs | Reduction of 26% in the frequency ($p < 0–05$) and 30% in the severity ($p < 0.02$) of muscle cramps |
| Milutinovich et al. 1979 [20] | 15 | Hypertonic (50%) glucose | The relief of DMCs | 17 of 26 cramp episodes were completely relieved either during the initial hypertonic glucose injection or within 5 min after injection |
| Neal et al. 1981 [21] | 38 | Hypertonic dextrose (50% dextrose in water) | DMC relief: partial or complete | 89% of treatments with D50W resulted in complete relief vs. 40% of treatments with D5W. Partial relief was obtained in 5.5% of treatments with D50W vs 40% relief with D5W |
| Sherman et al. 1982 [22] | 20 | 50-mL vials containing 50% dextrose, 7.05% saline, or 5% dextrose | Relief of cramping | Hypertonic saline and hypertonic dextrose each produced similar relief of hemodialysis-related muscle cramps; both were superior to 5% dextrose |
| Ahmad et al. 1990 [23] | 82 | 20 mg/kg L carnitine | DMCs frequency | 36% of the patients in the carnitine group had one or more episodes of muscle cramps. The incidence of muscle cramping dropped to 13% in the final six dialysis procedures ($p < 0.02$) |
| Canzanello et al. 1991 [24] | 24 | 50 mL of dextrose 50% water, 100 mL of 25% mannitol solution, and 23.5% saline | DMCs frequency | The mean cramp duration was less for mannitol compared to D50W ($p < 0.05$), but not to saline |
| Roca et al. 1992 [25] | 40 | Vitamina E 400 UI | Frequency and severity of DMCs | Vitamin E group experienced a significant reduction in leg cramps, passing from approximately 10 cramps per month to 3.3 episodes. The pain reduced a mean of 1.4 points |
| Khajehdehi et al. 2001 [26] | 60 | Vitamin E 400 mg, vitamin C 250 mg, their combination or placebo | DMC frequency | Vitamins E, C, their combination, and placebo produced cramp reductions of 54%, 61%, 97%, and 7%, respectively |
| Chang et al. 2002 [27] | 10 | 12 mg creatine monohydrate | DMC frequency | The episodes of muscle cramps were decreased by 60% in the creatine group (control vs. creatine: 6.4 +/− 0.9 vs. 2.6 +/− 1.8 times 4 weeks, $p < 0.05$) |
| El-Hennawy and Zaib 2010 [28] | 19 | Vitamin E 400 UI | DMC frequency | The frequency of muscle cramps decreased 68.3% during vitamin E therapy |
| Oguma et al. 2012 [29] | 27 | 1 mg/dia biotin | DMC severity | Reduced the onset and the severity of cramps in 12/14 patients during and after HD |
| Mousavi et al. 2015 [30] | 15 | Gabapentin 300 mg | Frequency and severity of DMCs | The incidence and severity of symptomatic muscle cramp decreased in the gabapentin group ($p = 0.001$). |

(Continues)

**TABLE 1** | (Continued)

| Author and year | No. of patients | Intervention | Outcome | Result |
|---|---|---|---|---|
| Xu et al. 2021 [31] | 41 | Vitamin K2 360 mg/d | Frequency and severity of DMCs | Vitamin K2 reduced the frequency, duration, and severity of muscle cramps (all $p < 0.05$) |

The last vitamin that has been studied is vitamin B7. In a prospective randomized trial led by Oguma et al., 14 hemodialysis patients experiencing frequent muscle cramps were administered 1 mg/day of oral biotin. The study aimed to assess the response in pain intensity compared to baseline levels. The intensity of cramps was rated from 0 (*no pain*) to 4 (*excruciating, no tolerable pain*). Whereas half of the patients experienced a meaningful reduction of the pain greater than or equal to 2 points, the other half had just a 1 point improvement. There also was a reduced onset of cramps in 12/14 patients both during and after hemodialysis [29].

### 3.6 | Dextrose Solutions

Neal et al. performed a double-blind trial that investigated the effectiveness of 50% dextrose in water solution (D50W) to relieve DMCs compared to a control group receiving an identical volume (1 mL/kg for 15 s) of 5% dextrose in water solution (D5W). The results showed that from the 18 patients, 89% in the D50W group had complete relief, compared to 40% of the 15 patients in the D5W group ($p < 0.002$). There were no important side effects observed. They suggest that expansion of plasma volume with D50W is a safe and effective treatment for DMCs [21]. Canzanello et al. conducted a prospective, randomized, double-blind crossover study that aimed to compare the efficacy, safety, and impact on interdialytic weight gain and blood pressure control of hypertonic solutions (50% dextrose, 25% mannitol, and 23.5% saline) in treating DMCs. They included 24 stable chronic hemodialysis patients. Each patient was randomized to receive a 2-week treatment with each of the three agents for DMCs. No efficacy outcome (episodes and severity) improved, and mean cramp duration decreased with mannitol compared to dextrose (9 + 5 vs. 13 + 12 min, $p < 0.05$), but not to saline. The study had the inconvenience that not every patient had a cramp episode during the study period. All three agents were well tolerated; the only side effect reported was hyperglycemia during dextrose infusion [24]. Another double-blind trial by Milutinovich et al. evaluated the efficacy of hypertonic glucose (50%) versus normal saline for relieving DMCs in 15 chronically uremic, nondiabetic hemodialysis patients. When the cramp started, the ultrafiltration was decreased, and one of the vials was infused over 5 min. Of the 44 cramp episodes recorded, 17 out of 26 episodes treated with hypertonic glucose experienced complete relief, and 5 out of 18 episodes treated with normal saline were relieved ($p < 0.016$). No complications were observed with the administration of hypertonic glucose, suggesting its safety and effectiveness in treating DMCs [20].

Sherman et al. developed a double-blind controlled trial in which 20 nondiabetic patients undergoing chronic hemodialysis were randomly assigned to receive 50 mL intravenous doses of 7.05% saline, 50% dextrose, or 5% dextrose for the relief of DMCs. Of the 100 episodes treated, relief was reported after 3 min in 17 out of 26 episodes with hypertonic saline, 18 out of 26 episodes with 50% dextrose, and 5 out of 18 episodes with 5% dextrose. Hypertonic saline and hypertonic dextrose appeared to have similar efficacy, both being superior to 5% dextrose ($p < 0.05$). The author proposes hypertonic dextrose as a preferable option because of lower side effects on end-stage renal disease patients [22].

### 3.7 | Other Interventions

Catto et al. conducted a double-blind crossover randomized clinical trial, in which they compared the efficacy of an oral preparation of sodium chloride with placebo, in reducing the frequency and severity of muscle cramps in 19 patients undergoing maintenance hemodialysis for end-stage renal failure. Each patient received 14 tablets of sodium chloride (each contained 600 mg/10 meq for a total of 140 meq sodium) during each dialysis for 2 months and then 14 placebo tablets during each dialysis for 2 months. The study reported a statistically significant reduction of 26% in the frequency ($p < 0.05$) and 30% in the severity ($p < 0.02$) of DMCs with the administration of sodium chloride. No significant adverse effects were observed in blood pressure or body weight. Patient preference was also evaluated, 76% preferred sodium chloride, 12% preferred the placebo, and 12% had no preference ($p < 0.01$) [19].

Mousavi et al. evaluated gabapentin in a double-blinded randomized clinical trial that included 19 patients with end-stage renal disease (creatinine clearance < 10–15 mL/min/m$^2$) undergoing hemodialysis with at least six episodes of intradialytic muscle cramps per month. Initially, placebo was given before each dialysis session for 4 weeks, and then, after a 2-week washout period, they received 300 mg of oral gabapentin 5 min before starting hemodialysis for an additional 4 weeks. There was a total follow-up time of 10 weeks. A significant reduction of 20%–100% in the incidence and intensity of muscle cramps during the gabapentin intervention was observed ($p < 0.001$). Five patients (30%) became symptom-free, and the majority experienced a decrease of over 60% in cramp frequency. No side effects were reported during the study [30].

Creatine monohydrate was also evaluated as a potential intervention by Chang et al. This randomized, double-blinded study included 10 patients who were on maintenance hemodialysis and experienced frequent intradialytic muscle cramps. They were randomly assigned to receive either creatine monohydrate (12 mg dissolved in 100 mL water 5 min before starting HD) or placebo for 4 weeks, followed by a 4-week washout period. There was a 60% reduction in the frequency of muscle cramps

in the creatine monohydrate group during the treatment period (control vs. creatine: 6.4 +/− 0.9 vs. 2.6 +/− 1.8 times 4 weeks, $p < 0.05$), which did not occur in the placebo group. During the washout period, the incidence of cramps increased to previous levels in the intervention group. No adverse effects were observed during the trial [27].

Finally, Ahmad et al. conducted a 7-month, randomized, double-blind trial involving 82 stable, nondiabetic, hemodialysis patients in four different centers. They assessed the effects of 20 mg/kg intravenous L-carnitine versus placebo (equal volume of 0.9% saline). Thirty-eight patients were allocated to the L-carnitine group, whereas 44 were randomized to receive the placebo. In the L-carnitine group, the incidence of muscle cramping dropped to 13% in the final six dialysis procedures of the treatment phase ($p < 0.02$), and there was a significant reduction in intra-dialytic hypotension ($p < 0.02$). Clinical status showed a significant improvement in 50% of the L-carnitine group compared to 18.9% in the placebo group ($p < 0.005$). The authors concluded that L-carnitine in hemodialysis patients is associated with a decrease in dialytic symptoms, improvement in exercise capacity, and well-being [23].

## 4 | Discussion

Patients with end-stage renal disease undergoing dialysis commonly experience muscle cramps, a symptom that significantly impacts their quality of life and functional status. Muscle cramps are also a frequent cause for early termination of dialysis sessions [32]. For this relatively neglected symptom, treatment options are limited. This systematic review represents the first comprehensive effort to synthesize available pharmacological interventions for DMCs.

Our results point out that vitamins E and C are the most studied interventions so far and have consistently shown to reduce the frequency and the severity of the DMCs with a low incidence of adverse effects. However, these studies had a small sample of participants and a high risk of bias that cannot be overlooked. These fat-soluble vitamins have also been tried in the treatment of patients with cramps due to liver cirrhosis. A systematic review conducted in 2022, specifically targeting this population, identified 24 studies. Among them, two studies reported contradictory results regarding the effectiveness of vitamin E. For patients with cramps-related cirrhosis interventions, such as taurine, appear to be more beneficial [33]. Similarly, in the neurology field, an evidence-based review published by the American Academy of Neurology for the treatment of muscle cramps related to amyotrophic lateral sclerosis (ALS), peripheral neuropathies, and cramp fasciculation syndromes, advice to use quinine derivatives. This intervention presents a moderate benefit but carries a significant risk for adverse events. Moreover, the pharmacokinetics are often altered in dialysis patients, rendering it an unreliable option. The review also mentions naftidrofuryl, calcium channel blockers such as diltiazem, and vitamin B as an option to treat cramps related to neurological conditions [13]. None of these options have been assessed in patients undergoing hemodialysis and cannot be recommended. This exemplifies that although the symptom appears to be the same, the underlying pathophysiology may vary as a result of the underlying disease, and the most effective treatment approach can differ accordingly. As the research on DMCs develops, it is crucial to consider the fact that patients undergoing hemodialysis may be receiving it for various underlying conditions. Hence, variations in treatment outcomes for DMCs may arise too, due to the diverse etiologies of end-stage renal disease.

The other intervention that had multiple studies is the hypertonic dextrose solutions. The logic behind this intervention is that the expansion of the plasma volume by the increased plasma osmolarity can mitigate DMCs that are caused by the volume contraction [24]. Although some studies got positive results, not all of them did, the risk of bias was also high, the trials had small samples, and the intervention did present mild to moderate adverse effects. Other interventions such as sodium chloride, gabapentin, creatine monohydrate, or L-carnitine have only been investigated in a single study each. The most promising intervention among them is L-carnitine, which is a vitamin-like biofactor involved in the metabolism of fatty acids. The study by Ahmad et al. had the highest recruitment of participants, had a low risk of bias, was performed in multiple sites, and found a positive result. However, the enrolled participants were nondiabetic hemodialysis patients and had a 13% cramp reduction. This leaves the question if L-carnitine can be useful in diabetic hemodialysis patients and if this reduction is really meaningful. It is challenging to determine, considering that no study utilized patient-reported outcome measures (PROM) or investigated how DMCs improvement affected the quality of life for patients. Given these preliminary positive results with L-carnitine, robust, high-quality trials are warranted to better understand the benefit and safety of this intervention in the treatment of patients with DMCs. Currently, two studies are being conducted regarding DMCs treatment and can be found in *clinicaltrials.gov*. One of them concentrates on a non-pharmacological intervention called sujok therapy [34]. The pharmacologic intervention trial explores the use of topical magnesium; however, it was last updated in 2017, and right now, its present status is unknown [35]. As part of our review, we aspire to stimulate renewed research interest in this field, fostering further exploration and enhancement of knowledge surrounding the most promising interventions outlined herein.

Our study has several limitations to consider. First, during the study retrieval process, there was not a full text available for some promising studies. Second, most studies included had a high risk of bias due to concerns in the randomization process, so our results should be interpreted with caution. Third, the samples, interventions, and effect assessment in the included studies were heterogeneous, which resulted in the lack of plausibility to perform a meta-analysis. Fourth, we only included studies that reported a pharmacological treatment in an adult population, so it is likely that we miss non-pharmacological treatments such as exercise and massage that may equally be effective and have a safetier profile, and we do not know if the current interventions apply to children. Furthermore, we did not explore preventive interventions that could potentially alleviate the symptom before it manifests, which is preferable to waiting for patients to experience the symptom. Lastly, the studies use scores to assess DMCs' severity that are not

specific, and their reliability is highly questionable. A systematic PROM to improve assessment and management should be integrated [36]. This horizon of research awaits to be developed to guarantee a better evaluation of end-stage renal disease patients' symptoms, as the tools currently used do not include DMCs [37, 38].

## 5 | Conclusions

In conclusion, dialysis-related muscle cramps present a challenging symptom, significantly impacting patients' well-being, exacerbated by the limited evidence on pharmacological interventions. This systematic review provides a comprehensive summary of the efficacy and safety of the current interventions investigated thus far. Vitamins E and C emerge as the most promising treatments, given their demonstrated efficacy and safety in reducing the frequency, severity, and duration of DMCs. Although L-carnitine also shows potential, further investigation is warranted. Future studies should adhere to high-quality standards, incorporate patient-reported outcomes, and utilize well-defined, robust samples to address previous gaps and advance our understanding and management of dialysis-related muscle cramps, ultimately improving patient outcomes.


### Acknowledgments

The authors thank their institution's support.


### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### References


1. D. Lupu and A. H. Moss, "The Role of Kidney Supportive Care and Active Medical Management Without Dialysis in Supporting Well-Being in Kidney Care," *Seminars in Nephrology* 41, no. 6 (2021): 580–591.

2. A. Amro, B. Waldum-Grevbo, N. von der Lippe, F. B. Brekke, C. Miaskowski, and I. Os, "Symptom Clusters From Dialysis to Renal Transplantation: A Five-Year Longitudinal Study," *Journal of Pain and Symptom Management* 51, no. 3 (2016): 512–519.

3. S. Chaiviboontham, N. Phinitkhajorndech, and J. Tiansaard, "Symptom Clusters in Patients With End-Stage Renal Disease Undergoing Hemodialysis," *International Journal of Nephrology and Renovascular Disease* 13 (2020): 297–305.

4. X. Cao, L. Tian, and C. Lin, "Symptom Clusters in Patients Receiving Haemodialysis: A Systematic Review of Observational Studies," *Journal of Clinical Nursing* 26, no. 17–18 (2017): 2545–2557.

5. M. S. Y. Thong, S. van Dijk, M. Noordzij, et al., "Symptom Clusters in Incident Dialysis Patients: Associations With Clinical Variables and Quality of Life," *Nephrology, Dialysis, Transplantation* 24, no. 1 (2009): 225–230.

6. A. Amro, B. Waldum, T. Dammen, C. Miaskowski, and I. Os, "Symptom Clusters in Patients on Dialysis and Their Association With Quality-Of-Life Outcomes," *Journal of Renal Care* 40, no. 1 (2014): 23–33.

7. A. Amro, B. Waldum, N. von der Lippe, et al., "Symptom Clusters Predict Mortality Among Dialysis Patients in Norway: A Prospective Observational Cohort Study," *Journal of Pain and Symptom Management* 49, no. 1 (2015): 27–35.

8. J. E. Flythe, J. D. Powell, C. J. Poulton, et al., "Patient-Reported Outcome Instruments for Physical Symptoms Among Patients Receiving Maintenance Dialysis: A Systematic Review," *American Journal of Kidney Diseases* 66, no. 6 (2015): 1033–1046.

9. S. S. Chen, S. Al Mawed, and M. Unruh, "Health-Related Quality of Life in End-Stage Renal Disease Patients: How Often Should We Ask and What Do We Do With the Answer?" *Blood Purification* 41, no. 1–3 (2016): 218–224.

10. K. J. Cox, M. B. Parshall, S. H. A. Hernandez, S. Z. Parvez, and M. L. Unruh, "Symptoms Among Patients Receiving In-Center Hemodialysis: A Qualitative Study," *Hemodialysis International* 21, no. 4 (2017): 524–533.

11. D. Santini, G. Armento, R. Giusti, et al., "Management of Orphan Symptoms: ESMO Clinical Practice Guidelines for Diagnosis and Treatment," *ESMO Open* 5, no. 6 (2020): e000933.

12. A. S. You, S. S. Kalantar, K. C. Norris, et al., "Dialysis Symptom Index Burden and Symptom Clusters in a Prospective Cohort of Dialysis Patients," *Journal of Nephrology* 35, no. 5 (2022): 1427–1436.

13. H. D. Katzberg, A. H. Khan, and Y. T. So, "Assessment: Symptomatic Treatment for Muscle Cramps (an Evidence-Based Review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology," *Neurology* 74, no. 8 (2010): 691–696.

14. M. S. Ulu and A. Ahsen, "Muscle Cramps During Hemodialysis: What Can We Do? New Approaches for Treatment and Preventing," *Electronic Journal of General Medicine* 12, no. 3 (2015): 277–281.

15. S. N. Davison, S. Rathwell, S. Ghosh, C. George, T. Pfister, and L. Dennett, "The Prevalence and Severity of Chronic Pain in Patients With Chronic Kidney Disease: A Systematic Review and Meta-Analysis," *Canadian Journal of Kidney Health and Disease* 8 (2021): 2054358121993995.

16. A. Grandinetti, T. S. Hilliard-Boone, K. R. Wilund, et al., "Patient Perspectives of Skeletal Muscle Cramping in Dialysis: A Focus Group Study," *Kidney360* 4, no. 6 (2023): e734–e743.

17. G. A. Wells, B. Shea, D. O'Connell, et al. "The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses," (2023), https://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

18. J. Popay, H. M. Roberts, A. J. Sowden, et al., "Guidance on the Conduct of Narrative Synthesis in Systematic Reviews a Product From the ESRC Methods Programme," *ESRC Methods Programme* 1, no. 1 (2006): 5–9.

19. G. R. Catto, F. W. Smith, and M. Macleod, "Treatment of Muscle Cramps During Maintenance Haemodialysis," *British Medical Journal* 3, no. 5876 (1973): 389–390.

20. J. Milutinovich, U. Graefe, W. C. Follette, and B. H. Scribner, "Effect of Hypertonic Glucose on the Muscular Cramps of Hemodialysis," *Annals of Internal Medicine* 90, no. 6 (1979): 926.

21. C. R. Neal, E. Resnikoff, and A. M. Unger, "Treatment of Dialysis-Related Muscle Cramps With Hypertonic Dextrose," *Archives of Internal Medicine* 141, no. 2 (1981): 171–173.

22. R. A. Sherman, K. A. Goodling, and R. P. Eisinger, "Acute Therapy of Hemodialysis-Related Muscle Cramps," *American Journal of Kidney Diseases* 2, no. 2 (1982): 287–288.

23. S. Ahmad, H. T. Robertson, T. A. Golper, et al., "Multicenter Trial of L-Carnitine in Maintenance Hemodialysis Patients. II. Clinical and Biochemical Effects," *Kidney International* 38, no. 5 (1990): 912–918.

24. V. J. Canzanello, B. Hylander-Rossner, R. E. Sands, T. M. Morgan, J. Jordan, and J. M. Burkart, "Comparison of 50% Dextrose Water, 25% Mannitol, and 23.5% Saline for the Treatment of Hemodialysis-Associated Muscle Cramps," *ASAIO Transactions* 37, no. 4 (1991): 649–652.

25. A. O. Roca, D. Jarjoura, D. Blend, et al., "Dialysis Leg Cramps. Efficacy of Quinine Versus Vitamin E," *ASAIO Journal* 38, no. 3 (1992): M481–M485.

26. P. Khajehdehi, M. Mojerlou, S. Behzadi, and G. A. Rais-Jalali, "A Randomized, Double-Blind, Placebo-Controlled Trial of Supplementary Vitamins E, C and Their Combination for Treatment of Haemodialysis Cramps," *Nephrology, Dialysis, Transplantation* 16, no. 7 (2001): 1448–1451.

27. C. T. Chang, C. H. Wu, C. W. Yang, J. Y. Huang, and M. S. Wu, "Creatine Monohydrate Treatment Alleviates Muscle Cramps Associated With Haemodialysis," *Nephrology, Dialysis, Transplantation* 17, no. 11 (2002): 1978–1981.

28. A. S. El-Hennawy and S. Zaib, "A Selected Controlled Trial of Supplementary Vitamin e for Treatment of Muscle Cramps in Hemodialysis Patients," *American Journal of Therapeutics* 17, no. 5 (2010): 455–459.

29. S. Oguma, I. Ando, T. Hirose, et al., "Biotin Ameliorates Muscle Cramps of Hemodialysis Patients: A Prospective Trial," *Tohoku Journal of Experimental Medicine* 227, no. 3 (2012): 217–223.

30. S. S. Beladi Mousavi, A. Zeraati, S. Moradi, and M. B. Mousavi, "The Effect of Gabapentin on Muscle Cramps During Hemodialysis: A Double-Blind Clinical Trial," *Saudi Journal of Kidney Diseases and Transplantation* 26, no. 6 (2015): 1142.

31. D. Xu, A. X. Yang, R. Ren, Z. Shan, Y. M. Li, and J. Tan, "Vitamin K2 as a Potential Therapeutic Candidate for the Prevention of Muscle Cramps in Hemodialysis Patients: A Prospective Multicenter, Randomized, Controlled, Crossover Pilot Trial," *Nutrition* 97 (2022): 111608.

32. D. G. Moledina and W. F. Perry, "Pharmacologic Treatment of Common Symptoms in Dialysis Patients: A Narrative Review," *Seminars in Dialysis* 28, no. 4 (2015): 377–383.

33. S. Kalia, P. Nath, M. Pathak, and A. C. Anand, "Treatment of Muscle Cramps in Patients With Cirrhosis of Liver: A Systematic Review," *Journal of Clinical and Experimental Hepatology* 12, no. 3 (2022): 980–992.

34. D. Candan. "The Effect of Sujok Therapy on Symptom Burden and Comfort Level in Patients Undergoing Hemodialysis Treatment-Contemp Clin Trials 2023," Clinical Trials identifier (NCT number): NCT05939505.

35. N. Boudvill. "Topical Magnesium and Muscle Cramps in Dialysis Patients," Contemporary Clinical Trials, (2016), Clinical Trials identifier (NCT number): NCT03082625.

36. J. M. Evans, A. Glazer, R. Lum, et al., "Implementing a Patient-Reported Outcome Measure for Hemodialysis Patients in Routine Clinical Care: Perspectives of Patients and Providers on ESAS-R:Renal," *Clinical Journal of the American Society of Nephrology* 15 (2020): 1299–1309.

37. S. N. Davison, G. S. Jhangri, and J. A. Johnson, "Cross-Sectional Validity of a Modified Edmonton Symptom Assessment System in Dialysis Patients: A Simple Assessment of Symptom Burden," *Kidney International* 69 (2006): 1621–1625.

38. S. N. Davison, G. S. Jhangri, and J. A. Johnson, "Longitudinal Validation of a Modified Edmonton Symptom Assessment System (ESAS) in Haemodialysis Patients," *Nephrology, Dialysis, Transplantation* 21 (2006): 3189–3195.