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Research Article

Evaluation of the Effect of Gabapentin in Management of Uremic Pruritus in Hemodialysis Patients

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Abstract

Background: Gabapentin is an antiepileptic agent that has analgesic properties in neuropathic pain. Given that few studies have assessed the effect of low dose of gabapentin on uremic pruritus, this study aimed to evaluate the effect of gabapentin on pruritus of hemodialysis patients.

Materials and Methods: This clinical trial study was conducted on dialysis patients who referred to Shafa hospital, Kerman. In this regard, 40 patients consumed 100 mg gabapentin for one week. Then patients did not take any medication within washout period and consumed 100 mg placebo for one week. Assessment of pruritus severity was done by visual analogue scale (VAS). Hematocrit, calcium, phosphor, creatinine and albumin were evaluated. These measurements were done before and after treatments with placebo and gabapentin.

Results: The main places of pruritus location in dialysis patients were back (90 %), abdomen (80%), shoulder (80%), and head (70%). The mean pruritus severity before treatment, after treatment with placebo and gabapentin was 8.3± 1.5, 6.73 ± 1.17 and 4.58 ± 1.50, respectively. Significant difference was seen before and after treatment, in terms of pruritus severity ($p<0.1$). In addition, there was significant difference between gabapentin and placebo groups, regarding severity of pruritus ($p<0.1$). No significant difference was seen before and after treatment, regarding biochemical parameters ($p>0.05$).

Conclusion: According to findings, it seems that gabapentin can be an effective and safe treatment for pruritus of patients on hemodialysis. The therapeutic approach chosen for these patients is based on the neuropathic hypothesis.

Keywords: abdominal trauma; hemoperitoneum; pancreas trauma

Introduction

Uremic pruritus is an ordinary and serious symptom for patients with renal failure. It is a dermal disorder experienced by patients who suffer from chronic and progressive renal failure (1-3). More than half of patients under dialysis including hemodialysis or peritoneal dialysis and nearly 30% of the sick individuals with kidney failure who are not under hemodialysis complain of pruritus (4). Pruritus may be classified to peripheral including neuropathic and dermal, central including psychogenic, neuropathic, neurological or mixed origins. Although the incidence of pruritus is common, there is little knowledge on laboratory and clinical findings (1).

Moreover, the mechanism of uremic pruritus is not clear (1). Various hypotheses have been suggested to illustrate the pathogenesis of uremic pruritus. Factors including involvement of peripheral nervous system (1) may also be played. So far various treatments with different mechanisms were proposed, however, neither treatment was able to cure this debilitating complication (1, 5).

Gabapentin is a powerful anticonvulsant drug (6،7) and has a similar structure to gamma aminobutyric acid neurotransmitter (8-11). The mechanism of action is unclear (6). This drug was initially approved only for use in the control of seizures (6). It was soon used in the treatment of chronic pain syndromes, particularly neuropathic pain (6). Since pain and pruritus have same mechanism and gabapentin is effective for treating neuropathic pain, the use of gabapentin may be appropriate to treat pruritus in patients on hemodialysis (12). It seems that the efficacy of gabapentin on uremic pruritus is through the neural calcium channels (1, 13).

In addition, gabapentin is removed primarily via the kidney. It is also eliminated by hemodialysis. The use of this medication was associated with longer half-life in patients on hemodialysis compared to those with normal kidney function; therefore, these patients require lower doses at less frequent intervals compared to patients with normal kidney function. In addition, accumulation of gabapentin in plasma and diffusion to

cerebrospinal fluid in patients with renal insufficiency has been also observed (12).

The proposed dose of gabapentin for stabilization the serum level of hemodialysis patients is 200-300 mg for every dialysis session. However, doses of 100 mg have also been suggested to reduce the risk of neurotoxicity (14-17). Given that few studies have assessed in this regard and the effect of gabapentin with dose of 100 mg on uremic pruritus, this study aimed to evaluate the effect of 100 mg gabapentin on uremic pruritus of hemodialysis patients.

Materials and Methods

This clinical trial study was conducted on dialysis patients who referred to Shafa hospital, Kerman, Iran to evaluate gabapentin efficacy on pruritus of hemodialysis patient. Current study was ratified by medical ethics committee of Kerman University.

Inclusion and exclusion criteria were as following.

Inclusion criteria

- Age range between 18- 80 years old.
- Absence of liver disease.
- Absence of skin diseases associated with pruritus.
- No use of antacids.

Exclusion criteria

- Incidence of side effect.
- Patient dissatisfaction.
- Not taking medication.
- Taking antihistamin or other medication for treating their purities other than gabapentin.

At beginning the study, 50 patients with dialysis were chosen. After evaluation of inclusion and exclusion criteria, 40 dialysis patients were entered to study. In this regard, patients consumed 100 mg gabapentin for one week. Then patients did not take any medication within washout period and in the next step consumed 100 mg placebo for one week (size and color were similar to medication). Assessment of pruritus severity was done by visual analogue scale (VAS). It as a psychometric measuring tool was developed to document the features of disease- symptom. VAS records severity of pruritus scores on a 0 to 10.

After taking blood from patients, hematocrit (HCT) was assessed by electrical impedance method Sysmex k-1000 instrument. After separating serum via eppendorf centrifuge, parameters including calcium (Ca), phosphor (P), creatinine (Cr), and albumin were evaluated before and after treatment (gabapentin and placebo groups) through Pars Azmoon Kit. These measurements were done at the end of each of three phases.

In addition, data including age, sex, duration and cause of dialysis were extracted from medical records.

Statistical analysis

Data were entered to SPSS, version 19. Friedman test and willcoxon signed ranks test were used for analysis of data. $P<0.05$ was considered statistically significant.

Results

In current study, the age range of patients was 30-75 years with mean age 59 ± 13.05 years old. The mean duration of dialysis was 30.4 ± 35 months. Among patients, 40 % were female and 60% male. The most important cause of dialysis in patients was diabetes (50%), hypertension (HTN) (10%), infection (10%), kidney stone (10%) cyst (10%) and no cause (10%). Table 1 shows location of pruritus in dialysis patients.

Location of pruritus	Number (percent)
Head	32 (80)
shoulder	32 (80)
Back	36 (90)
Hand	28 (70)
Foot	28 (70)
Face	20 (50)
Abdomen	32 (80)
Chest	24 (60)

Table 1: Pruritus location in dialysis patients

As shown in Table 1, the main places of pruritus location in dialysis patients was back (90 %), abdomen (80 %), shoulder (80 %), and head (70 %). Comparison of patients in 3 groups in terms of parameters including calcium, phosphor, creatinine, hematocrit and albumin is shown in **Table 2.**

Variables	Mean± SD (Before treatment)	Mean± SD (After treatment)	
		Gabapentin group	Placebo group
Calcium (mg/dl)	8.9 ± 0.6	9.30 ± 0.58	9.2 ± 0.7
Phosphor (mg/dl)	5.6 ± 2.2	5.7 ± 2.08	5.3 ± 1.9
Creatinine (mg/ dl)	9.29 ± 3.56	8.81± 4.27	8.50 ± 3.8
Hematocrit (%)	35.7 ± 5.4	38.5 ± 5.10	39.1 ± 6.3
Albumin (gr/dl)	3.53 ± 0.7	3.3 ± 0.48	3.7 ± 0.62

Table 2: Comparison of patients before and after treatment in terms of parameters including calcium, phosphorous, creatinine, hematocrit and albumin

As demonstrated in Table 2, no significant difference was seen before and after treatment, regarding variables including calcium, phosphor, creatinine, Hematocrit and albumin ($p>0.05$).

The severity of pruritus in patients before and after treatment is shown in **Table 3.**

Variable	Mean	Minimum	Maximum	p-value
Before treatment	8.3 ± 1.5	7	10	0.005
Treatment with gabapentin	4.58 ± 1.50	1.86	6.43	
Treatment with placebo	6.73 ± 1.17	4.89	8.57	

Table 3: The mean pruritus severity in patients before and after treatment

As shown in Table 3, significant difference was seen before and after treatment, in terms of pruritus severity ($p<0.005$). In addition, there was significant difference between gabapentin and placebo groups, regarding severity of pruritus ($p<0.005$).

Discussion

Pain and pruritus are associated with undesirable sensations which reduce quality of life in these patients (12). The sensation of pruritus and pain motivates a same pattern of cortical areas of the brain including the motor cortex; but, no central itch center has been recognized (18). When a pruritogen innervates unmyelinated C-nerve fiber endings, pruritus occurs, which is anatomically same to pain way. After stimulating the C-nerve fibers, impulses were transferred to the dorsal horn of the spinal cord, finally activate the somatosensory cortex and translate to sensation of pruritus (19). Pruritus can be divided to 2 types; peripheral (pruritoceptive) and central (20, 21). It is postulated that combination of neuropathic and neurogenic origin are involved. The neuropathic assumption is that the peripheral nerve damage caused via neuropathy which happens in more than 65% of patients under hemodialysis, leads to reduce threshold of perception (12).

In current study, the mean pruritus before treatment, after treatment with placebo and gabapentin was 8.3 ± 1.5, 6.73 ± 1.17 and 4.58 ± 1.505, respectively. In addition, there was significant difference between gabapentin and placebo groups, regarding severity of pruritus. It seems that gabapentin can be useful for pruritus therapy.

Gunal et al., assessed the use of gabapentin for treatment of pruritus in hemodialysis patients (6). They enrolled 25 patients under hemodialysis and randomly assigned them to two groups. One group consumed gabapentin for 4 weeks and other group placebo for 4 weeks. Severity of pruritus was measured by visual analogue scale. These findings showed that mean pruritus score before treatment, after placebo and gabapentin administration was 8.4 ± 0.94, 7.6 ± 2.6 and 1.2 ± 1.8, respectively. They concluded that gabapentin can be considered as a safe and effective medication to treat pruritus in hemodialysis patients. The findings of this study were consistent with our study. It is noteworthy that gabapentin was impressive in all patients, except one. It may be due to that majority of cases had neuropathic origin and minority of them had neurogenic origin. It indicates that one or both of mechanisms such as neuropathy and neurogeny are involved.

Vila et al., evaluated the role of gabapentin in treatment of pruritus and reported gabapentin as effective option. They also reported that gabapentin seems to be well-tolerated secondary therapy option for patients with pruritus who did not respond to conventional therapy. In addition, they suggested a dose of 100- 300 mg gabapentin (12). Maciel et al., assessed the effectiveness of gabapentin in treatment of pruritus. In this regard, 20 patients with pruritus were treated with 300 mg gabapentin. The findings showed that the use of gabapentin is responsible for a significant reduction of pruritus. It seems that gabapentin is a beneficial option for cure of severe pruritus caused by nostalgia paresthetica (9). Gunal et al., assessed the effect of gabapentin for pruritus in hemodialysis patients. The findings showed that the mean score of pruritus before the study was 8.4 ± 0.94. The mean score of pruritus after taking placebo and intervention was 7.6 ± 2.6 and 1.2 ± 1.8, respectively. According to findings of this study, gabapentin is an effective and safe medication for curing pruritus in hemodialysis patients, in accordance of our study. These findings supported the neuropathic hypothesis of pruritus in these patients (6).

Razeghi et al., evaluated the efficacy of gabapentin in uremic pruritus in patients undergoing hemodialysis. In this regard, 100 mg gabapentin were given in each session of hemodialysis for four weeks. In the next step, placebo was given for these patients for 4 weeks. Between two treatment phases, one week was assigned as washout period and VAS score recorded. The findings showed that the mean pruritus score was 6.44 ± 8.4, 15 ± 11.2 and 81.11 ± 11.07 during gabapentin taking, washout, and placebo phases, respectively. Based on findings of this study, gabapentin is an effective agent for treating pruritus (1). In addition, administration of 100 mg gabapentin was more preferable than 300 mg, because of more cost-beneficial and fewer complications.

Naini et al., evaluated the effect of gabapentin in treatment of hemodialysis patients with pruritus (22). These patients consumed 400 mg gabapentin and placebo for 4 weeks. Efficacy was measured with a VAS score (0-10). The mean score of VAS at base line was 7.2 ± 2.3. Moreover, the mean score of VAS in placebo and gabapentin groups was 6.7 ± 2.6 and 1.5 ± 1.8, respectively. These findings indicate the decrease of pruritus after intervention than placebo. Lau et al., assessed the effect of gabapentin for pruritus in hemodialysis patients and reported that dose of 100 mg gabapentin after hemodialysis decrease adverse events in these patients (23). Based on findings of this study, gabapentin is a promising medication for the treatment of uremic pruritus. However, further studies are needed to establish the appropriate dosing in patients on hemodialysis.

In addition, there was no significant difference between 3 groups (before treatment and after treatment), regarding calcium, phosphor and creatinine in our study. Freethi et al., reported that the mean values of creatinine, calcium and phosphorus in patients with chronic kidney disease were 4.9 ± 2.23 mg/dl, 9.8 ± 0.456 mg/dl and 4.19 ± 0.404 mg/dl respectively, which was higher than control group (24). The difference between our study in comparison to Freethi study was absence of control group. Moreover, we used gabapentine medication, while Freethi et al., and did not use any intervention. Gunal et al., assessed the efficacy of gabapentin for treatment of pruritus in hemodialysis patients. The findings showed that there was no significant difference before and after treatment, regarding plasma levels of phosphate, calcium, albumin, dialysis efficiency and parathyroid hormone which were consistent with our study (6). Considering chronic hemodialysis, a relation was seen between serum chemical biomarkers including serum phosphorous, calcium, and calcium-phosphor product with survival of patient individuals. They reported that a suitable level of calcium- phosphor product may recover the survival of patients on chronic hemodialysis (25), however, we did not consider survival of hemodialysis patients.

Furthermore, the main place of pruritus location in dialysis patients was back. Maciel et al., assessed efficacy of gabapentin in pruritus therapy and reported that the most common symptoms in these patients was pruritus, macula on the back, and back pain (9). Simon et al., reported that back, face, and arms are the most localized itch (26).

Conclusion

According to findings of current study, it seems that gabapentin can be an effective and safe treatment for pruritus of patients on hemodialysis. The therapeutic approach chosen for these patients is based on the neuropathic hypothesis.

Conflict of interest

There is no conflict of interest.

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