Original Article

Pregabalin and Amitriptyline as Monotherapy or as Low-Dose Combination in Patients of Neuropathic Pain: A Randomized, Controlled Trial to Evaluate Efficacy and Safety in an Eastern India Teaching Hospital

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Abstract

Objectives: The main objective is to compare efficacy and safety of pregabalin and amitriptyline monotherapy with their low-dose combination in patients of neuropathic pain (NeuP). **Methodology:** In this parallel-group, open-label interventional study at the Neurology Outpatient Department of Bankura Sammilani Medical College, a total of 147 patients were randomly allocated into three groups and were prescribed the following drugs – Group P (n = 42) pregabalin 150 mg once daily, Group A (n = 34), amitriptyline 25 mg once daily, and Group Z (n = 37) = pregabalin (75 mg) + amitriptyline (10 mg) as combination once daily. They were followed up after 4, 8, and 12 weeks. Efficacy was assessed by NeuP symptom inventory score (NPSI) and safety was assessed by treatment-emergent adverse events. **Results:** Final assessment was done on 92 patients (P = 31, A = 31, Z = 30). Males were predominant (71.7%). NPSI score significantly decreased in every group from baseline ($P < 0.0001$). There was no difference of NPSI score between groups at any level of follow-up. Percentage of adverse drug reactions were maximum (44.9%) in amitriptyline monotherapy group and lowest in combined group. However, amitriptyline monotherapy was the cheapest treatment option among these three. **Conclusion:** Combining pregabalin and amitriptyline at low doses proved to be equally effective but more tolerable compared to individual higher dosage monotherapy. However, if tolerability is good, amitriptyline monotherapy can be an attractive choice in economically challenged group of patients.

Keywords: Amitriptyline, controlled trial, low-dose combination therapy, neuropathic pain, pregabalin, randomized

Introduction

Neuropathic pain (NeuP), over the past few decades, has become a serious global health problem. It has turned to be a nightmare for the patient and a tough challenge for the physician. International Association for the Study of Pain (IASP) has defined NeuP in 2008 as " Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[1] The patient feels an unusual burning, tingling, or electric shock-like sensation, often associated with depression, anxiety, and sleep disorders. As evident from two population-based studies from Europe, the prevalence of NeuP is 7%–8% among the population.[2,3] In a study done at Tata Memorial Hospital, Mumbai, 25.14% of cancer patients attending pain clinic were found to be suffering from NeuP.[4]

Among the available class of medicines for management of NeuP, gabapentinoids (pregabalin, gabapentin), and tricyclic antidepressants (amitriptyline and others) have shown the most promising results. In 2004, USFDA approved the use of pregabalin for the treatment of NeuP.[5] On the other hand, amitriptyline has been recommended by the European Federation of Neurological Sciences 2010[6] and National Institute for Clinical Excellence (NICE) guideline 2013.[7] Moreover, the NICE guideline 2013 advocated that it might be helpful to use low-dose combination therapy of suitable drugs to improve efficacy and minimize toxicity among recipients.[7] In spite of substantial increase in the number of trials and introduction of newer agents, treatment failed to reach pain control in <50% of patients.[8] It is noteworthy that none of the drugs can modify the disease process and are meant only for subjective pain control. Tricyclic antidepressant, though highly effective in NeuP, is associated with a number of adverse drug reactions (ADRs), including dry mouth, sedation, and postural hypotension, especially when given in high doses. Likewise, pregabalin though relatively safe, frequently is associated with somnolence and postural hypotension which severely affect the quality of life among recipients. In spite

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of thorough search through published literature, we did not find any study which incorporated this two first-line drugs in a low-dose combination and compared its efficacy with individual monotherapy at a higher dosage. Under these circumstances, we performed this study at the Neurology Outpatient Department (OPD) of Bankura Sammilani Medical College to find out the suitable regimen with maximum efficacy and tolerability and patient compliance and also at a low cost.

Aims and objectives

Primary objective was to compare efficacy of pregabalin (150 mg) monotherapy, amitriptyline (25 mg) monotherapy, and pregabalin (75 mg) plus amitriptyline (10 mg) as combination therapy in reducing NeuP as measured by comparing change of NeuP symptom inventory (NPSI) score[9] from baseline over three follow-up visits (after 4 weeks, 8 weeks, and 12 weeks from inclusion). Secondary objectives were to assess safety of investigational drugs in three aforesaid treatment groups by recording incidence of treatment-emergent adverse events (TEAEs) and also changes in hemodynamic (blood pressure [BP] and electrocardiography [ECG] finding) and biochemical parameters (blood glucose, serum creatinine, and serum glutamic pyruvic transaminase [SGPT]) from baseline over three follow-up visits (after 4 weeks, 8 weeks, and 12 weeks from inclusion).

Methodology

It was a randomized, parallel-group, open-label interventional study carried out at the Neurology OPD of Bankura Sammilani Medical College for duration of 12 months from February 1, 2015 to January 31, 2016.

Null hypothesis

There is no difference in change of mean NPSI score from baseline over three follow-up visits (after 4, 8, and 12 weeks) at either level between pregabalin monotherapy (150 mg), amitriptyline monotherapy (25 mg), and pregabalin (75 mg) plus amitriptyline (10 mg) as combination therapy.

Patients of 18–75 years of age, who presented to the Neurology OPD within that stipulated period were included in the study if they are diagnosed by consultant neurologist as patients suffering from NeuP, scored ≥4 at DN_4 NeuP diagnostic questionnaire[10] and numeric pain rating scale[11] at baseline presentation. Patients who needed surgical intervention for the primary disease, serum creatinine level ≥1 mg%, SGPT level >3 fold of normal value, cardiac conduction defect, known allergy/contraindication to any of the study medication, benign hyperplasia of prostate or history of urinary retention, and pregnant and lactating mothers were excluded from the study.

Sample size

A sample size of 91 (approximately) was determined assuming predetermined value of level of significance as 0.05, power of the study as 80%, expected difference in change of NPSI score between two groups at least 10 from baseline, and standard deviation of NPSI being 13.927 as determined by a pilot study. Assuming 20% dropout, the adjusted sample size was set to be 114 in three groups. We decided to include 38 patients in each group. They were randomized using computer-generated random numbers into three treatment groups.

Parameters to be studied

NPSI score[9] was used to estimate the intensity of NeuP. Change of NPSI score in individual group reflected efficacy of respective drug. Final score ranges from 0 to 100. A greater score indicates more severe pain. Safety was assessed by comparing the incidence of adverse events that emerged as a result of treatment in each group and also recording the changes in physiological and biochemical parameters in these groups.

Ethical consideration

This study was done following the principles of the Declaration of Helsinki for study on human subjects. This study was conducted only after obtaining proper written approval from the Institutional Ethics Committee. Written informed consents were obtained from every study patient or their legal representatives.

Clinical Trial Registry India registration

This trial was registered in Clinical Trial Registry India (CTRI) under Indian Council for Medical Research, Government of India. The registration number is CTRI/2016/08/007163.

Procedure of data collection

After getting approval from the institutional ethical committee and informed written consent from the patients, we enrolled the patients on the basis of aforesaid inclusion and exclusion criteria. After arrival of the patients at neurology OPD, consultant neurologist examined them. Those who were diagnosed by him completed a printed preformed validated DN_4 NeuP questionnaire.[10] Those who scored ≥4 were taken as having NeuP. At baseline level, a Numeric Pain Rating Scale assessment was done. Those who scored ≥4 were taken as having significant pain. In addition, a baseline assessment of NPSI score[9] was done. These were accompanied by necessary baseline laboratory investigations, that is, complete blood count, blood sugar, liver function test, urea, creatinine estimation, 12-lead ECG, etc. Then, the patients were randomly allocated into three groups using preset computer-generated random numbers and were prescribed the following drugs by consultant neurologist. Group P patients were given pregabalin 150 mg once daily dose, Group A patients received amitriptyline 25 mg once daily dose, and Group Z patients received pregabalin (75 mg) + amitriptyline (10 mg) as combination Once daily.

As the etiology of NeuP was diverse among the patients, the cotreatment (control of blood glucose, physiotherapy, etc.,) were allowed to continue in them. The study medications (pregabalin or amitriptyline) were added with those treatment protocols. Nonsteroidal anti-inflammatory drugs were used as rescue medication if required. No opioid was prescribed to avoid

any similar mechanism of action overlapping with the study medications.

Patients were followed up for three visits, after 4 weeks, 8 weeks, and 12 weeks interval from the day of starting treatment. At the end of follow-up after 12 weeks, all baseline investigations were repeated. The dropouts or withdrawal if any along with reasons for the same were recorded.

For safety assessment, we calculated the total number of TEAEs in the three groups. Causality was assessed by Naranjo's ADR Causality Assessment Scale and severity was assessed by Hartwig's Modified Severity Assessment Scale. Moreover, we also looked for any change of baseline physiological and biochemical parameters which were repeated after 12 weeks and any difference in changes between the groups were noted.

Analysis of data

Data were analyzed with the help of SPSS version 22 and GraphPad Prism version 5 (IBM statistics for Windows, IBM corpn, Armonk, New York, USA, Graph Pad software, La Jolla, CA, USA). Normality of distribution of the data was checked using one-sample Kolmogorov–Smirnov test and Shapiro–Wilk test. For estimating the change in NPSI score within a particular group from baseline, we used Friedman's ANOVA followed by Dunn's *post hoc* analysis. Whereas for estimating difference between different treatment groups at different follow-up visits, we used Kruskal–Wallis *H*-test (Kruskal–Wallis ANOVA) followed by Dunn's *post hoc* analysis. All analyses were two sided. $P < 0.05$ was considered as statistically significant.

Results

After screening 147 patients, 110 patients were enrolled. However, 18 patients (16.4%) were lost to follow-up. Final analysis was done on 92 patients. The flowchart for patient encounter is given in Figure 1.

Out of 92 patients, 66 were male (71.7%). Mean age of the patients was 48.61 years. However, the groups were comparable with respect to age ($P = 0.070$) and gender distribution ($P = 0.244$). There were no statistically significant differences among groups in terms of BMI, systolic and diastolic BP, fasting blood glucose, serum creatinine, and SGPT level. As per diagnosis by consultant neurologist, different etiologies of NeuP were found among the study groups and the result is presented in Figure 2.

At baseline, the study groups were comparable in terms of mean NPSI score as Kruskal–Wallis test yielded no significant difference between groups ($P = 0.7897$). Still after 4, 8, and 12 weeks, there was no significant difference in mean NPSI score between the groups ($P > 0.05$). Regarding changes within a group, Friedman's ANOVA reveals that mean NPSI score decreased significantly in all three groups from baseline over three follow-up visits. At every follow-up, *P* value is significant in all three groups. Table 1 shows distribution of NPSI score among three groups over three follow-up visits compared to the baseline.

Figure 3 shows the means plot of NPSI score in three groups over the period of follow-up.

Altogether, we encountered a total of 89 ADRs in 61 patients with 1.46 ADRs per patient. Sedation was the most common ADR accounting for 42.7% of ADRs. Amitriptyline group patients suffered from maximum percentages of ADRs (44.9%) among all three groups. According to Naranjo's Causality Assessment Scale, 83.2% of ADRs were probable and rest were possible, whereas none were deemed as definite or doubtful. All of the ADRs were mild in severity which did not require any treatment, discontinuation of therapy, hospitalization, or caused serious damage to the recipients. Figure 4 shows the distribution of ADRs in all groups

Discussion

Despite having a number of treatment options, the management of NeuP still remains suboptimal. Occurrence of ADRs on long-term use and high cost of treatment often reduces compliance to treatment. Hence, it is of utmost importance to treat using a drug(s) with optimum balance between efficacy and safety and also available at an affordable cost. We found very few studies comparing individual monotherapy with low-dose combination therapy in the management of NeuP. Amitriptyline and pregabalin have two different targets of action to reduce the hypersensitivity of NeuP. Hence, there may be a synergism of effect in NeuP whenever they are given in combination.

In our study, 16.3% of patients were lost to follow-up. Poor compliance due to excessive drowsiness and postural hypotension were the leading causes of dropout. Pregabalin group suffered from maximum percentages of dropouts. Mean age of the patients (48.6 years) was less than that found in the studies done by Toelle *et al*.[12] (61 years), Banerjee *et al*.[13] (53.5 years), Padmini *et al*.[14] (57 years), Tanenberg *et al*. (61.9 years),[15] etc. All treatment groups were comparable in terms of age and gender distribution which minimizes

Table 1: Distribution of neuropathic pain symptom inventory score among three groups over three follow-up from baseline

	P	A	Z	*P* (Kruskal-Wallis)
Baseline (D_0)	54.581±11.162	51.226±13.615	56.433±12.400	0.7897
After 4 weeks (D_1)	40.839±9.812	38.258±12.220	37.967 10.666	0.3106
After 8 weeks (D_2)	31.290±7.395	31.129±12.672	27.900±9.167	0.1560
After 12 weeks (D_3)	24.129±6.125	23.452±8.801	21.133±6.977	0.0911
P (Friedman's ANOVA)	<0.0001	<0.0001	<0.0001	

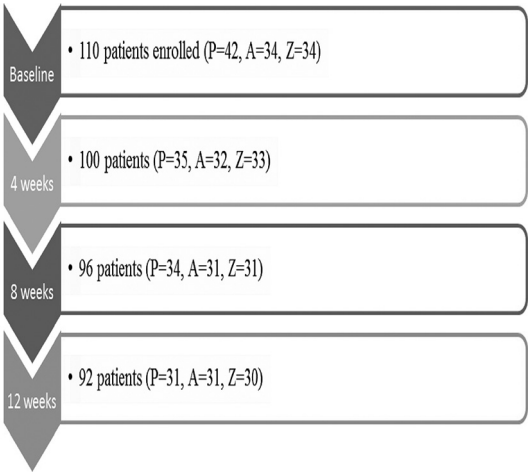

Figure 1: Flowchart of patient enrollment and follow-up

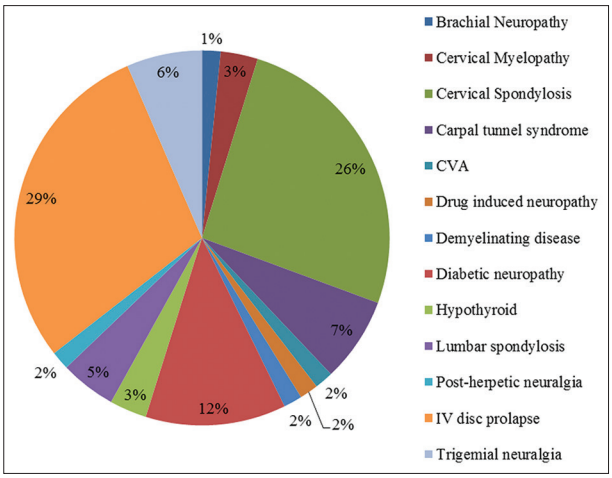

Figure 2: Different etiologies of neuropathic pain

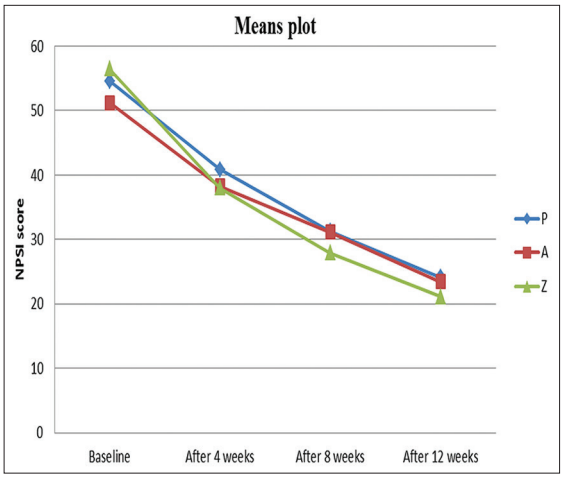

Figure 3: Means plot of neuropathic pain symptom inventory score in three groups

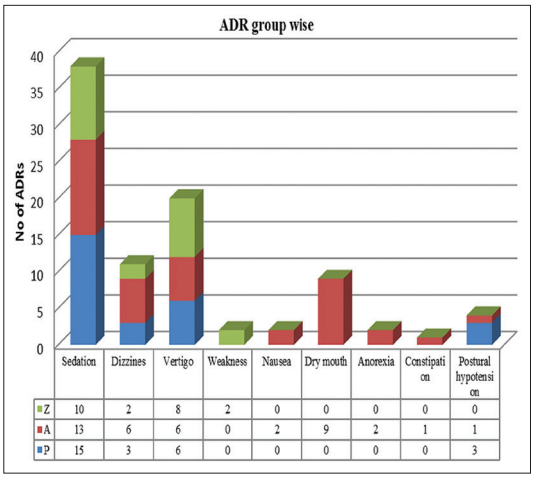

Figure 4: Distribution of adverse events in all groups

chance of selection bias in our study, as subjective pain perception can vary according to age and gender.

While examining the etiology of NeuP, we found intervertebral disc prolapse with radiculopathy was the most common cause followed by cervical spondylosis. Recently published studies were done in specific neuropathic conditions, that is, diabetic neuropathy, postherpetic neuralgia, etc. However, the NICE guidelines 2013[7] and also IASP guideline 2015[8] recommended that clinical trials should be done on the basis of symptomology rather than the etiology-specific classification. Here, the drugs act to decrease the subjective pain sensation rather than acting as a disease-modifying agent. Ghosh *et al*.[16] used NCV study as a tool for inclusion of the patients. However, NCV study was only optional in our study, as none of these drugs tend to change the NCV pattern of the patients and significant pain can be present in patients of normal NCV study.

As per subjective pain control, all three groups showed significant reduction of pain from baseline ($P < 0.0001$). Changes at all levels of study were significant. Similar result was found in earlier studies[12-15,16] where these two drugs proved their efficacy in reducing NeuP. For statistical analysis, Devi *et al*.[14] used repeated-measures ANOVA followed by Bonferroni's *post hoc* test. However, we found that NPSI scores in all treatment groups were distributed in a nonparametric manner. Thus, for assessing changes within groups, we had chosen Friedman's ANOVA followed by Dunn's *post hoc* test.

Regarding between group variations of NPSI score, we did not find any significant difference among three groups at any level of study. This implies that change in NPSI score from baseline was not different in three groups. Low-dose combination of pregabalin and amitriptyline yielded similar pain reduction to their higher dose monotherapy. Achar *et al*.[17] found that combined pregabalin and amitriptyline showed better pain reduction than individual monotherapy groups. They used either pregabalin 75 mg twice daily or amitriptyline 25 mg once daily, and in the third group, they used both the drugs adding the same dose of monotherapy group. Here, the third group was given a clear-cut advantage of higher dosage which imposed an inequality among the groups and selection bias at baseline. In our study, the combined group patients received

both the drugs at lower doses, for which the combined group showed similar result with monotherapy groups.

For safety assessment, ADRs were common in all treatment groups, but all were mild in nature and did not require any action. All the drugs were lipophilic and hence have a good brain penetration. For these reasons, CNS adverse effects were predominant, manifested by sedation, dizziness, vertigo, nausea, anorexia, etc. Dry mouth, owing to anticholinergic action, was exclusively found in amitriptyline group in nine patients. In the combined group, patients suffered from less percentage of ADRs than the individual pregabalin or amitriptyline groups. Similar kind of ADRs was found in earlier studies. Baseline physiological and biochemical parameters remained unchanged after treatment of 12 weeks except systolic BP in combined group decreased significantly from baseline after 12 weeks.

As per cost of therapy, amitriptyline 25 mg monotherapy was the cheapest, accounting for INR 80–90/1–1.5 US dollar per month, whereas pregabalin 150 mg costs for 450 INR/7–8 US dollar per month and low-dose combination of these two costs 300 INR/4–5 US dollar per month.

Limitations

Our study had some limitations as follows: first, no placebo arm was included for ethical reasons. Second, it was only an open-label study. As no financial support was there, patients had to buy their own medicines from fair price shop or retail medicine shop. For this reason, double blinding was not possible. Third, study duration was only 12 weeks which is relatively short to measure the long-term effects of the drugs. Fourth, no dose escalation was done at any level. The patients who remained nonresponsive at lower dosage might have shown response if the dose was increased within a tolerable limit. Finally, concomitant therapy was a big confounding factor in this study. In some groups, (i.e., diabetic neuropathy) the symptomatic improvement might have also been aided by improvement of causative factors also (i.e., improved glycemic control) which might have skewed the result.

Conclusion

In this open-label, parallel group, 12 weeks, interventional study, we found that pregabalin and amitriptyline, both as individual monotherapy and low-dose combination, were highly effective in reducing NeuP from baseline. Combining pregabalin and amitriptyline at low doses proved to be equally effective as individual monotherapy group where either drug had been used at higher doses. Amitriptyline was associated with maximum number of ADRs. Combined group also had better tolerability than individual monotherapy groups. Considering efficacy, safety, and cost, combined low-dose pregabalin and amitriptyline proved to be most optimum drug with best combination of high efficacy, better tolerability, and improved cost-effectiveness in adult patients of NeuP among all four treatment options. However, if tolerability is good, amitriptyline can be a very attractive choice in economically challenged group of patients. In future, we plan to undertake this study for longer duration and with double blinding.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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