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Original Article

COMPARISON OF PREGABALIN AND NORTRIPTYLINE ON SLEEP, QUALITY OF LIFE IN POSTHERPETIC NEURALGIA: A PROSPECTIVE, RANDOMISED, OPEN-LABEL, PARALLEL STUDY

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ABSTRACT

Objective: Aim of the present study was to compare the effects of pregabalin and nortriptyline on sleep and quality of life in patients of postherpetic neuralgia (PHN).

Methods: The present study was conducted in 48 patients of PHN attending the outpatient department (OPD) of Dermatology, Government Medical College Jammu. Based on inclusion/exclusion criteria patients were randomized into two treatment groups. One group received pregabalin 150 mg/day and the other group was treated with nortriptyline 25 mg/day. The patients were followed up to eight weeks and assessed for Sleep (Medical Outcomes Study sleep scale) and quality of life (Euro QOL-5D-5L score). Clinicians Global Impression of Change (CGIC) score and Patient Global Impression of Change (PGIC) score were used to evaluate overall clinical improvement.

Results: Both drugs significantly improved all parameters studied ($p<0.0001$). On comparison, both drugs had similar effects on sleep and quality of life. However, pregabalin was found to be better than nortriptyline at eight weeks on CGIC ($p<0.004$) and PGIC ($p<0.0003$) scores.

Conclusion: Both pregabalin and nortriptyline were equally effective in improving sleep and quality of life. Overall clinical improvement was better with pregabalin than nortriptyline at eight weeks.

Keywords: Postherpetic neuralgia (PHN), Pregabalin, Nortriptyline, MOS, CGIC, PGIC and EQ-5D-5L score

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INTRODUCTION

Postherpetic neuralgia (PHN) is a complication that occurs due to reactivation of latent varicella-zoster virus in the sensory ganglia and pain persists or recurs four weeks to six months after the healing of the skin lesions [1]. Pain follows the typical dermatome distribution of the rash [2]. Neuropathic pain is often associated with sleep disturbance [3]. Both pain and sleep are known to have a negative impact on quality of life [4, 5].

Treatment of PHN includes topical Lidocaine 5% or capsaicin 8%, while systemic therapy is comprised of tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors, opioids, anticonvulsants and even intrathecal corticosteroids [6]. Among them TCAs and antidepressants are most commonly used.

TCAs are widely prescribed in neuropathies and painful conditions like fibromyalgia [7]. TCAs inhibit the reuptake of serotonin and/or norepinephrine by presynaptic neuron, and increase their concentrations in synaptic cleft. TCAs also desensitize adenylyl cyclase, activate GABA-B receptors, down-regulate beta-adrenergic and serotonin receptors [8].

Amitriptyline is metabolised into nortriptyline, an active metabolite by enzyme CYP2C19. Nortriptyline blocks the reuptake of norepinephrine more potently than serotonin in comparison to amitriptyline. Secondary amines (nortriptyline, desipramine) have advantage over tertiary amines (amitriptyline and imipramine) because of their better safety profile in terms of sedation, postural hypotension, and anticholinergic effects [9, 10]. However, nortriptyline in a trial in patients with neuropathic pain has shown 60% of treated patients showed anticholinergic effects (dry mouth) [11]. Therefore all TCAs should be given with caution especially in elderly patients because of their anticholinergic effects and cardiac toxicity [12].

Gabapentinoids (gabapentin and pregabalin) are effective in neurological painful conditions including chemotherapy-induced peripheral neuropathy (CIPN) [13].

Gabapentinoids are widely used in PHN. Pregabalin has been approved by FDA for the treatment PHN [14]. Pregabalin binds with alpha2-delta protein of presynaptic voltage-gated calcium channels causing a decrease in calcium entry resulting in reduced depolarisation in the nerve terminals which causes the decline of excitatory neurotransmitters release in the pain pathways [15, 16]. Pregabalin is preferred over gabapentin because of its better bioavailability, and predictable pharmacokinetic properties.

Pain is known to interfere with sleep and quality of life. Most of studies have evaluated the efficacy in ameliorating pain by TCAs and anticonvulsants individually in PNH [17]. However, there is a scarcity of studies examining effect of TCAs and antidepressants on sleep and quality of life in patients of PHN and these parameters are important in patients wellbeing. Therefore the present prospective, randomized, open label, parallel trial was conducted to evaluate and compare the effect of pregabalin and nortriptyline on quality of life and sleep interference in patients of PHN.

MATERIALS AND METHODS

The study was conducted in the Postgraduate Department of Pharmacology in collaboration with Postgraduate Department of Dermatology, SMGS Hospital, and Government Medical College Jammu after taking approval from the Institutional Ethics Committee, GMC Jammu vide no IEC/GMC/2019/829

A written, informed consent was obtained. The patients reporting to the dermatology OPD, diagnosed by the dermatologist as post herpetic neuralgia on the basis of a positive history of herpes zoster followed by persistent pain (moderate to severe) lasting for more than 4 w or recurrence of pain after rash had subsided were included. All basic principles of bioethics were followed.

Inclusion and exclusion criteria

Patients of both genders ≥ 18 y of age, diagnosed as postherpetic neuralgia and having pain at least moderate to severe (VAS score ≥ 40 mm) and who gave consent were included. While patients with

Pregnancy and lactation, Hypersensitivity to any of the test drugs cardiac disease, seizure disorder, liver disease, impaired kidney functions, already on Gabapentinoids or TCAs, severe depression with suicidal tendency, or suffering from any other significant pain conditions (HIV infection, diabetic neuropathy, cancer pain, fibromyalgia) were excluded from the study.

Treatment protocol

Prior to intervention, clinical evaluation with complete medical history was done. The eligible patients after meeting the inclusion and exclusion criteria were enrolled and randomized into two groups (A and B).

Group A patients received oral Pregabalin 75 mg twice a day at 12 hourly intervals for 8 w. Provision of incremental increase (75 mg BD) up to maximum 600 mg/day was kept based on patient response and tolerability. While Group B patients received oral Nortriptyline 25 mg once a day at bedtime for 8 w. Provision of incremental increase (25 mg weekly) up to a maximum 100 mg/day was kept on basis of patient response and tolerability. Provision of rescue treatment in the form of opioid analgesics was kept in patients with inadequate response. Patients in both the treatment groups were assessed on follow-up visits at 2, 4 and 8 w. Dose selection for both the drugs based on the most commonly used dose in earlier studies [18].

Sleep interference was assessed on Medical Outcomes Study sleep scale (MOS sleep scale). This scale measures six dimensions of sleep, including initiation, maintenance (e. g. staying asleep), quantity, adequacy, somnolence (e. g. drowsiness) and respiratory impairments (e. g. shortness of breath, snoring) [19].

Quality of life was assessed on Euro QOL-5D-5L index at baseline and end of 8 w. It comprises of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension had 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent was asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions [20].

Overall impression of improvement in patient's condition was rated by Clinicians Global Impression of Change score (CGIC) at the baseline and end of the 8 w [21]. It is a 7 point scale based on clinician observation, 1-very much improved, 2-much improved, 3-minimally improved, 4-not changed, 5-minimally worse, 6-much worse and 7-very much worse.

Patient Global Impression of Change score–PGIC. It is a 7 point scale was self-rated by the patient with 1-No change, 2-Almost the same, 3-A little better, 4-Somewhat better, 5-Moderately better, 6-Better and a definite improvement, 7-A great deal better and a considerable improvement [22].

Statistical analysis

The student t test (paired) was applied for intragroup changes from baseline and student t test (unpaired) was applied for intergroup comparison. p value of<0.05 was considered statistically significant.

RESULTS

A total of forty-eight patients of Postherpetic were enrolled and all completed the study.

Medical outcomes study sleep scale (MOS)

MOS sleep scale was significantly increased in both groups from baseline score (p<0.0001) (table 1) on intergroup comparison no statistically significant difference was observed (table 2).

Table 1: Effect of pregabalin and nortriptyline on MOS sleep score

Treatment group	Baseline	2 w	4 w	8 w
Pregabalin Group (n=24,Mean+SD)	35.54±3.01	41.38±.24####	48.25±5.05####	55.96±5.52####
Nortriptyline Group (n=24,Mean+SD)	35±2.83	40.7±2.75####	47.05±3.93####	53.65±5.17####

The data is shown as mean±SD showing unpaired t test in comparison to respective baselines #p<0.05, ##p<0.01, ###p<0.001, ####p<0.0001, NS not significant

Table 2: Comparative effect of pregabalin and nortriptyline on MOS sleep

Duration	Pregabalin group n= 24, mean+SD	Nortriptyline group n= 24, mean+SD	p value	Statistical significance
Baseline	35.54±3.01	35.0±2.83	0.525	NS
2 W	41.38±3.24	40.7±2.75	0.437	NS
4 W	48.25±5.05	47.05±3.93	0.363	NS
8 W	55.96±5.52	53.6+5.17	0.141	NS

The data is shown as mean±SD showing unpaired t test in comparison to respective baselines #p<0.05, ##p<0.01, ###p<0.001, ####p<0.0001, NS not significant

Euro QOL-5D-5L Score evaluation revealed significant improvement in quality of life in both groups at 8 w (p<0.0001) (table 3). Only numerical decrease in pregabalin treated group was observed on comparison with nortriptyline (table 4).

Table 3: Effect of pregabalin and nortriptyline on Euro quality of life 5D-5L score (EQ-5D-5L)

Treatment group	Baseline	8 w
Pregabalin group (n=24 Mean+SD)	12.50±3.43	6.17±1.27####
Nortriptyline (n=24 Mean+SD)	12.15±3.25	6.65±1.60####

The data is shown as mean±SD showing Paired t test in comparison to respective baselines #p<0.05, ##p<0.01, ###p<0.001, ####p<0.0001, NS not significant

Table 4: Comparative effect of pregabalin and nortriptyline on quality of life score (EQ-5D-5L)

Duration	Pregabalin group n= 24, mean+SD	Nortriptyline group n= 24, mean+SD	p value	Statistical significance
Baseline	12.50±3.43	12.15±3.25	0.718	NS
8 W	6.17±1.27	6.65±1.60	0.255	NS

The data is shown as mean±SD showing Paired t test in comparison to respective baselines #p<0.05, ##p<0.01, ###p<0.001, ####p<0.0001, NS not significant

Table 5: Effect of pregabalin and nortriptyline on CGIC score

Treatment group	Baseline	8 w
Pregabalin (n=24, mean+SD)	5.79±0.72	1.33±0.48####
Nortriptyline(n=24, mean+SD)	6.0±0.37	2.00±0.97####

The data is shown as mean±S. D showing Paired t test in comparison to respective baselines #p<0.05, ##p<0.01, ###p<0.001, ####p<0.0001, NS not significant

Table 6: Comparative effect of pregabalin and nortriptyline on clinicians global impression of change score (CGIC)

Duration	Pregabalin group n=24, mean+SD	Nortriptyline group n= 24 mean+SD	p-value	Statistical significance
Baseline	5.79±0.72	6.0±0.37	0.210	NS
8 W	1.33± 0.48	2.00±0.97	0.004**	S

The data is shown as mean±SD showing the comparison between the groups at baseline and 8 w using student unpaired t test *p<0.05, **p<0.01, ***p<0.001, NS not significant

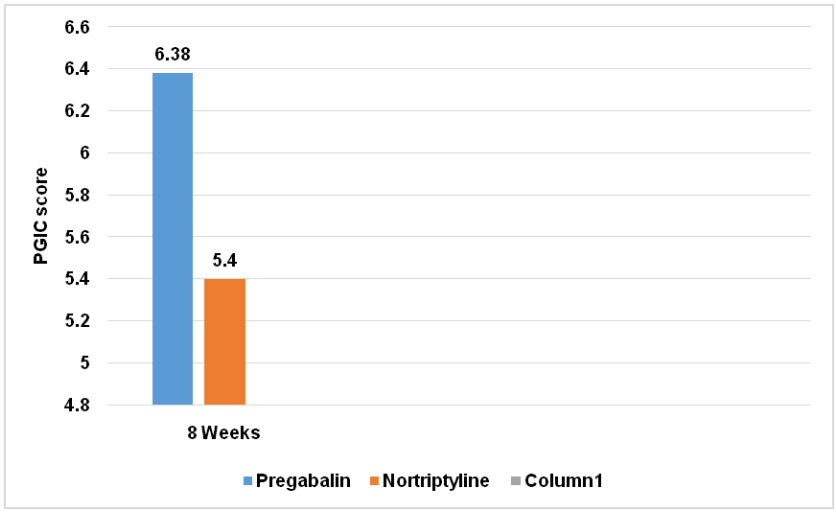

Fig. 1: Comparative effect of pregabalin and nortriptyline on PGIC score

Clinicians global impression of change score (CGIC)

Overall significant improvement in patient's condition was observed by CGIC scale (p<0.0001) in both treatment groups (table 5). However, the intergroup comparison revealed more improvement with pregabalin at 8 w (P=0.004) (table 6).

Patient global impression of change score (PGIC)

Showed overall improvement in both the groups. On comparison, pregabalin had the dominant effect (P=0.0003). (fig. 1)

DISCUSSION

Neuropathic pain is known to adversely affect the quality of life and sleep and more than 50% of patients with PHN have sleep disturbances [23].

In the present study, the effects of pregabalin and nortriptyline in patients of PHN on sleep and quality of life were evaluated. MOS sleep score and quality of life (EQ-5D-5L) were significantly improved by both pregabalin and nortriptyline.

Sabatowski R *et al.* 2004 [24] have recorded reduced mean sleep interference scores and increased health-related quality-of-life (HRQoL) in patients of PHN receiving pregabalin (150 or 300 mg/day). Effect was observed as early as first week and was maintained throughout the study of eight weeks.

Similarly, other reports have also recorded an improvement in EQ-5D-5L and sleep scores with Pregabalin in neuropathic pain. Improvements in sleep and quality of life were marginally related to the reduction in pain intensity. However, improvement in sleep quality was a significant predictor of better quality of life [25, 26]. Similar to our observations, improvement with pregabalin on domains of sleep disturbance and PGIC has also been reported [27].

Pregabalin is well documented to improve sleep parameters in painful conditions like fibromyalgia and also in generalized anxiety disorders [28]. Pregabalin primarily affects sleep maintenance and has a direct effect that is distinct from its analgesic, anxiolytic and anticonvulsant effects [29].

It is well recognized that most of the antidepressants lead to activation of serotonergic 5-HT2 receptors and increased noradrenergic and dopaminergic neurotransmission by modulating wakefulness, rapid eye movement and sleep duration. But antidepressants with prominent antihistaminic action increase sleep continuity like sedative TCA (amitriptyline, doxepin, trimipramine) and sedative antidepressants (mirtazapine, trazodone, nefazodone, mianserine). These antidepressants with strong antagonism at serotonergic 5-HT2A receptors in some patients show improvement of sleep quality even after the first drug dose [30].

In the present trial CGIC scores were found to be reduced while PGIC scores increased. Our results are in agreement with another study showing improvement on these parameters by pregabalin [31]. On comparing, pregabalin was found to be more effective than nortriptyline at 8 w on various parameters CGIC (p=0.005) and PGIC score (p=0.0003). Achar A *et al.*, 2013 [32] has recorded improvement with pregabalin in PHN patients.

Current study suffers from few limitations of being the short duration of 8 w and had a small sample size.

CONCLUSION

Both pregabalin and nortriptyline were effective in improving sleep, quality of life and overall condition in PHN. Pregabalin was found to be better than nortriptyline at 8 w on CGIC and PGIC scales and it could be a promising option, though more trials in the future with large sample size and longer duration are needed.

CONFLICT OF INTERESTS

None

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AUTHORS CONTRIBUTIONS

Dr. Kanika Khajuria conducted the study collected evaluated data and prepared the manuscript. Dr Seema Gupta designed and supervised project, while Dr Dinesh Kumar supervised the statistical analysis. Dr Dev Raj Dogra supervised work at the hospital site and Dr Vijay Khajuria assisted in final manuscript drafting.

CONFLICT OF INTERESTS

The authors declare no conflict of interest associated with this study

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