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The Effects of Gabapentin Therapy on Pruritus, Quality of Life, Depression and Sleep Quality in Pruritic Hemodialysis Patients

Kaşıntılı Hemodiyaliz Hastalarında Gabapentin Tedavisinin Kaşıntı, Yaşam Kalitesi, Depresyon ve Uyku Kalitesine Etkisi

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Objectives: We aimed to determine possible changes in pruritus, quality of life, depression and sleep quality in pruritic hemodialysis (HD) patients with gabapentin therapy.

Patients and Methods: Fourteen adult HD patients (7 men, 7 women; mean age 59.7±17.2 years; range 41 to 88 years) with history of pruritus of more than eight weeks were assigned to receive 8-week gabapentin (300 mg per day) therapy. The daily pruritus were recorded using visual analogue scale for each period of the study during one week preceding the trial, the active treatment phase, the placebo phase and the intervening 1-week washout period. Sleep quality was determined with a modified post-sleep inventory, quality of life with a short form of Medical Outcomes Study (SF-36), depression using the Beck Depression Inventory.

Results: The mean pruritus score and total of post-sleep inventory were decreased significantly with gabapentin therapy (p=0.01 and p=0.002 respectively). Physical and mental component scales of SF-36 increased, whereas cognitive and somatic depression index decreased with gabapentin.

Conclusion: We concluded that beneficial effects of gabapentin therapy on pruritus, quality of life, depression and sleep quality are clinically important in HD patients with pruritus. Gabapentin therapy should be taken into account as an important choice of therapy in pruritic HD patients.

Key words: Gabapentin; pruritus; quality of life; hemodialysis.

Amaç: Gabapentin tedavisi ile kaşıntı şikayeti olan hemodiyaliz (HD) hastalarında kaşıntı, yaşam kalitesi, depresyon ve uyku kalitesindeki olası değişiklikleri tespit etmeyi amaçladık.

Hastalar ve Yöntemler: Sekiz haftadan daha uzun süreli kaşıntı öyküsü olan 14 HD hastasına (7 erkek, 7 kadın; ort. yaş 59.7±17.2; dağılım 41-88) günde 300 mg gabapentin 8 hafta süre ile verildi. Çalışma öncesi 1 hafta, aktif tedavi fazı, plasebo fazı ve araya giren 1 haftalık temizlenme fazı esnasında görsel analog ölçeği kullanılarak günlük kaşıntı skorları kaydedildi. Uyku kalitesi modifiye uyku-sonrası kaydı ile, yaşam kalitesi Tıbbi Sonuç Çalışması Kısa Form-36 şekli (SF-36) ile ve depresyon da Beck Depresyon kaydı kullanılarak değerlendirildi.

Bulgular: Gabapentin tedavisi ile ortalama kaşıntı skorunda ve toplam uyku-sonrası kaydı skorunda anlamlı derecede düşüş gözlendi (sırasıyla p=0.01 ve p=0.002). SF-36'nın fiziksel ve mental komponent skorları gabapentin tedavisi ile artarken, bilişsel ve somatik depresyon indeksleri gabapentin ile azaldı.

Sonuç: Gabapentin tedavisi kaşıntı şikayeti olan hemodiyaliz hastalarında kaşıntı, yaşam kalitesi, depresyon ve uyku kalitesi üzerinde klinik olarak önemli yararlı etkilere sahiptir. Gabapentin tedavisi kaşıntısı olan hemodiyaliz hastalarında önemli bir tedavi seçeneği olarak göz önünde bulundurulmalıdır.

Anahtar sözcükler: Gabapentin; kaşıntı; yaşam kalitesi; hemodiyaliz.

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Renal itch is a localized or generalized itch affecting patients with chronic renal failure (CRF), where there is no primary skin disease and no systemic or psychological dysfunction that might cause pruritus.[1] The term `uremic pruritus' is somewhat unhelpful as itch occurs in chronic but not acute renal disease and does not result from raised serum urea levels. The prevalence of renal itch has increased with a growing population in CRF. Itch is a severe and distressing symptom of renal disease.[2] In contrast to other complications of CRF such as anemia and hypertension, very little progress has been made in determining the mechanism or treatment of renal itch.

Prevalence of depression in chronic hemodialysis (HD) patients varies between 30-100%.[3] Despite some improvements in dialysis therapies, depression remains an important problem in HD patients. Hemodialysis patients have decreased functional capacity and quality of life (QOL) as well as in other chronic diseases. Factors such as age, anemia and erectile dysfunction were related to decline in QOL of HD patients.[4]

Gabapentin, a potent anticonvulsant drug, has an unknown mechanism of action. Initially approved only for use in controlling seizures, it showed promise in the treatment of chronic pain syndromes, especially neuropathic pain; Gabapentin is eliminated primarily through the kidney and removed by HD. The recommended dose for HD patients is 200–300 mg after each HD session.[5]

The effect of gabapentin on pruritus, depression, quality of life and sleep quality is not well known. In this study, we aimed to determine possible changes in pruritus, quality of life, depression and sleep quality in pruritic HD patients with gabapentin therapy.

PATIENTS AND METHODS

Fourteen adult HD patients (7 men, 7 women; mean age 59.7±17.2 years; range 41 to 88 years) from our HD unit were included in the study. Patients younger than 18 years, pregnant and lactating women were excluded. A dermatologist evaluated the cases with pruritus. The characteristics of cases with pruritus are shown in Table 1. Hemodialysis was performed for 4-5 h thrice weekly via a polysulphone dialyzer and bicarbonate dialysis fluid. All patients had histories of pruritus of more than eight weeks. Their pruritus was not relieved by antihistamines, nicergoline or moisturizers. None of the patients had concomitant dermatological, liver or metabolic diseases associated with pruritus. Any medication with presumed antipruritic effects was discontinued one week before the study. The patients were asked to record the severity of their pruritus on a visual analogue scale once a day. The scale is consisted of a 10-cm horizontal line marked from 0 (denoting no itch) to 10 (denoting worst possible imaginable itch). On a random and blinded basis, patients were assigned to receive eight weeks of gabapentin therapy.

There was a 1-week washout period between the sequential treatment phases. The daily pruritus scores of patients were collected for each period of the study during one week preceding the trial, the active treatment phase, the placebo phase and the intervening washout period. The median of the scores for each period was accepted as the score of that period. Gabapentin 300 mg was administered orally for eight weeks at the end of HD sessions. No side effect was observed in any of the 14 cases receiving therapy and none of the cases was discharged from the study. A reduction in scores of 50% was considered as the desired improvement in symptoms during treatment. Predialysis blood samples were drawn for hematocrit, serum calcium, phosphate, albumin and parathyroid hormone levels.

A questionnaire with a set of clinical variables, as well as a modified post-sleep inventory (PSI), was applied to all patients. The PSI was developed by Webb et al.[6] to permit an adequate description of subjective responses to a preceding period of sleep. The PSI consisted of a questionnaire with three groups of opposing statements separated by an analogical 0 to 10 rating scale. The aim was to classify the patient's understanding about his or her sleep quality in terms of feelings at bedtime (score PSI-1), quality of nocturnal sleep (score PSI-2), and feelings at awakening (score PSI-3). A total score (PSI-4) was also calculated as follows: (PSI-1 + PSI-2 + PSI-3) / 3. To interpret the PSI scores, a score of 0 reflects a positive opinion about the patient's sleep quality, while a score of 10 reflects a very negative opinion.[7]

In order to evaluate QOL of the patients, a short form of Medical Outcomes Study (SF- 36) was used, which was adapted to the Turkish population.[8] The test consisted of 36 items, which were assigned to 8 dimensions, namely, functional capacity (10 items), physical aspect (4 items), body pain (2 items), general health status (5 items), vitality (4 items), social aspect (2 items), emotional aspect (3 items), and mental health (5 items). Each scale was scored with a range from 0-100. The first four items were physical component scale (PCS) and the remaining four items were mental component scale (MCS).[9] It has been shown that these two summary scales adequately represent values of their individual scale components with 80% and 85% variability.[10] The higher the scale the better the QOL. This scale has been commonly used and validated in patients with end-stage renal disease (ESRD).[11]

Depression was assessed by using the Beck Depression Inventory (BDI), which was validated and commonly used in patients with ESRD.[3,12,13] Patients were grouped as normal (BDI < 11), borderline depression (BDI 11 - 14), mild (BDI 15 - 21) and moderate to severe depression (BDI > 21). Patients who had BDI score 15 were accepted as fulfilling the diagnostic criteria for depression.

Table 1. Baseline Characteristics of the Patients

Parameter	Mean±SD (n=14)	Minimum	Maximum
Age (years)	59.7±17.2	41	88
Dialysis duration (months)	49.6±47.8	8.0	168
Hematocrit (%)	33.4±4.0	28.1	44.8
Serum albumin (g/dl)	3.9±0.3	3.5	4.4
Calcium (mg/dl)	8.9±0.7	7.4	10.0
Phosphate (mg/dl)	5.0±0.9	2.7	6.1
Parathyroid hormone (pg/ml)	288±117	139	497
Kt/V	1.33±0.17	1.0	1.7
C-reactive protein	9.7±8.8	1.0	27.9

The local ethics committee approved the study design. Informed consent was obtained from each patient.

Statistical analysis: Numerical variables were given as mean ± SD. The differences in mean values were analysed by Wilcoxon signed ranks test. A p value less than 0.05 were accepted as significant.

RESULTS

Changes in different parameters with gabapentin are shown in Table 2. The mean pruritus score was decreased significantly from 7.6±1.2 to 1.3±1.4 with gabapentin therapy (p=0.01). Total of post-sleep inventory (PSI-4) also significantly decreased from 5.8±3.3 to 1.8±1.8 (p=0.002).

Physical and mental component scales of SF-36 increased, whereas cognitive and somatic depression index decreased with gabapentin (Table 2).

DISCUSSION

The activity of the nervous system plays an important role in the mechanism of uremic pruritus.[14] In pruritus, excessive sensitivity to pruritic stimuli may result from nerve fiber damage. It has been demonstrated that uremic patients on hemodialysis develop abnormal innervations. The efficacy of topical capsaicin cream used to treat uremic pruritus supports the importance of the neurogenic factors.[15] Substance P may be acting as a neurotransmitter in uremic pruritus. Capsaicin can deplete substance P from the peripheral neurons and thereby can alleviate itching.[16]

Because of the use of biocompatible HD membranes and the improvement in HD efficacy, the incidence of pruritus in HD patients has declined from an estimated 85% in the 1970s and 50-60% in the 1980s to a current estimated incidence of 22%.[17] The mechanism of pruritus in HD patients is unknown and most of the treatments are ineffective. Several hypotheses have been proposed to explain the pathogenesis of this pruritus. Suggested causes include xerosis,[18] involvement of the peripheral nervous system,[14,15] opioid system involvement,[19] mast cells and hormones (histamine and serotonin), altered divalent ion metabolism, hyperparathyroidism[20,21] and derangements of the immune system.[22] Currently, two major concepts for the pathophysiology of pruritus in HD patients are the opioid and the cytokine hypotheses.[20]

As an agent effective for the treatment of pruritus, gabapentin relieved pruritus in our HD patients. Gunal et al.[23] also showed that gabapentin therapy impressively relieved pruritus in their HD patients. Manenti et al.[24] determined that pruritus relived by gabapentin in five HD patients in their pilot study.

Despite different reports on prevalence of depression, it is the most common psychiatric illness in patients with ESRD. Several studies have estimated that depression occurs in 20% to 49% of dialysis patients and the majority of these patients were on HD.[25] As renal insufficiency progresses, patients may experience symptoms

Table 2. Pruritis score and other parameters before and after gabapentin therapy

	Before gabapentin (n=14)	After gabapentin (n=14)
Pruritis score	7.6 ± 1.2	1.3 ± 1.4*
Post-sleep inventory	5.8 ± 3.3	1.8 ± 1.8*
Physical component scale	45.1 ± 20.6	75.3 ± 11.4*
Mental component scale	56.9 ± 18.8	80.8 ± 10.3*
Beck Depression Inventory	13.6 ± 5.2	7.1 ± 3.7*
Cognitive Depression Index	9.2 ± 4.6	5.0 ± 3.3*
Somatic Depression Index	4.4 ± 2.3	2.1 ± 1.7*

*p<0.01 (Wilcoxon signed ranks test)

that may affect their daily lives. Several reasons such as loss of renal function, loss of role at work and in family, loss of sexual function account for the high prevalence of depression in HD patients. It was demonstrated that serial measurement of depression is one of the predictors of mortality in HD patients.[12] For that reason, diagnosis and treatment of this common problem may be very important for improvement of high mortality rate in this group of patients.

Our study is the first to evaluate gabapentin efficacy on depression in HD patients. There are only studies on depressive patients having bipolar disorder with normal renal function. Young et al.[26] determined that depression was relieved with gabapentin therapy in 15 bipolar depressive patients, also in Wang et al.'s[27] study gabapentin was helpful in bipolar depression. In our study the value of BDI decreased with gabapentin.

Walters et al.[28] assessed QOL at the initiation of dialysis therapy and found that QOL scores were significantly lower at the start of HD than in patients with established long-term HD. Of note, the majority of patients in this study started dialysis therapy with anemia and hypoalbuminemia.

Our study is also the first to investigate the effect of gabapentin on QOL in HD patients. Rodrigues et al.[29] showed that QOL improved with gabapentin therapy in patients with primary orthostatic tremor. It is very important that in pruritic HD patients QOL increased significantly with gabapentin therapy in our study.

Disturbance in sleep are common in patients with ESRD on dialysis and include delayed sleep onset, frequent awakening, restlessness and daytime sleepiness. Total sleep quality significantly improved in our patients.

We concluded that beneficial effects of gabapentin therapy on pruritus, quality of life, depression and sleep quality are clinically important in HD patients with pruritus. Gabapentin therapy should be taken into account as an important choice of therapy in pruritic HD patients.

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