Comparison Between Pregabalin and Sertraline for Treatment of Uraemic Pruritus in Patients on Maintenance Haemodialysis: A Single-Centric Study

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ABSTRACT

Objective: To compare oral pregabalin with oral sertraline for treatment of uraemic pruritus.
Study Design: Randomised controlled trial.
Place and Duration of the Study: Department of Nephrology, Pak Emirates Military Hospital Rawalpindi, Pakistan, from October 2023 to January 2024.
Methodology: Patients with end-stage renal disease having pruritus for at least 6 weeks were included. Exclusion criteria comprised other dermatological or systemic diseases associated with pruritus, mental health issues, thrice-a-week haemodialysis schedule, and use of other treatments for uraemic pruritus. They were randomised to receive either pregabalin 75mg daily or sertraline 50mg daily for six weeks using computer-generated sequences. The Urdu version of the 5-D Itch scale was used to document the severity of pruritus at the baseline and at the end of therapy. Side effects to the treatment were also monitored.
Results: There were 8 (16.67%) females and 40 (83.33%) males, with a mean age of 52.19 ± 12.19 years. The baseline 5-D Itch scale scores were equal in both groups. Mean improvement in 5-D Itch scale scores was 3.75 ± 1.26 and 2.08 ± 1.18 with pregabalin and sertraline, respectively ($p < 0.001$). Side effects were reported by 2 (8.33%) patients on pregabalin and none using sertraline ($p = 0.489$).
Conclusion: Pregabalin was found to be more effective than sertraline in treating uraemic pruritus, though with a statistically insignificant trend towards a higher frequency of side effects.

Key Words: *Chronic renal failure, Pruritus, Renal dialysis, Selective serotonin reuptake inhibitors, Uraemia.*

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INTRODUCTION

Uraemic pruritus (UP) has been reported in as many as 38% to 84% of end-stage renal disease (ESRD) patients undergoing haemodialysis (HD).[1] There is a high variability in prevalence between different countries and different dialysis units, and this changes even with the renal replacement therapy that the patients are on. This disturbing skin manifestation frequently goes unrecognised, under-reported, and untreated.[2] It contributes to the depression, inadequate sleep, and compromised quality of life that plague patients with renal failure.[3] UP comes under the umbrella of chronic pruritus, which is more than 6 weeks in duration. Exact underlying pathogenesis has not been clearly established.

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However, multiple mechanisms have been postulated, including accumulation of uraemic end products, immune system dysregulation, uraemic neuropathy due to toxic effects of hyperphosphataemia, hypercalcaemia, urea, and imbalance in Kappa and Mu opioid receptor activation.[4]

As the underlying aetiology is not clearly understood, there are no clear guidelines available for the treatment of UP. In the past, many treatment options have been proposed and trialed, ranging from local therapies; such as capsaicin, emollients, and topical glucocorticoids, to oral treatments; such as antihistamines, gabapentinoids, antidepressants, injectable agents such as difelikefalin and other options including ultraviolet phototherapy. All these treatments have not only subjected to trials but are also being used extensively in clinical practice. Each one has variable efficacy and side effects. The only curative treatment for UP is renal transplant, which many patients in developing countries either do not have access to or cannot afford.[5]

Pakistan is a lower-middle-income developing country. Access to advanced healthcare, including HD, is not free and patients have to bear the expenses. This, coupled with the financial burden of arranging logistic resources on the clientele, demands the effective use of cheaper, yet effective options for

the management of chronic medical conditions. Whereas pregabalin is easily available and routinely used in a number of other medical conditions as well, it requires dose adjustment at reduced glomerular filtration rates.[6] Patients on pregabalin might require additional / supplemental doses, as its small molecular size makes it dialysable during an HD session.[7] This study was thus performed to determine the efficacy of another routinely used medicine, sertraline in comparison to pregabalin. The results of the study would not only help clinicians to use an evidence-based approach but would also serve as a stepping stone for the development of guidelines for the management of UP in the Pakistani population.

METHODOLOGY

This randomised clinical trial was conducted from October 2023 to January 2024 at the Dialysis Unit of Pak Emirates Military Hospital, Rawalpindi, Pakistan after obtaining approval from the hospital's Institutional Ethical Board, vide letter number A/28/EC/535/23. The protocol was registered in the Iranian Clinical Trial Registry (registration no: IRCT20240208060941N1). A sample size of 48 patients was calculated assuming 67.16% and 22.25% reduction in severity of itching on a visual analogue scale with pregabalin and sertraline, respectively, as previously quoted by Abd El Wahab, *et al*.[8] This calculation was done using Epitools sample size calculator for comparison of two proportions. This test had two tails, with alpha of 5% and power of 80%.

Both male and female patients aged ≥19 years, on twice weekly HD for ESRD for at least six months and having UP for at least six weeks, were included in this study. Exclusion criteria were other dermatological or systemic diseases associated with pruritus (such as acute hepatitis, chronic liver disease, pregnancy, and hypothyroidism), mental health issues affecting the ability to respond to 5-D Itch scale (such as psychosis, obsessive-compulsive disorder, and substance abuse), patients on thrice-a-week HD schedule and non-consenting individuals. Moreover, individuals already on some treatment for UP were generally excluded, except for patients on oral antihistamines, for whom there was a washout period of two weeks before participation in this study. Patients were enrolled from the HD unit using convenience sampling.

Using online computer-generated sequences, patients were randomly allocated to pregabalin or sertraline groups. A detailed history was then taken to document demographic details, comorbid conditions, and HD-related parameters. The Urdu version of 5-D Itch scale was used to document the baseline severity of pruritus. Patients were prescribed pregabalin 75mg once a day orally or sertraline 50mg once a day orally, depending on the group they were allocated to, for a period of six weeks. They were followed up every two weeks in the HD unit and side effects to treatment were inquired. The Urdu version of 5-D Itch scale was again used to document the severity of pruritus at the end of therapy. On both occasions, the questionnaire was self-administered but the first author of this study was available to answer patients' queries and to ensure that there was no missing data on these forms. He was blinded to the treatment being given, whereas the patients and dialysis nurses were not.

Data were analysed using Statistical Package for Social Sciences (SPSS) version 22. Qualitative variables were represented using frequencies and percentages while for quantitative variables, mean ± SD was used. Independent-samples t-test was used to compare 5-D Itch scores before and after the treatment between the two groups, as well as the magnitude of reduction in scores in the two treatment arms. Fisher's Exact test was used to compare frequencies of side effects amongst patients on pregabalin and sertraline. Statistical significance was set at <5%.

RESULTS

The flow of participants through different stages of the study is depicted in the Consort diagram in Figure 1. Amongst the 48 patients included in data analysis, 8 (16.67%) were females while 40 (83.33%) were males. The mean age of the participants was 52.19 ± 12.19 years. Baseline characteristics of these individuals are shown in Table I.

The mean 5-D Itch scale scores were equal in both the groups to begin with, but after six weeks of treatment, these were much lesser amongst patients treated with pregabalin as compared to sertraline, as shown in Table II. Mean improvement in 5-D Itch scale scores was 3.75 ± 1.26 and 2.08 ± 1.18 with pregabalin and sertraline, respectively (p <0.001). Amongst patients on pregabalin, only 2 (8.33%) reported excessive somnolence, whereas those using sertraline did not report any adverse effect to the treatment (p = 0.489). No severe side effects were reported during this study period.

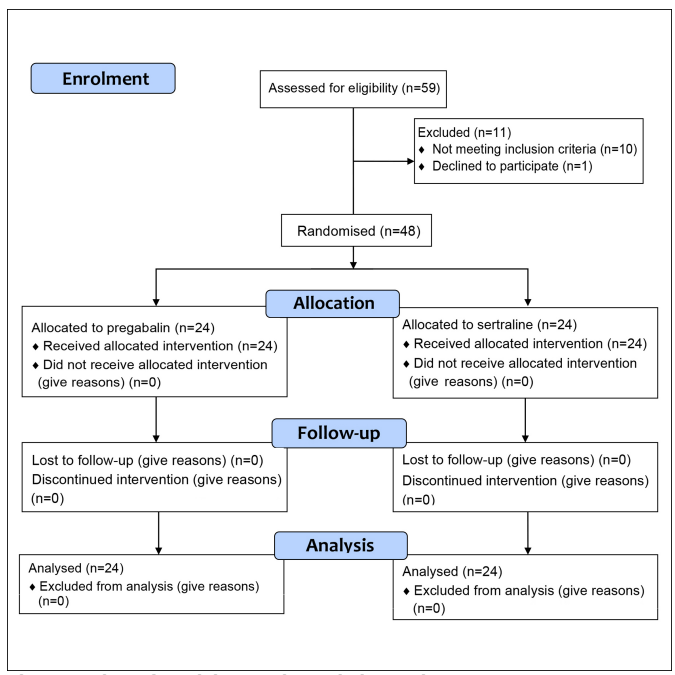

Figure 1: Flow of participants through the study.

Table I: Baseline characteristics.

Variable		Total (n = 48)	Pregabalin (n = 24)	Sertraline (n=24)
Age (years)		52.19 ± 12.19	53.21 ± 12.29	51.17 ± 12.26
Gender	Male	40(83.33%)	18 (75%)	22 (91.67%)
	Female	8(16.67%)	6 (25%)	2 (8.33%)
Comorbidities	Diabetes mellitus	15(3.25%)	10 (41.67%)	5 (20.83%)
	Hypertension	45 (93.75%)	23 (95.83%)	22 (91.67%)
	Stroke	1 (2.08%)	-	1 (4.17%)
	Ischaemic heart disease	10 (20.83%)	6 (25%)	4 (16.67%)
Haemodialysis vintage (Years)		4.42 ± 3.22	4.13 ± 3.42	4.71 ± 3.07
Prior use of antihistamines		45 (93.75%)	23 (95.83%)	22 (91.67%)
Haemoglobin (g/dL)		10.34 ± 1.74	10.25 ± 2.00	10.42 ± 1.47
Serum calcium (mmol/L)		1.98 ± 0.33	2.04 ± 0.36	1.92 ± 0.28
Serum phosphate (mmol/L)		1.68 ± 0.73	1.62 ± 0.62	1.74 ± 0.84
Serum albumin (g/L)		37.98 ± 4.92	36.83 ± 5.76	39.13 ± 3.69
Serum iPTH (pmol/L)		41.00 (12.50 - 69.50)	43.50 (17.0 - 71.75)	28.50 (10.25 - 62.50)
Serum ALT (U/L)		34.90 ± 7.99	32.97 ± 7.33	36.84 ± 8.29
Serum alkaline phosphatase (U/L)		227.98 ± 30.11	226.97 ± 24.77	228.99 ± 35.17

iPTH: intact parathyroid hormone.

Table II: Comparison of 5-D Itch Scale scores in the two treatment arms.

	Pregabalin (n = 24)	Sertraline (n = 24)	p-values*
Before treatment	19.96 ± 2.65	19.79 ± 2.41	0.821
After treatment	16.21 ± 2.25	17.71 ± 2.24	0.025
Change	3.75 ± 1.26	2.08 ± 1.18	p <0.001

**Comparison made using Independent-samples t-test*

DISCUSSION

The results of this study have shown pregabalin to be clearly superior for the treatment of UP as compared to sertraline. There was a slightly higher risk of side effects with pregabalin, but this was not statistically significant. The sample size for this study was calculated for comparison of efficacy, and not to analyse potential differences in frequencies of side effects.

Selective serotonin reuptake inhibitors (SSRI) are known to reduce serum levels of inflammatory markers like histamine and interleukins. Keeping this mechanism in view, the European S2k Guideline on chronic pruritus recommends using sertraline for UP.[9] Different clinical trials have shown sertraline to be effective in the management of UP. In a double-blinded randomised controlled trial performed on 60 patients in Egypt, sertraline was found to be more effective than placebo over 8 weeks of treatment period as assessed by both the visual analogue scale and 5-D Itch scale.[10] Similar results were obtained in another double-blind randomised clinical trial from Southern Iran.[11] In a single-arm study, Shakiba *et al.* found that the use of sertraline for four months reduced the intensity of itching amongst 19 patients from Iran.[12] However, no definitive recommendations could be made for the use of sertraline because of the lack of a comparator arm in that study.

In contrast to sertraline, there is a greater volume of evidence available for the use of pregabalin in UP. It acts on α2δ subunit of calcium channels in the dorsal column of the spinal cord, likely using its neuro-inhibitory pathway.[13] A Cochrane systematic review on interventions for UP found high-quality evidence from five randomised controlled trials to support a greater reduction in itching on the visual analogue scale with Gamma-aminobutyric acid (GABA) analogues as compared to placebo.[14] In an observational study from Saudi Arabia, the use of pregabalin 75mg after each HD session was associated with a 12-points reduction in 5-D Itch scale score after six weeks.[15] In a network meta-analysis including data on 1,180 patients, pregabalin was found to have the same efficacy as antihistamines.[16] There are published trials comparing pregabalin with different other agents, such as gabapentin, doxepin, and ondansetron.[17-19]

However, comparison of pregabalin with sertraline has not been the subject of many trials. Despite extensive literature search, the authors found only one trial directly comparing these two drugs in uraemic pruritus. This was an eleven-week long, randomised crossover study, conducted on 21 patients by Abd El Wahab *et al.* in Egypt.[8] Pregabalin was found to be more effective than sertraline in controlling chronic kidney disease (CKD) associated pruritus (reduction of 67.16 ± 12.46% and 22.25 ± 18.49%, respectively), similar to what this study has shown. However, pregabalin was safer than sertraline, unlike the data from this study.

There are not many tools for the assessment and quantification of pruritus that could be easily used in clinical trials. All of them have their own advantages and limitations. The 5-D Itch scale was introduced in 2010. It measures pruritus in five distinct dimensions including degree, duration, direction, disability, and distribution.[20] The reason for choosing this instrument for this study was the ease of answering the questions quickly, ability to quantify the responses, and the fact that this questionnaire is sensitive to changes over time. Moreover, the Urdu version has previously been tested in a Pakistani cohort and was found to be reliable and valid in assessing pruritus in ESRD.[21] It helped immensely in overcoming the language barrier faced by the majority of the patients.

The standards of care for patients with ESRD dictate HD to be done three times a week.[22] In this part of the world, most patients have two sessions of HD every week because of different challenges, may they be logistic, financial or even related to support from close family members. This has already been documented in several publications, both from this hospital and other centres from Pakistan.[23,24] Considering this fact, patients on thrice-a-week HD schedule were deliberately excluded, since they were expected to be fewer in number. Additionally, intensification of HD improves UP, so a comparison of such patients with the ones getting dialysed two times a week is not justifiable.

A similar study comparing these two therapeutic interventions has not been reported in Pakistan previously. The strengths of this study include the use of an externally well-validated Urdu version of a questionnaire that measures pruritus beyond just the degree or severity, has been validated in patients with ESRD and is much easier for patients to comprehend as compared to other English language-based generic questionnaires. Moreover, having a physician blinded to the treatment assist in the complete filling in of questionnaires also added to the reliability of the study.

In addition to the limitations associated with single-centric studies, there was no blinding of patients to the treatment for UP because of resource constraints. Both agents were used in a fixed dose and no adjustments were made as per the response of the patients. This could have affected the development of side effects as well. Whereas this study observed patients for six weeks only, affected patients would generally need treatment for much long periods to keep UP suppressed. It is not clear how these drugs would behave in the long run. There was a statistically insignificant higher frequency of side effects with pregabalin. Since the safety of any drug is of paramount importance, studies planned in the future should take the incidence of side effects into consideration while performing sample size calculations.

CONCLUSION

Pregabalin was found to be more effective than the sertraline in treating UP. However, this comes at a slightly higher risk of side effects.

ETHICAL APPROVAL:
This study was conducted after approval from the Institutional Ethical Board of Pak Emirates Military Hospital, Rawalpindi, Pakistan, vide letter number A/28/EC/535/23.

PATIENTS' CONSENT:
Informed consent was taken from all participants after explaining the study protocol and addressing the queries in detail.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AA: Data collection, analysis, and drafting of the manuscript.
ARA: Data analysis / interpretation and critical revision of the manuscript.
MI: Study design, data collection, and drafting of the manuscript.
All authors approved the final version of the manuscript to be published.

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