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Research Article
Sertraline Versus Pregabalin in Treatment of Pruritus in Maintenance Hemodialysis Patients: A Single-center Prospective, Cross-over Study

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Abstract

Background and Objective: Uremic Pruritus (UP) is a distressing symptom occurring in end-stage renal dialysis patients. It compromises overall life quality. Pregabalin and sertraline can effectively ameliorate UP. The aim of the study is to investigate which medication is more effective in treatment of UP in patients receiving hemodialysis. **Methodology:** This is an 11 week long randomized, prospective and cross-over study. Patients were randomly assigned to either sertraline 50 mg daily or pregabalin 75 mg daily. After 4 weeks of treatment, another 3 weeks were passed without treatment for drug washout then cross-over was performed and patients received the another drug for 4 weeks. Visual Analogue Scale (VAS) was used to evaluate pruritus at each week's visit and adverse effects of study drugs reported by the patients were registered. Baseline laboratory data and demographic characteristics were recorded from patient charts. **Results:** Twenty one (12 males and 9 females) patients completed the study. Mean age was 48.86±14.18 years. Pregabalin improved pruritus more significantly than sertraline as percent of decline in VAS score after pregabalin treatment (67.16±12.46%) was significantly more than that for sertraline (22.25±18.49%) and reported side effects with pregabalin were less than that of sertraline. **Conclusion:** Pregabalin significantly improves UP more than sertraline with fewer side effects.

Key words: Uremia, pruritus, sertraline, pregabalin, hemodialysis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Pruritus or itch is defined as a displeasing feeling that irritates the desire to scrape. Uremic Pruritus (UP) is a common and distressing symptom occurring in 42-75% of end-stage renal dialysis (ESRD) patients, even in patients who are adequately dialyzed[1]. It compromises overall life quality, affects sleep quality and interferes with work and social relations[2-4]. Despite advances in many aspects of ESRD related complications, pruritus still remains one of the most challenging clinical problems for both clinicians and patients[5].

The precise mechanism of UP is yet to be fully elucidated. A number of factors have been supposed to be related to pruritus in uremic patients. These factors can be grouped into uremia-related (Uremic itching, xerosis, anemia, secondary hyperparathyroidism, high serum levels of phosphorous, magnesium, aluminum and substance P, elevated cutaneous content of divalent ions as calcium and phosphorus, hypervitaminosis A, accumulation of pruritogenic substances that cannot be removed by dialysis, peripheral neuropathy, the chronic inflammatory condition and high prevalence of HLA-B35) and uremia unrelated (Drug related reactions, senility, hepatitis, hypercalcaemia and diabetes mellitus) factors[6].

Although, plasma histamine level and mast cells number increase in uremic patients, it was suggested that they have no relationship with the extent of pruritus[7]. On the other hand, neuropathy and abnormalities of nerve terminals and fibers, which are common findings in uremic patients, diminish the threshold of perception of peripheral stimuli and facilitate sensation of itch with stimulants that will not lead to itch under normal conditions[8]. In addition, central transmission and sensitization processes similar to those observed in chronic pain are important mechanisms in the pathogenesis of chronic pruritus. Therefore, it was hypothesized that a drug designed as a potent therapy for neuropathic pain also might have a favorable effect on UP[9].

Several efforts to alleviate possible contributing factors have been done by delivering adequate dialysis. Regardless of the best attempts at prevention and control, most of the hemodialysis patients continue to suffer from chronic pruritus[4]. Pregabalin is an anticonvulsant drug used for neuropathic pain. There are some studies showing beneficial effects of pregabalin on neuropathic pain in patients on hemodialysis, yet few studies showed relief of chronic UP with pregabalin treatment[5,10]. Selective Serotonin Reuptake Inhibitors (SSRI) were used effectively to reduce the severity of pruritus[11,12]. Sertraline hydrochloride is a SSRI that is used effectively in treatment of major depressive disorders. Previously, sertraline was used with success in treatment of cholestatic pruritus[13,14]. Regarding UP, it was found that sertraline reduced pruritus in patients with ESRD[1,15,16]. Therefore, the aim of this study was to compare the effects of sertraline and pregabalin on pruritus in hemodialysis patients.

MATERIALS AND METHODS

Study population: All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and subsequent amendments or comparable ethical standards. The study design was approved by the Institutional Review Board of Mansoura, Faculty of Medicine, Egypt (Code number R1/16.01.04). Informed consent was obtained from all individual participants included in the present study.

All patients (n = 60) in Mansoura University, Hospital Hemodialysis Centre were screened for eligibility. Originally patients with pruritus (n = 23) were planned to be recruited in the study. Hemodialysis was performed for 4 h thrice weekly via a polysulphone high-flux dialyzer using bicarbonate containing dialysate containing 138 mmol L^{-1} sodium, 1.75 mmol L^{-1} calcium and 34 mmol L^{-1} bicarbonate. Criteria for inclusion in the study were as follows: Prior diagnosis of UP for at least 3 months that not responding to ordinary measures e.g., antihistamines, emollients and topical antipruritics undergoing maintenance hemodialysis for at least 6 months, achievement of dialysis adequacy ($Kt\ V^{-1}$>1.2) and age >18 years.

Exclusion criteria were as follows: The presence of hepatic, cardiopulmonary and uncontrolled psychiatric disease, metabolic diseases, pain syndromes, specific dermatologic disease, which may cause pain and/or pruritus, abnormal blood counts (hemoglobin <10 g dL^{-1}, white blood cells <2500 mm^{-3} and platelet count <10×10^3 μL^{-1}), presence of active malignancy, pregnancy, lactation and patients with untreated hypothyroidism. Patients with serum levels of parathyroid hormone >330 pg mL^{-1}, serum calcium (albumin-corrected) >10.2 mg dL^{-1}, serum phosphorous >5.5 mg dL^{-1}, calcium phosphorous product concentrations >70 mg^2 dL^{-2} were also excluded because they had significantly higher odds of having moderate-to-extreme pruritus[17]. Any medication with presumed antipruritic effect was discontinued 2 weeks before the study and during the

wash out period. Patients under pregabalin or sertraline treatment before enrolment underwent washout for 6 weeks before randomization.

Study design: This is an 11 week long, open-label, prospective, randomized cross-over study that was conducted at Mansoura University, Hospital Hemodialysis Centre. Patients were randomized into either pregabalin (11 patients) or sertraline (12 patients) treatment arms using computer generated random numbers. Two patients received sertraline were withdrawn from the study because one of them developed drug allergy, while the other showed confusion and abnormal behavior. After a 4 week treatment period, patients underwent a 3 week drug washout. Then a crossover was performed and reversed treatment groups for another 4 week period. All patients were instructed to complete the Visual Analogue Scale (VAS) for assessment of pruritus at the baseline evaluation. The same questionnaires were repeated after each treatment phase. Pregabalin was administered at a dose of 75 mg day^{-1} at bed time and sertraline was administered at a dose of 50 mg day^{-1} at bed time. These doses were determined based on recommendations of manufacturers of the respective medications. Patients were asked not to use benzodiazepines, muscle relaxants, opioid analgesics or non-steroidal anti-inflammatory drugs, tricyclic antidepressants and antiepileptic drugs without informing the investigator physicians.

Efficacy and safety assessments: The patients were asked to record the severity of their pruritus on a VAS. The scale consisted of a 10 cm horizontal line marked from 0 (denoting no itch) to 10 (denoting worst possible imaginable itch). Pre-dialysis blood samples were drawn for complete blood count, liver functions (SGPT, SGOT, bilirubin, albumin and alkaline phosphatase), blood urea nitrogen, serum calcium, phosphate and parathyroid hormone levels. The patients were monitored for drug-related adverse events at each week's midweek hemodialysis session.

Statistical analysis: Data was analyzed using Statistical Package for Social Sciences (SPSS) version 15 (IBM Corporation, USA). Qualitative data was presented as number and percent. Quantitative data was presented as Mean±Standard Deviation and (min-max). Student t-test was used to compare between two groups. The value of $p<0.05$ was considered to be statistically significant.

RESULTS

Twenty one patients completed the entire course of the study. Patients were 12 males (57.1%) and 9 females (42.9%). Their ages ranged from 24-80 years (48.86±14.18). Mean time of hemodialysis was 5.6±3.6 years. Seven patients were hypertensive and 2 patients were diabetic. The duration of pruritus ranged from 2-10 years (4.9±2.53). All patients were treated unsuccessfully with different antihistamines and topical moisturizers. Eleven patients reported night exacerbation of itching and sleep disturbance before start of sertraline therapy, while 6 patients experienced same complaint before start of pregabalin. Table 1 shows the basic laboratory data characteristics of the entire study population and there were no critical values. No features of malnutrition,

Table 1: Baseline laboratory characteristics

Test	Number	Minimum	Maximum	Mean	Standard deviation	Reference range
HB (g dL^{-1})	21	10	12.6	11.31	0.64	M: 13.2-16.2 F: 12-15
WBC (cell mm^{-3})	21	2500	7900	5560	1340	3500-9000
PLT ($\times 10^3$ μL^{-1})	21	97	399	192.76	65.79	140-450
MCV (fL)	21	81.4	95	89.27	3.64	80-100
Hematocrit (%)	21	25	41.3	30.38	5.51	M: 42-52% F: 35-47%
Blood urea nitrogen1 (mg dL^{-1})	21	86	188	136.29	29.7	7-18
Blood urea nitrogen 2 (mg dL^{-1})	21	27	84	57.19	17.15	7-18
Calcium (Ca) (mg dL^{-1})	21	6.1	9.6	8.37	0.91	8.4-10.2
Phosphorus (PO_4) (mg dL^{-1})	21	4.6	5.5	5.39	0.28	3.3-5.5
Ca×PO_4 product (mg^2 dL^{-2})	21	29.28	52.8	45.19	5.84	
Parathyroid hormone (pg mL^{-1})	21	42	330	146.87	108.86	50-330
Bilirubin (mg dL^{-1})	21	0.8	0.9	0.8	0.02	0.1-1
Albumin (g dL^{-1})	21	3.7	4.9	4.28	0.3	3.2-4.8
SGPT (IU L^{-1})	21	20	44	25.33	6.88	21-70
SGOT (IU L^{-1})	21	20	42	28.76	8.37	17-59
Alkaline phosphatase (IU L^{-1})	21	71	178	108.07	34.86	38-130
Kt V^{-1}	21	1.3	1.7	1.5	0.31	>1.2

Kt V^{-1}: Kt stands for dialyzer clearance multiplied by time (mL min^{-1}) and V for volume of water a patient's body contains

Table 2: Changes in Visual Analogue Scale (VAS) with sertraline and pregabalin treatments in patients with uremic pruritus

	Mean±SD		
	VAS before treatment	VAS after treatment	p-value
Pregabalin group (n = 21)	7.52±1.63	2.48±1.12	<0.001
Sertraline group (n = 21)	6.86±1.98	5.52±2.54	<0.001

SD: Standard deviation, p: Calculated probability and p significant if <0.05

Table 3: Comparison of the Visual Analogue Scale (VAS) in sertraline and pregabalin groups

	Mean±SD			
	Pregabalin group (n = 21)	Sertraline group (n = 21)	p-value	t-test
VAS before treatment	7.52±1.63	6.86±1.98	0.241	1.190
VAS after treatment	2.48±1.12	5.52±2.54	<0.001	-5.025
VAS decrease (%)	67.16±12.46	22.25±18.49	<0.001	9.231

SD: Standard deviation, p: Calculated probability, p significant if <0.05, t: Student t-test

Table 4: Side effects related to pregabalin and sertraline treatments

Side effects	Pregabalin	Sertraline
Dizziness	2	2
Nausea	-	1
Drug allergy	-	1
Confusion and unusual behavior	-	1

severe anemia or inadequate dialysis were detected (plasma albumin 4.28±0.3 g dL^{-1}, hemoglobin 11.31±0.64 g dL^{-1} and Kt/V 1.5±0.31, respectively). All patients had self-reported pruritus symptoms at baseline evaluation. Mean VAS score at baseline before start of pregabalin was 7.52±1.63 (range 5-10), while it was 6.86±1.98 (range 3-10) before start of sertraline. There was no significant difference between sertraline and pregabalin regarding VAS score before treatment (Table 2 and 3). Each of sertraline and pregabalin improved pruritus significantly. Mean VAS score after treatment with pregabalin was 2.48±1.12 (range 1-5) while it was 5.52±2.54 (range 2-10) after treatment with sertraline (Table 2).

Pregabalin improved pruritus more significantly than sertraline as VAS score after treatment was significantly lower with pregabalin (p<0.001) than with sertraline. In addition, percent of decline in VAS score after pregabalin treatment (67.16±12.46%) was significantly more than that for sertraline (22.25±18.49%), respectively (p<0.001) (Table 3). Furthermore, all the patients reported disappearance of night exacerbation of itching and sleep disturbance with pregabalin, while 4 patients only showed same improvement with sertraline therapy. There was no significant difference between sertraline and pregabalin regarding the frequency of side effects despite a trend of being more frequent and more serious with sertraline (Table 4).

DISCUSSION

Generally there are two main types itching: Pruritoceptive (peripheral, arising from skin) and neurogenic (neuropathic). Uremic Pruritus (UP) is a common symptom in patients needing dialysis although the prevalence of UP decreased by more than half with usage of improved dialysis technology[18]. Renal transplantation is the only known cure for UP, however, this is not available for every ESRD patient. In a survey performed on kidney transplant patients the prevalence of pruritus was 10% on compared to ESRD patients[19], which was 60%. Several treatment modalities were tried to relieve UP. First, optimizing the dialysis strategy and correction of divalent ions and anemia are mandatory. Antihistamines and emollients constitute the backbone of treatment. However, 30-50% of pruritic patients do not respond to these treatment options[5]. Other medications that can be favorable in patients with UP include oral activated charcoal, cholestyramine, gabapentin, nicergoline, opioid antagonists, a leukotriene inhibitor, erythropoietin, heparin, lidocaine, thalidomide, fatty acids, topical capsaicin or linoleic acid and UVB[19].

The common concurrence of chronic pruritus and the neuropathy may lend support to neuropathic hypothesis of UP. This hypothesis assumes that the peripheral nerve damage caused by uremic neuropathy, which occurs in more than 65% of patients on maintenance hemodialysis, results in a decreased perception threshold[20]. Thus, irritative stimuli or skin disorders such as simple xerosis, while not intense enough to cause pruritus in a healthy person may lead to itch in uremic patients[5]. In addition, some symptom or signs of peripheral sensorimotor neuropathy and dysautonomia occurred with significant relationship between the severity of the pruritus and the presence of paresthesia[20]. Pregabalin was found to be effective in unspecified chronic itch[21], cetuximab-related itch[22] and pruritus related to Brown-Sequard Syndrome[23]. Solak *et al.*[5] and Aperis *et al.*[10] evaluated pregabalin in the treatment of UP. There was a statistically significant difference between VAS values before and after 4-6 weeks treatment period. It can be speculate that pregabalin may have affected pruritus through the way it affects neuropathic pain[5]. The results of these studies are in line with the results of the present study.

Pregabalin is derivative of the inhibitory neurotransmitter Gamma Amino Butyric Acid (GABA). The principal mechanism

of action is that it binds to the α2δ subunit of the voltage-dependent calcium channel in the central nervous system and reduces calcium influx into nerve terminals leading in turn to reduced neurotransmitter release and attenuation of postsynaptic excitability[24]. Pregabalin also decreases the release of neurotransmitters such as glutamate, noradrenaline and substance P and inhibits the release of calcitonin gene-related peptide, a mediator of itching[25].

On the other hand, several studies have revealed that SSRI could reduce the severity of pruritus[12,26]. Sertraline was used with success and considered first line in treatment of cholestatic pruritus[13,14]. Chan *et al.*[1], Arcoraci and Discepolo[15] and Shakiba *et al.*[16] used sertraline in ESRD patients with the aim of treatment of pruritus and found improvement in the pruritus sensation. The findings of the present study are in agreement with these studies that showed significant decrease in the itching perception in ESRD patients after treatment with sertraline.

Present study showed that pregabalin improved pruritus more significantly than sertraline as VAS score after treatment was significantly lower with pregabalin than with sertraline. In addition, percent of decline in VAS score after pregabalin treatment was significantly higher than that for sertraline. Furthermore, all patients reported disappearance of night exacerbation of itching and sleep disturbance with pregabalin while only 4 patients showed same improvement with sertraline therapy. Sertraline and pregabalin were generally well tolerated, however, some side effects were observed with their use. The most important was withdrawal of 2 patient after starting sertraline treatment due to development of drug allergy in one patient while the other showed confusion and unusual behavior.

Pregabalin is eliminated primarily by renal excretion and therefore, the dose should be adjusted in patients with reduced renal function. The recommended dose for hemodialysis patients is 25-75 mg day^{-1}. Pregabalin does not bind to plasma proteins and is fully dialyzable because of its small molecular size. Thus, hemodialysis patients may require supplemental dosing after dialysis to maintain plasma pregabalin concentrations within the desired range. Pregabalin has no significant pharmacokinetic drug interactions and the adverse reactions most frequently leading to discontinuation of therapy are dizziness and somnolence[27].

CONCLUSION

For the first time in the literature, this study showed that pregabalin is more superior to sertraline in treatment of UP in hemodialysis patients with fewer side effects. There are some limitations of this study. First, it was not a placebo-controlled or double blinded study. So, larger placebo-controlled randomized-blinded studies are clearly required considering the scope of the itch problem in these patients. Second, pruritus was not assessed on a daily basis. Only changes pretreatment and after each treatment phase were reported. However, patients were interrogated, while receiving dialysis in terms of the presence or absence of pruritus by hemodialysis physicians and these observations were in line with general results of the trial. One may also argue against the neuropathic nature of pruritus in these patients and suggest this may just be a coincidence.

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SIGNIFICANCE STATEMENT

- Uremic Pruritus (UP) is a common symptom in patients needing dialysis and kidney transplantation is the only known cure for UP, however, this is not available for every patient
- Several treatment modalities were tried to relieve UP, however, 30-50% of pruritic patients do not respond to these treatment options
- Pregabalin and sertraline can improve UP
- Current study showed that pregabalin significantly improves UP more than sertraline with fewer side effects

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