



A Study on the Efficacy and Safety of Pregabalin and Nortriptyline in Patients with Post-herpetic Neuralgia

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ABSTRACT

Post-herpetic neuralgia is commonest long-term complication of varicella-zoster virus reactivation. The occurrence of PHN in HZ patients is 5 to 30%. The objective of the current study was to compare the efficacy and safety of pregabalin and nortriptyline in patients with post-herpetic neuralgia. This is a prospective, randomized, double-arm, double-blinded study, carried out in GMC/GGH, Ongole, for a period of 1 year. The sample size was 300. One group received oral pregabalin 150 mg BD and others received oral nortriptyline 25 mg OD and a placebo for 8 weeks. The patients were asked for follow-up at the end of 4 and 8 weeks, respectively. The LANSS score was used to assess neuropathic pain and its severity. Mean LANSS score in the Pregabalin group at baseline was 18.89 ± 4.29 and the nortriptyline group was 17.97 ± 4.98 . After 8 weeks of treatment, they were reduced to 10.89 ± 3.94 and 9.92 ± 4.13 , respectively. The difference in the reduction of the LANSS score was significant at the end of the study. The majority of ADRs reported were mild in severity. In this study, both medications were effective in reducing pain in PHN, with pregabalin showing significant improvement at the end of the 8 weeks. Both drugs were safer with mild side effects.

Keywords: Post-herpetic neuralgia, varicella-zoster virus, Pregabalin, Nortriptyline, LANSS score

INTRODUCTION

Post-herpetic neuralgia (PHN) is the most common long-standing difficulty of reactivating the varicella-zoster virus (VZV). The primary characteristic feature of PHN is a lancinating/burning pain in a unilateral dermatomal pattern that lasts for ≥ 3 months after the onset of a herpes zoster (HZ) outbreak.[1] The condition arises from the reactivation of the latent varicella-zoster virus (VZV), which remains dormant in the sensory ganglia of the cranial nerves or the dorsal root ganglia of the spinal cord following a prior episode of chickenpox.[2] The occurrence of PHN in HZ patients is 5 to 30%[3,4], and elderly, immunocompromised states and psychological or physical trauma are some of the risk factors for the development of PHN.[5] Three basic treatment options are discussed in the literature for PHN.[6] The first is prevention, which concentrates on identifying the population at risk for contracting HZ and administering two doses of varicella vaccine. The second option is early identification and treatment of an acute HZ infection, as delay might become a risk factor for the development of PHN. The third option is symptomatic treatment of PHN via multimodal medication regimens, which includes oral anticonvulsants, antidepressants, or topical Lidocaine, topical capsaicin, tramadol, opioids (controversial), botulinum toxin and interventional procedures like nerve block, nerve stimulation and radio ablation. Even though many modalities of treatment are available, complete resolution of symptoms is rare, and PHN in some people is very severe, affecting patient's daily routine activities and

leading to reduced quality of life and psychological stress.[7] This is one reason for undertaking this study, and the other reason is that comparative studies are lacking in terms of the treatment modalities for their effectiveness in PHN. The objective of current study was to compare the efficacy and safety of pregabalin and nortriptyline in patients with post herpetic neuralgia.

MATERIAL AND METHODS

This is a prospective, randomized, double-arm, double-blinded study, carried out in collaboration with the dermatology outpatient department of a GGH, Ongole, for a period of 1 year in accordance with good clinical practices after the approval of the ethics committee (IEC/GMC-OGL/102/2023). Based on the previous studies, the calculated sample size was 313, taking the precision level as 5% of prevalence. After obtaining informed consent, patients were enrolled in the study according to the inclusion and exclusion criteria. All the 300 patients were randomized by computer-generated randomization into two groups, each group had 150 patients. One group received oral pregabalin 150 mg BD for 8 weeks and the other group received oral nortriptyline 25 mg OD and a placebo OD for 8 weeks. The patients were asked for follow-up at the end of 2 weeks and 8 weeks, respectively. The Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS) was used to assess neuropathic pain and its severity. It consists of seven items: Five sensory items and two examination findings (allodynia and pinprick test). More than 12

points out of 24 suggest a neuropathic pain. All the patients were asked to note down adverse drug reactions experienced by them during the study, and they were also asked about the adverse drug reactions during each hospital visit. The patients who had completed the total study duration were only considered for the final assessment.

Inclusion Criteria

Adult patients (>18 years–65 years) of either gender. Patients having a LANSS score >12 and who gave consent were included in the study.

Exclusion Criteria

Patients with pregnancy and lactation. Patients hypersensitive to any of the test drugs, cardiac disease, seizure disorder, liver disease, impaired kidney functions, or who are already on gabapentinoids or Tricyclic antidepressants. Patients with other painful conditions like diabetic neuropathy, cancer pain and fibromyalgia.

RESULTS

Out of the 313 patients, a total of 300 patients had completed the total study duration, of which 172 were male, and 128 were female. The mean age of the sample was 54.1 ± 4.3 years. Mean LANSS score in the pregabalin group at baseline was 18.89 ± 4.29, and in the Nortriptyline group was 17.97 ± 4.98. After 4 weeks of using the treatment, a significant difference was found in both groups and the mean LANSS score was decreased to 16.97 ± 5.1 & 15.78 ± 5.01, respectively. After 8 weeks of treatment, the score was reduced to 10.89 ± 3.94 in the pregabalin group and 9.92 ± 4.13 in the nortriptyline group. The reduction in LANSS score in both pregabalin (Table 1) and nortriptyline (Table 2) groups before the start of the study and after 4 and 8 weeks was significant, with a *p-value* of < 0.00001. The difference in the reduction of LANSS score between the two groups was significant at the end of the study, with a *p-value* of 0.0383 (*p-value* < 0.05), indicating that pregabalin showed improved efficacy when compared with nortriptyline (Table 3).

Adverse drug reactions in pregabalin group were reported by 84 patients and the reactions were nausea (n=28), headache (n=17), weigh gain (n=10), somnolence(n=5) and constipation(n=5). Adverse

drug reactions reported in nortriptyline were nausea (n=16), vomiting (n=13), dry mouth (n=7) and drowsiness (n=5) in 42 patients. Majority of the ADRs were mild in severity in pregabalin (n=71) and in nortriptyline group (n= 33).

DISCUSSION

Study sample has more males than females which is supported by the study done by Tanenbaum HC *et al.* [8] and contrary to the study done by Cintia Muñoz-Quiles *et al.*[9]

A sample size of 79.6 % was in the age group of 51 – 65 years and most common involvement of thoracic dermatome (71.34%) which is similar to the studies done by Amicizia D *et al.*[10] and Weaver, Bethany A *et al.*[11]. This indicates that the increasing age is a risk factor for development of PHN. The reason is that Herpes zoster virus in old age, which is located in the dorsal root ganglion gets reactivated which in turn leads to the degeneration of the spinal nerve sensory system and increased neuropathic pain.[12]

Mean LANSS score was significantly decreased in the Pregabalin group from baseline (18.89 ± 5.29) to 8 weeks later (10.89 ± 3.94). Similar findings were seen in the studies done by R.H. Dworkin *et al.*[13] and Kopel J *et al.*[14] Pregabalin is structurally similar to GABA and it decreases the release of excitatory neurotransmitters which are involved in causing neuropathic pain by binding to alpha2-delta protein subunit of voltage-gated calcium channels.[15]

Effectiveness of Nortriptyline was proved by the significant reduction in Mean LANSS score from baseline (17.97 ± 4.98) to 8 weeks later (9.92 ± 4.130), supported by the studies of M. Cuneyt Ozmen *et al.*[16] and Watson CP *et al.*[16] Nortriptyline inhibits the reuptake of Noradrenaline and increases its levels acting within dorsal root ganglia on β2-adrenoceptors expressed by non-neuronal satellite cells. This stimulation of β2-adrenoceptors reduces the neuropathy-induced production of TNFα, resulting in the relief of neuropathic pain. Antagonism of N-methyl-D-aspartate (NMDA) glutamate receptors shown by nortriptyline also contributes to decrease in neuropathic pain.[17,18]

The current study shows that there is significant difference in the effectiveness of pregabalin and nortriptyline in PHN, which is

Table 1: Mean LANSS score in Pregabalin group

Study medications	Baseline	4 weeks	8 weeks	<i>p-value</i>
Pregabalin	18.89 ± 4.29	16.97 ± 5.1	10.89 ± 3.94	< 0.00001

Table 2: Mean LANSS score in

Study medications	Baseline	4 weeks	8 weeks	<i>p-value</i>
Nortriptyline	17.97 ± 4.98	15.78 ± 5.01	9.92 ± 4.13	< 0.00001

Table 3: Mean LANSS score in both the groups

Study Medications	Baseline	4 weeks	8 weeks
Pregabalin	18.89 ± 4.29	16.97 ± 5.1	10.89 ± 3.94
Nortriptyline	17.97 ± 4.98	15.78 ± 5.01	9.92 ± 4.13
			<i>p</i> = 0.0383 (<i>p</i> value <0.05)

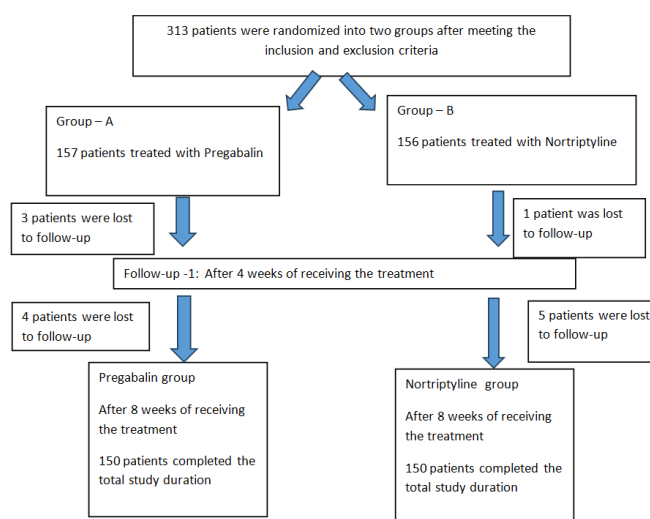


Fig 1: Flow diagram representing the study

similar to the study done in 48 patients by Jour *et al*[19] study in which pregabalin was found to be more effective than nortriptyline (Fig 1).

A total of 84 patients in the pregabalin group and 42 patients in nortriptyline group reported ADRs. No serious adverse event/ ADR was occurred during the entire study.

Limitations of the study

Single centered study and short duration of the study.

CONCLUSION

In this study both pregabalin and nortriptyline were effective in reducing pain in PHN. However, pregabalin showed significant improvement than nortriptyline at the end of the 8 weeks. Both the drugs were safer with mild side effects, though fewer ADRs were noted in nortriptyline group. However further studies are needed to assess the long-term efficacy and safety.

CONFLICT OF INTEREST

No conflict of interest.

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