

# Muscle Cramps During Hemodialysis

## What can we Do? New Approachs for Treatment and Preventing

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### ABSTRACT

Muscle cramps are the most prevalent intradialytic complication and an important difficulty for patients. The frequency of muscle cramps is about 35-86% during haemodialysis. Excessive ultrafiltration, intradialytic hypotension, electrolyte-mineral disturbances, hypoosmolality are the most frequent causes. Muscle cramps can be treated by isotonic-hypertonic saline or hypertonic dextrose solutions. Also, preventing hypotension, profiling sodium, vitamin E and C can be used to prevent. There are new advances to treat and prevent this inconvenience, and we aimed to review the causes and approaches for treatment and preventing muscle cramps during hemodialysis.

**Key words:** Muscle cramps, hemodialysis, end stage renal disease.

### Hemodiyaliz Esnasında Kas Krampları

Biz ne yapabiliriz ? Önlenmesi ve Tedavisi için Yeni Yaklaşımlar

### ÖZET

Kas krampları en yaygın intradialitik komplikasyonlardan biridir ve hastalar için hayat kalitesini etkileyen önemli bir zorluktur. Hemodiyaliz sırasında görülen kas krampları sıklığı yaklaşık 35-86%'dir. Aşırı ultrafiltrasyon, intradialitik hipotansiyon, elektrolit-mineral bozuklukları, hipoosmolalite en sık nedenlerindedir. Kas krampları izotonik-hipertonik sodyum veya dekstroz çözeltileri ile tedavi edilebilir. Diyaliz sırasında hipotansiyonun önlenmesi, sodyum profili, vitamin E ve C tedavileri de kas kramplarının önlenmesinde etkili bulunmuştur. Bunun yanında umut vadeden yeni gelişmeler mevcuttur. Bu derlemede hemodiyaliz sırasında görülen kas kramplarının nedenleri, önlenmesi ve tedavi yaklaşımlarını gözden geçirmeyi amaçladık

**Anahtar kelimeler:** Kas krampları, hemodiyaliz, son dönem böbrek hastalığı.

### INTRODUCTION

Muscle cramps are among the most frequent complications that can be seen during hemodialysis (HD) and so painful. They may occur in 35-86% of HD patients. They are typically found in lower extremities and may be severe enough to compromise haemodialysis treatment (kaze). In a study in London in 2011, intradialytic cramps were the commonest symptoms reported (74%) with hypotension (76%) (1). Causes of the muscle cramps during HD are still unknown (2). Excessive dialysis ultrafiltration (UF), intradialytic hypotension or tissue hypoxia and elevation of serum creatine kinase may lead to an abnormal utilization of energy by muscles and thus result in muscle cramps (3). Many approaches for the treatment

of HD related cramps have been proposed, but most have been associated with serious side effects and none have been conclusively effective (4). We aimed to review the causes, treatment and the preventing methods of this problem.

### Etiology

**Hypotension:** Intra-dialytic hypotension (IDH) is defined as a fall in systolic or mean arterial pressure of more than 20 mmHg that results in clinical symptoms, and occurs in 20-30% of HD treatments hypotension. It is the most frequent cause of the muscle cramps during HD (5). Its etiology is multifactorial including poor cardiac function, inter-dialytic fluid gain, incorrect ideal body weight (IBW), excessive UF and the short duration of conventional HD.

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Received: 12.03.2014, Accepted: 17.03.2014

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Recurrent episodes of IDH are associated with significant morbidity as well as mortality (6). In a multi-center cross-over study, hypotension-prone patients were treated both with standard HD (sHD, applying a constant ultrafiltration rate) and HD applying a blood volume controlled ultrafiltration rate (cHD). And found less symptomatic events were seen during cHD: 13% for symptomatic hypotension, and 32% for cramps (7).

**Hypoosmolality:** Hypoosmolality, is the second most frequent cause of the muscle cramps during HD (8). Changes in osmolarity causes acute adverse side-effects of hemodialysis such as hypotension, muscle cramps, osmotic imbalance (9).

**Electrolyte-mineral disturbances:** Disturbances in electrolyte and mineral metabolism, such as elevated plasma calcium, phosphorus, and decreased sodium, potassium and magnesium levels can cause muscle cramps, increased morbidity and mortality risk in HD and peritoneal dialysis (PD) patients (10). Alteration of plasma sodium concentration during hemodialysis strongly influence fluid distribution between extracellular and intracellular fluid volume and leads to more efficient ultrafiltration and muscle cramps during HD (9). A prospective study about the dialysate sodium profile found that, sodium profiling may not benefit every dialysis patient and should be individually evaluated (11). In addition to sodium; calcium and phosphorus levels can lead to muscle cramps. It has been suggested that hypercalcaemia, hyperphosphataemia, hypermagnesaemia and hypomagnesaemia could cause muscle cramps (12). In an other study, patients with moderately elevated plasma phosphorus and calcium levels, the risk of muscle cramps and pain was found as 20% increased when compared with patients who met the K/DOQI (Kidney/Dialysis outcomes Quality Index) target (13).

**Elevated plasma IPTH concentrations:** Increases of PTH levels can lead to muscle cramps in HD patients. It has been suggested that, plasma IPTH concentration below the advised target was associated with a lower risk of cramps (13).

**Carnitine deficiency:** L-carnitine is a quaternary amine known to transfer long chain fatty acids from cytoplasm into the mitochondrial matrix to be oxidized (14). Carnitine plays a pivotal role in energy metabolism (15). There is marked reduction in the production of carnitine in end-stage renal disease patients, and is significantly reduced in HD patients (16,17). L-carnitine is extensively

removed by the dialyser during a single dialysis session, due to the compound's low molecular weight and high hydrophilicity in combination with its lack of protein binding. Chronic haemodialysis treatment has been shown to be associated with a reduction in plasma and tissue L-carnitine concentrations and an accumulation of acyl-carnitines (18).

**Vitamin C deficiency:** Vitamin C levels have been reported to be low in uraemia, and shown that subclinical vitamin C depletion might contribute to HD cramps (19).

**Elevated serum leptin levels:** Leptin, a middle molecule uremic toxin, is able to affect neuronal activity. In a study to determine the association between leptin and hemodialysis-related muscle cramps, it was found that; elevated serum leptin levels were associated with frequency of hemodialysis-related cramps (20).

#### **Preventing and Treatment**

**Preventing hypotension:** Preventing hypotension by using automatic blood volume controlled ultrafiltration can be effective to preventing muscle cramps. In a multi-center cross-over study, 56 hypotension-prone patients were treated both with Standard HD (sHD, applying a constant ultrafiltration rate) and HD applying a blood volume controlled ultrafiltration rate (cHD). In the end of the study, less symptomatic events were seen during cHD: 13% for symptomatic hypotension, and 32% for cramps. And they concluded that, less intradialytic morbid events were observed with cHD than with sHD, and pre- to post-dialytic changes in blood pressure were less pronounced (7).

**Profiling Sodium:** HD administration with decreasing Na concentration can be beneficial for preventing muscle cramps. For example, HD can began with 146 - 150 mEq/L Na<sup>+</sup> and then can be reduced to 135 - 140 mEq/L at the end of the HD session. Higher dialysate sodium concentrations also reduce the incidence of muscle cramps with hypotension during HD. Profiling of dialysate sodium and bicarbonate also reduces cramping significantly (9). In a study, a significant decline in the occurrence of cramps, in the mean interdialytic weight gain and a tendency to reduce the number of hypotensive episodes were detected in patients using variable sodium profiling (21).

**Isotonic-hypertonic saline solutions or hypertonic dextrose solutions:** Isotonic-hypertonic saline solutions with hypertonic dextrose solutions can be use in muscle cramps with hypotension during HD. And. In a study, the safety and efficacy of dextrose solution, and saline solu-

tion were found equivalent, and without leading to any complications (22). Especially administration of hypertonic saline solution, up to the final 15 minutes of HD is safe therapy for hypotension and muscle cramps (23). The benefits of dextrose solutions (% 20 or %50 ) 25 - 50 ml have been shown in the previous studies. In a study comparing the effect of saline 0.9% , saline 3%, isotonic glucose 5% , glucose 20%, hypertonic glucose infusion during dialysis was resulted with a greater increase in relative blood volume than equal volumes of other solutions (24).

**Mannitol:** It has been indicated that; mannitol infusion beneficial for reducing muscle cramps during HD via its effect on body fluids distribution. The efficacy of mannitol infusion is similar to dextrose solution and saline solution and any side effects were not shown (25).

**Vitamin E:** Vitamin E (200 IU) has been recommended to taken at nights to decrease muscle cramps during HD. In a study, the frequency of muscle cramps decreased significantly during vitamin(vit) E therapy with the reduction of 68.3% (26). In another placebo-controlled, double-blind study, treatment with the combination of vit E and vit C was safe and effective in reducing HD cramps (27). Roca et al. recommended vit E as the initial treatment of leg cramps in dialysis (28).

**Vitamin C:** It has been shown that vitamin C levels are lower in HD patients than in healthy controls due to their vitamin C restricted diets (29). Combination therapy was significantly more effective than treatment with either vitamin E or C given alone (27). Prolonged vitamin therapy may be associated with serious adverse effects. Vitamin C therapy is known to produce hyperoxaluria, oxalate containing urinary stones, and renal damage (30). However, the short term vitamin supplementation was well tolerated in patients and no vitamin related side effects, including urinary stone formation were seen (27). The safety of prolonged therapy has yet to be evaluated in HD patients.

**Carnitine:** Regular carnitine supplementation in hemodialysis patients may reduce the incidence of intradialytic muscle cramps, hypotension, asthenia, muscle weakness, and cardiomyopathy (31,32). The effects of L-carnitine on relieving muscle cramps were shown in various studies, as well (31-33). In a study, hemodialysis patients suffering from hemodialysis-related symptoms were randomly assigned to receive intravenous L-carnitine 20 mg/kg and relieved of dialysis related symptoms and cramps

(34). And recently, it was recommended for daily use in hemodialysis patients (35).

**Magnezyum:** Magnesium (Mg) is a common mineral in our diets and extra oral supplements of this mineral are available. It is usually used by older adults, pregnant women and athletes for muscle cramps. study Magnesium was found beneficial in reducing both cramp frequency and cramp pain (36). Recently it is considered to use in HD patients suffering from muscle cramps. It was reported that, during one of the acute cramps 4 mEq of magnesium in the form of 10% MgSO<sub>4</sub> was administered intravenously, this brought a sudden and dramatic relief of the cramp, which did not recur during the dialysis (34). Although there are many studies about the effects of Mg on muscle cramps with patients who have normal renal functions, studies on HD patients are so limited.

**Quinine:** Quinine decreases the excitability of the motor end plate and reduces the muscle contractility. Most patients consider quinine as beneficial for their leg cramps, but Quinine should be used in a small dose and cautiously, especially in the elderly patients with renal failure, and should be avoided in patients with liver disease (4). Quinine is known to have toxicity on hematologic, renal, neurologic, cardiac, and endocrine systems and it is recommended as 325 mg at nights or 2 hours before HD session, for 10 days (37).

**Physiotherapy:** It is known that, immediate relief from cramp may be obtained by passively stretching the affected muscle (38). The use of regular stretching exercises to prevent cramps was proposed before and it was concluded that, stretching of the muscle with cramp and massage can be beneficial for muscle cramps in HD patients (39).

**The traditional herbal medicine:** The traditional herbal medicine, shao-yao-gan-cao-tang (Japanese name: Shakuyaku-kanzo-to), consists of equal amounts of paeony and licorice roots, and has been used in Japan and China for muscle cramps. To determine whether this medicine is able to prevent frequent and unendurable muscle cramps in HD patients, Shakuyaku-kanzo-to et al. administered this medicine 6 g per day prospectively for 4 weeks to five HD patients who were suffering from frequent muscle cramps. And they suggested that; administration of Shakuyaku-kanzo-to is a safe, effective treatment for preventing muscle cramps in patients undergoing HD (40).

**Creatine monohydrate:** Creatine monohydrate has been used by athletes to increase muscle mass and improve performance (41). It can increase muscle phosphocreatine stores and transfer its phosphate group to ADP when muscles need energy (42). And the muscle membrane can be stabilized and cramps reduces as muscle energy utilization is improved. Creatine monohydrate has a paradoxical importance, that can lead to muscle cramps when used in individuals with normal renal functions. (43). In a study, creatine monohydrate was given to the HD patients and found significantly decrease the incidence of muscle cramps during HD. Patients developed no anorexia, nausea, vomiting, or other uraemic symptoms in 4 weeks of creatine administration. Further long-term observation may be indicated to determine the clinical significance of elevated pre-dialysis creatinine. And the authors concluded that; Creatine monohydrate may be safe in uraemic patients, at least for short-term use (44).

In conclusion, muscle cramps during HD are important difficulties and situations disturbing the quality of life of the patients. There are many new advances to treat and prevent this common clinical problem such as minimizing interdialytic weight gain, prolonging dialysis session time to reduce ultrafiltration rate, using sodium modeling, and avoiding hypotension may reduce cramps during dialysis. They may be treated with bolus hypertonic saline or dextrose and local heating and massage of the cramped muscle. Prevention of cramps may include a trial of vitamin E. Further and long-term, large-scale studies are mandatory to confirm the effects and safety of new advances.

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