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Original Article

The Effect of Gabapentin on Muscle Cramps during Hemodialysis: A Double-blind Clinical Trial

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ABSTRACT. Hemodialysis-associated muscle cramps (HAMC) are a common complication during hemodialysis (HD) sessions. A number of pharmacologic agents have been evaluated to prevent and or diminish HAMC; however, none of them has an established role. To the best of our knowledge, this is the first study to evaluate the possible effect of gabapentin on HAMC. In a double-blinded clinical trial, we compared the possible effect of gabapentin with a placebo in prevention and or diminishing episodes of HAMC in HD patients who had experienced frequent intradialytic muscle cramps. At first, placebo was given before each dialysis session for four weeks and then, after a two-week washout period, 300 mg of gabapentin was given before each dialysis session for four weeks to verify the effect of gabapentin on HAMC. Overall, 15 patients (seven men and eight women; mean age, 52.02 years) with frequent intradialytic muscle cramps were enrolled in the study. The incidence of symptomatic muscle cramp decreased in the gabapentin group compared with the placebo group, with a significant difference between them (P = 0.001). The intensity of muscle cramps also decreased in the gabapentin group (P = 0.001). There was no significant association between HAMC in male and female patients (P = 0. 397), mean age of HD patients (P = 0.226) and cause of end-stage renal disease (P = 0.551). According to the results of our study, gabapentin prescription before each HD session significantly reduced the frequency and the intensity of muscle cramps during HD without any major side-effects.

Introduction

Although life expectancy and survival of patients with end-stage renal disease (ESRD) has improved since the introduction of hemodialysis (HD) in the early 1950s, many complications with multiple and poorly understood underlying mechanisms commonly occur during HD treatment. Some of them include hemodialysis-associated muscle cramps (HAMC), hypotension during HD, ventricular and supraventricular arrhythmias, nausea and vomiting, chest and back pain, headache,

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itching, allergic reactions to dialyzer or medications and fever and chills.[1-6]

Muscle cramps are prolonged involuntary and often painful contraction of the muscles that often occur in the muscles. They are common in adults and almost everyone experiences a muscle cramp at some time in their life. Muscle cramps are also an important and common complication of HD that occur in about 35–80% of HD patients.[7-9] It most commonly involves the muscles of the lower limb; however, other muscles including the hands, arms and abdomen may also be affected during HD. The severity of cramps occurring with dialysis treatment may be very high and therefore it has a significant negative impact on health-related quality of life among HD patients. In some patients, it can be severe enough to necessitate discontinuation of HD and it is reported as the most common cause of stopping HD and a significant cause of underdialysis.[7-9]

Different strategies and number of pharmacologic agents have been evaluated to prevent and/or diminish the severity of HAMC; however, because of a small number of comparative studies having conflicting results, there are no generally accepted guidelines for the prevention of muscle cramps during HD.

The aim of this study was to evaluate the possible effect of gabapentin for the prevention of HAMC episodes and/or diminishing the severity of muscle cramps during HD.

Materials and Methods

Study design

The study was a cross-sectional, double-blind, and controlled clinical trial that was approved by the Ethics Committee of the Chronic Renal Failure Research Center of the Ahvaz Jundishapur University of Medical Sciences.

We used a standardized questionnaire to collect general information such as age, gender, vital signs, causes of ESRD, date of onset of HD and length of time receiving HD services, the record of previous drugs and the incidence and intensity of intradialytic muscle cramps.

A muscular cramp episode was defined as a painful involuntary muscle contraction that lasted for more than 1 min during HD.

The drug and placebo were provided to the patients free of cost by the Chronic Renal Failure Research Center. The period of study was four months from March 2011 to August 2011. The nature of the clinical trial was explained to the HD patients and written informed consents were obtained from them. The goal of the study was reduction of the HAMC episodes. Primary end points of the study were prevention of HAMC episodes and/or diminishing the severity of muscle cramps during HD.

Patients

The study was performed on ESRD patients who were undergoing HD treatments at the Imam Hospital, Ahvaz, Southwestern Iran. ESRD was defined as permanent and irreversible advanced loss of kidney function due to any cause with creatinine clearance <10–15 mL/min/1.73 m^2 requiring maintenance HD therapy.

All HD patients were monitored for one month and patients with six episodes of intradialytic muscle cramp per month or more were included in the study and those with the following characteristics were excluded: Electrolyte disturbance, hemodynamic instability during HD and patients who had used other preventive measure for prevention of muscle cramp such as vitamin E, benzodiazepine, quinine sulfate, hypertonic sodium and or bicarbonate solution.

Drug administration

This study was performed in three stages:

1. Placebo administration (1 month) in the first month of the study.
2. Washout period (2 weeks later).
3. Gabapentin administration (1 month after the washout period).

By using a double-blind protocol, placebo and 300 mg gabapentin was administrated to patients 5 min before starting HD. The occurrence of painful muscle cramp episodes and severity of this complication was recorded

during these three stages. Severity of HAMC recorded was based on numerical measurement by asking patients (0 = painless, 10 = severe pain).[10] To make sure that any changes observed were related to the administration of gabapentin, this drug was administrated during the third stage.

Hemodialysis methods

HD was performed for 9–12 h, three or four times a week using Fresenius machines. We used synthetic (polysulfone) dialyzer membranes and bicarbonate-buffered dialysate for all our patients. The other characteristics of dialysate were sodium 135–140 mmol/L, potassium 2 mmol/L and calcium 1.5 mmol/L, magnesium 0.5 mmol/L and bicarbonate 35–40 mmol/L. Blood flow rate and dialysate flow rate were maintained at 250–400 mL/min and 500 mL/min, respectively. Dialysate temperature was 36.58°C (97.84°F) during HD. The rate of ultrafiltration during each HD session was determined individually by the nephrologist according to clinical evaluation.

Statistical analysis

Results are expressed as mean ± SD. Difference between two stages (gabapentin and placebo administration) was analyzed by Student's paired T test. We used the SPSS version 15 software for statistical analysis. A *P*-value <0.05 were considered significant.

Results

Patients in this study consisted of eight females and seven males, with an average age of 52.02 years. No patients expired during this study. The cause of end-stage renal dialysis in eight subjects was hypertension, diabetes mellitus in three subjects and glomerulonephritis in four subjects. Frequency of dizziness, nausea, stupor and ataxia was not increased during the gabapentin period and the drug was tolerated very well.

The data gathered from the query forms were analyzed using the SPSS program. Before applying any kind of data analyzing test, the normality of distribution of our test group was verified. By using the one-sample Kolmogorov–Smirnov test, the normality of distribution was rejected (P = 0.392, SD = 1.207). Therefore, we used non-parametric tests.

Based on the results of two related sample tests after one month of gabapentin prescription, the frequency of muscle cramp episodes decreased between 20% and 100% in all subjects.

The test result (P <0.001) showed a significant difference in the frequency of muscle cramps. Five patients (30%) became totally symptom free. Relatively speaking, in 93.3% of the subjects, muscle cramp frequency was decreased by more than 60%. The frequency of muscle cramp episodes is shown in Table 1.

Based on the results of two related samples test (sign test) during the gabapentin period, the intensity of muscle cramps in all test subjects was decreased (P <0.001) (Table 2). The frequency and variance of muscle cramp intensity is shown in Table 3. Test subjects had shown a 12–100% decrease of the muscle cramp intensity during the gabapentin period.

Difference in frequency (P = 1.00) and intensity (P = 0.581) of muscle cramps between placebo periods and before treatment were tested and there was no significant difference.

Discussion

Muscle cramps cause a lot of physical and psychological problem in HD patients. Although pathogenesis and exact mechanism of HAMC

Table 1. The frequency of muscle cramp episodes during placebo and gabapentin periods.

	No. of patients	Minimum cramp episodes	Maximum cramp episodes	Mean	Std. deviation	Variance
F_1	15	4.00	9.00	6.7333	1.83095	3.352
F_3	15	0.00	4.00	1.2000	1.20712	1.457

F_1 = frequency of muscle cramp during the placebo period.

F_3 = frequency of muscle cramp during the gabapentin period.

Table 2. Comparison of muscle cramp intensity during the placebo and gabapentin periods.

		No. of patients
Average of muscle cramp intensity in the gabapentin period compared with the average of muscle cramp intensity in the placebo period	a. Negative differences	15
	b. Positive differences	0
	c. Ties	0
	Total	15

a. Average of intensity in the gabapentin period < average of intensity in the placebo period.
b. Average of intensity in the gabapentin period > average of intensity in the placebo period.
c. Average of intensity in the gabapentin period = average of intensity in the placebo period.

Table 3. Average of muscle cramp intensity during the placebo and gabapentin periods.

	No.	Mean	Std. deviation	Minimum	Maximum
Average of intensity in the placebo period	15	4.62	6.83	5.7260	0.72899
Average of intensity in the gabapentin period	15	0.00	6.00	2.7887	2.19332

are still unknown, one or more of the following factors including hypovolemia, hyponatremia, tissue hypoxia, hypomagnesemia, carnitine deficiency and elevated serum leptin levels may be implicated in the development of intradialysis muscle cramping.

Because HAMCs occur most frequently near the end of the HD session, it seems that from the above factors, plasma volume contraction and changes in plasma osmolality, either alone or in combination, are the most likely underlying mechanisms of this complication.[10-16]

Treatment of cramps occurring during dialysis treatment is aimed at two goals: (i) possible interventions to prevent the cramps and (ii) reduction of the frequency of cramps and relieving symptoms when they occur.[17]

According to the important role of hypovolemia and changes in plasma osmolality in the development of muscle cramp during HD, strategies such as the prevention of dialysis-associated hypotension, the minimization of interdialytic weight gains to avoid high rates of ultrafiltration required to achieve the patient's dry weight during HD and the use of high concentrations of sodium in the dialysate are the more generally accepted measures for prevention of HAMC.[9,17-20]

However, in a substantial number of patients, HAMCs are not completely prevented by these strategies. In addition, these measures cannot be used in many patients, especially in those patients who are in need of ultrafiltration during HD.[17] Therefore, it is necessary to evaluate some other strategies and pharmacologic agents for the prevention or reduction of the frequency of dialysis-associated cramps.

Gabapentin, a structural analogue of GABA, is a new and safe anticonvulsive drug that is also used for a variety of different conditions. It has been demonstrated that gabapentin reduces neuropathic pain while also decreasing abnormal neural excretion and increasing verge of nerve activation.[21] In the management of neuropathic pain, gabapentin is an attractive therapeutic option compared with other anticonvulsants, tricyclic antidepressants and opioids because of its relative lack of interactions and serious adverse effects.

Small studies have also suggested that gabapentin is also effective for muscle cramps.[22] However, to the best of our knowledge, we did not find any study that had evaluated the possible effect of gabapentin on HAMC among HD patients.

Our study shows that gabapentin at a dose of 300 mg orally 5 min before starting HD can significantly reduce the frequency of muscle cramp episodes during HD between 20% and 100% in all subjects. In addition, the data from our clinical trial also showed that the intensity of muscle cramps is decreased by the use of gabapentin.

In a small, open-label clinical trial, Mariano

et al evaluated the efficacy and safety of gabapentin among 30 non-uremic patients with frequent (>5 cramps/week) and long-lasting muscle cramps. They found that a dose of 600 mg/d of gabapentin is effective in reducing the frequency and severity of muscle cramps within two weeks. After three months of therapy with a mean dosage of 892 ± 180 mg, muscle cramps disappeared in all of the patients and the therapeutic effect of gabapentin persisted as long as six months.[22]

In comparison to the Mariano et al study, the dosage of gabapentin used in our trial was at a lower dosage. We administered the drug at a dosage of 300 mg only three times a week 5 min before starting HD. The elimination half-life of gabapentin is 5–7 h, and it is eliminated unchanged from the systemic circulation by renal excretion.[23-26] Among patients undergoing HD, especially in anuric subjects, the elimination half-life is increased to about 132 h on non-HD days.[27] Therefore, the dosage of gabapentin, as we did, should be reduced among patients with compromised renal function or those undergoing dialysis.

In our study, gabapentin was well tolerated and was not associated with any side-effects. It appears that it may be due to the time of administration of gabapentin in our study (before each HD). Although the elimination half-life of gabapentin is very long in uremic patients, HD has a significant effect on gabapentin elimination and the apparent half-life is reduced to 3.8 h during dialysis days.[27]

Although gabapentin did not induce any reported adverse effect in our trial, it is known to be associated with a few side-effects, including somnolence, dizziness, asthenia, ataxia and fatigue.[28,29] As an example, by reviewing data from controlled clinical trials, Ramsay reported that the most common side-effects of gabapentin are somnolence, dizziness, asthenia, ataxia and fatigue, which occurred in 20%, 18%, 13% and 11% of patients, respectively.[28]

In a large open-label multicenter study, McLean et al evaluated the tolerability and safety of gabapentin as an adjunctive therapy for seizure control among 2216 patients during a period of 16 weeks. They showed that gabapentin can induce somnolence, dizziness and asthenia in 15.2%, 10.9% and 6.0% of patients, respectively. The most serious adverse effect of gabapentin in the study of McLean et al was convulsions, which occurred in 0.9% of patients.[29]

In addition to the above-mentioned side-effects, case reports have suggested that gabapentin may cause reversible acute renal allograft dysfunction by a mechanism involving renal afferent vasoconstriction and serious skin eruptions such as Stevens–Johnson's syndrome.[30,31] This is a valuable information to be kept in mind by the nephrologists while treating post-renal transplant patients.

Conclusion

HAMCs are an important and common complication of HD having a significant negative impact on health-related quality of life among HD patients.

Our study shows that gabapentin, a new and safe anticonvulsive drug at a dose of 300 mg orally 5 min before starting HD, can significantly reduce the frequency and the intensity of muscle cramps during HD without any major side-effects. Although the results of our study are interesting, our study is limited by the short duration and small number of patients enrolled in the study. In addition, our study was a single-center study. Multi-center clinical trials with a longer duration and larger number of patients are needed to further evaluate the effect of gabapentin for the prevention and reduction of the intensity of muscle cramps during HD.

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