Creatine monohydrate treatment alleviates muscle cramps associated with haemodialysis

Chiz-Tzung Chang, Chin-Herng Wu, Chih-Wei Yang, Jeng-Yi Huang and Mai-Szu Wu

Department of Nephrology, Chang Gung Memorial Hospital, Taipei, Taiwan

Abstract

Background. Muscle cramp is a common complication of haemodialysis. The exact mechanism of this complication is still unknown. Many approaches have been used to relieve the muscle cramping but have had variable effects. One of the possible mechanisms of haemodialysis-associated muscle cramps (HAMC) is the disturbance of muscle energy metabolism. Creatine monohydrate can enhance muscle metabolism. We evaluated the clinical effect of creatine monohydrate on HAMC.

Methods. Ten patients with frequent muscle cramps during haemodialysis were randomly selected into two groups, control and placebo. In a double-blind manner, 12 mg of creatine monohydrate or placebo was given to each patient before each dialysis session for 4 weeks. The incidence of muscle cramp during haemodialysis was compared between the two groups. Dialysis adequacy, haemodynamic status, and side-effects were also evaluated. We continued to observe and compare the patients during a 4-week washout period to verify the effect of creatine monohydrate.

Results. The frequency of symptomatic muscle cramps decreased by 60% in the creatine monohydrate treatment group (6.2 ± 0.8 vs 2.6 ± 1.8 times/4 weeks, P < 0.05) during the treatment period. This decreasing incidence of muscle cramps disappeared in the washout period in the creatine group (6.6 ± 1.1 times/4 weeks). There was no difference in the incidence of muscle cramps in the placebo group. The haematocrit, Kt/V, serum albumin, and haemodynamics remained unchanged in both groups during the treatment and washout periods. Serum creatinine increased slightly after creatine monohydrate treatment (10.7 ± 3.2 vs 12.4 ± 3.2 mg/dl, P < 0.05). No adverse effect was found in either group during the treatment and washout periods.

Conclusion. These data suggest that creatine monohydrate can reduce the incidence of HAMC and that it may be a safe agent.

Keywords: creatine monohydrate; haemodialysis; muscle cramps; muscle metabolism; placebo control; single-unit study

Introduction

Painful muscle cramps often complicate haemodialysis. They may occur in 35–86% of haemodialysis patients [1] and can be severe enough to compromise haemodialysis treatment [2]. The exact mechanism of intradialysis muscle cramping is still unknown, and a number of palliative measures have been employed without consistent effects [3]. Subnormal muscle metabolism is thought to be one of the major mechanisms underlying these muscle cramps [4]. Excessive dialysis ultrafiltration, intradialytic hypotension, or tissue hypoxia may lead to an abnormal utilization of energy by muscles and thus result in muscle cramps [5]. Creatine monohydrate has been used to increase muscle strength and work performance in elite athletes [6]. It may cause better muscle metabolism by increasing muscle creatine phosphate stores. Creatine phosphate can release a phosphate group to ADP and turn it into ATP [7], which is the major source of muscle energy. With those facts in mind, one might ask if administration of creatine monohydrate could alleviate the haemodialysis-associated muscle cramps (HAMC). To answer that question, we conducted a prospective randomized study to examine the effect of oral creatine monohydrate on HAMC.

Subjects and methods

Our cohort comprised 10 patients who were on maintenance haemodialysis in a single dialysis unit in University Hospital.
and one-way ANOVA. We used the SPSS™ program for statistical analysis. A $P$ value $<$0.05 was considered significant.

Results

The baseline haemodynamic and biochemical parameters before creatine monohydrate or placebo treatment were similar in both groups (Table 1). No increase in dry weight was found in the creatine group after creatine monohydrate treatment (before vs after: 63.9 ± 18.3 vs 63.9 ± 18.3 kg, $P >0.05$). There was no significant change in the pre-dialysis blood pressures and ultrafiltration rates. The occurrence of a hypotensive episode was slightly decreased in the creatine group, but without statistical significance (control vs creatine: 7.2 ± 1.8 vs 5.8 ± 2.6 times/4 weeks, $P >0.05$). These results indicate that short-term oral creatine monohydrate intake did not induce significant haemodynamic changes during haemodialysis. The $Kt/V$, serum albumin, and haematocrit did not change in the groups either before or during the treatment (Table 1). The data suggested that creatine monohydrate did not influence the prescribed dialysis dosage, nutritional status, and erythropoiesis in our patients. The episodes of muscle cramps were decreased by 60% during the treatment period in the creatine group (control vs creatine: 6.4 ± 0.9 vs 2.6 ± 1.8 times/4 weeks, $P <0.05$). We did not observe any decrease in cramps in the placebo group (control vs placebo: 6.6 ± 1.1 vs 6.2 ± 0.8 times/4 weeks, $P >0.05$) (Figure 1). Serum creatinine increased by 16% in the creatine group (control vs creatine: 10.7 ± 3.2 vs 12.4 ± 3.2 mg/dl, $P <0.05$) (Table 1). The increase in serum creatinine was not associated with anorexia, nausea, vomiting, or other uraemic symptoms.

To further confirm that the observed effect comes from creatine, we continued to follow the patients after treatment (washout period) for an additional 4 weeks, considered as a washout period. During that 4-week washout period, the incidence of muscle cramps in the creatine group decreased to previous levels (6.4 ± 0.9 times/4 weeks, $P <0.05$). There was no significant change in the pre-dialysis blood pressures and ultrafiltration rates. The occurrence of a hypotensive episode was slightly decreased in the creatine group, but without statistical significance (control vs creatine: 7.2 ± 1.8 vs 5.8 ± 2.6 times/4 weeks, $P >0.05$). These results indicate that short-term oral creatine monohydrate intake did not induce significant haemodynamic changes during haemodialysis. The $Kt/V$, serum albumin, and haematocrit did not change in the groups either before or during the treatment (Table 1). The data suggested that creatine monohydrate did not influence the prescribed dialysis dosage, nutritional status, and erythropoiesis in our patients. The episodes of muscle cramps were decreased by 60% during the treatment period in the creatine group (control vs creatine: 6.4 ± 0.9 vs 2.6 ± 1.8 times/4 weeks, $P <0.05$). We did not observe any decrease in cramps in the placebo group (control vs placebo: 6.6 ± 1.1 vs 6.2 ± 0.8 times/4 weeks, $P >0.05$) (Figure 1). Serum creatinine increased by 16% in the creatine group (control vs creatine: 10.7 ± 3.2 vs 12.4 ± 3.2 mg/dl, $P <0.05$) (Table 1). The increase in serum creatinine was not associated with anorexia, nausea, vomiting, or other uraemic symptoms.

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There were no observed side-effects such as nausea or vomiting during the 4-week treatment period. No nausea and vomiting appeared during the 4-week
Serum GPT levels were the same before and during creatine monohydrate treatment (15.5 ± 3.6 vs 14.4 ± 2.7 IU/l). Four of the five patients in the creatine group asked to continue the creatine monohydrate treatment after the end of the study.

**Discussion**

Muscle cramp is one of the most common and uncomfortable complications experienced during haemodialysis. The exact mechanism of these muscle cramps is still unknown. It is often associated with intradialytic hypotension, excessive ultrafiltration, or elevation of serum creatine kinase [10]. The acute management of this painful complication has included hypertonic glucose, saline, or mannitol with inconsistent and variable effects [11]. Higher dialysate sodium concentrations also reduce the incidence of HAMC. Profiling of dialysate sodium and bicarbonate also reduces cramping significantly [2,5]. Long-term administration of vitamin E [11], quinine [11], and l-carnitine [12] have also been used to decrease the cramp but with equivocal results. These agents have in common the effects of increasing muscle energy usage and strength. ATP splits into ADP and phosphate and liberates the energy for muscle work. Abnormal muscle energy metabolism with subsequent lactic acid formation may be the cause of muscle weakness and painful muscle cramping [13].

Creatine monohydrate has long been used by elite athletes to increase muscle mass and improve performance [14]. It can increase muscle phosphocreatine stores and transfer its phosphate group to ADP when muscles need energy [15]; the need for anaerobic generation of ATP via the lactate pathway will be decreased [16], and the muscle membrane can be stabilized and cramps reduced as muscle energy utilization is improved [17].

In our study, creatine monohydrate significantly decreased the incidence of HAMC. There was no differences in dry weight, pre-dialysis blood pressure, ultrafiltration rate, and hypotension episodes in the creatine group before treatment or during the treatment, and washout periods. Haemodynamic factors were identical in the two groups. The results indicate that haemodynamic change did not play a role in the observed effect of creatine on muscle cramping. We believe that the reduction in muscle cramping may come from better utilization of energy in the muscle.

Paradoxically, creatine monohydrate can lead to muscle cramp when used in individuals with normal renal function. The possible mechanism of that side-effect is the change of cell volume induced by creatine. Creatine may enter muscle cells and increase intracellular osmolality. The accumulation of creatine within muscle cells leads to fluid shift from the extracellular compartment to intracellular spaces. The resulting shrinkage of extracellular fluid volume causes muscle cramping [18]. This volume-shifting mechanism might be compromised during haemodialysis by the concomitant controlled ultrafiltration, which simultaneously increases extracellular osmolality and decreases extracellular fluid.

Serum creatinine may increase in patients with renal insufficiency who take creatine monohydrate [19]. There was a small increase in serum creatinine levels in our patients. However, they 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. There were no changes in liver enzymes and serum albumin during 4 weeks of treatment, which may indicate the absence of hepatic side-effects as reported in the literature [20]. Creatine monohydrate may be safe in uraemic patients, at least for short-term use.

We conclude that creatine monohydrate might be used for the treatment of HAMC and that in the short-term this agent is safe for patients on maintenance haemodialysis. However, the number of our patients was small and the follow-up period short. Further
long-term, large-scale studies are mandatory to confirm the effects and safety of creatine monohydrate therapy in HAMC.

References


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