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Original Research Article

Is pregabalin better than gabapentin in treatment of neuropathic pain? An observation-based study at tertiary care centre of North India

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ABSTRACT

Background: The present study was undertaken to assess the efficacy of pregabalin and gabapentin in treatment of neuropathic pain at a government tertiary care hospital of Uttar Pradesh, India. Due to indiscriminate use of drugs for treatment of neuropathic pain, selection of an effective drug is need of hour.
Methods: Out of 130 patients, 62 patients were given pregabalin and 68 were given gabapentin. Douleur Neuropathique 4 questionnaire (DN4) which was used to diagnose patients of neuropathic pain. Efficacy of drug was based on their capability to decrease neuropathic pain at regular intervals.
Results: On comparing the efficacy of drugs by their ability to decrease neuropathic pain, there was a significant difference when comparing pregabalin and gabapentin, pregabalin being statistically significant than gabapentin.
Conclusions: On the basis present study efficacy of pregabalin 300 mg once daily brought better improvement of symptoms and sign than that of gabapentin 600 mg administered once daily dose. So pregabalin is a better drug than gabapentin.

Keywords: Nociception, Questionnaires, Neurotransmitters, Anticonvulsant

INTRODUCTION

Pain is a distressing feeling often caused by intense or damaging stimuli. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." In medical terminology, pain is regarded as a symptom of an underlying condition.[1-3] Pain is the most common reason for physician consultation in most developed countries.[4,5] Two types of pain are essentially common, i.e., nociceptive pain and neuropathic pain. The International association for the study of pain (IASP) defines Neuropathic pain as a "pain caused by a lesion or disease of the somatosensory nervous system."[6] The lesion or disease can be localized at the level of peripheral nervous system or central nervous system. Typical clinical manifestations of neuropathic pain are - spontaneous burning pain, electrical and shooting pain, allodynia, and hyperalgesia. The most commonly used screening method in OPDs for the diagnosis of neuropathic pain is DN4 questionnaire (Douleur Neuropathique 4 (DN4). The initial choices for the treatment of neuropathic pain are tricyclic anti-depressants (TCA), gabapentinoids, and serotonin norepinephrine reuptake inhibitors (SNRI). Sometimes tramadol is added either alone or in

combination with first line. Fixed-dose combination (FDC) of gabapentinoids i.e., pregabalin with TCA such as nortriptyline is synergistic and improves treatment adherence. The fact sheet of IASP for 2014-2015 reported 7%-8% prevalence of NeP in adults. Estimates of NeP vary considerably by aetiologies with 20% cancer-related NeP, 26% DN, 2.6%-10% of chronic PHN, up to 40% postsurgical NeP, 35% having HIV-related NeP, and 37% chronic low back pain (LBP) NeP. A recent meta-analysis identifies the prevalence of pain with neuropathic features having best estimates between 6.9% and 10%.[7] The management of neuropathic pain is grossly divided into different lines of treatment with respect to their utilization and acceptance. Medications form the basis of first- and second-line therapy for neuropathic pain. Tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentanoids, tramadol, lidocaine, and capsaicin are the most effective options.[3,5,8-12] Gabapentinoids include gabapentin and pregabalin. They are a group of anticonvulsant medications that act by blocking presynaptic alpha-2-delta calcium channels in the dorsal horn, inhibiting neurotransmitter release.[3,14,15] They are considered first line agents in the treatment of neuropathic pain by multiple international societies.[9,13,16] Gabapentin and pregabalin both have been shown to be effective in post herpetic neuralgia and diabetic peripheral neuropathy.[16-21]

METHODS

Study design, location and duration

Current study was designed as randomized, prospective, open labelled study conducted at department of pharmacology and Swaroop Rani Nehru Hospital, associated with Moti Lal Nehru medical college, Prayagraj, India from May 2020 to April 2021 for a period of 12 months.

Inclusion criteria

Patients of either sex, age ≥18 years, confirmed diagnosis of neuropathic pain based on clinical presentation and patient willing to give consent were included in the study.

Exclusion criteria

Age <18 years, other types of pain not confirmed to be neuropathic pain, patient not willing to give consent and patient with comorbid conditions were excluded from the study.

Procedure

The patients were evaluated on basis of proper history, presenting symptoms and past symptoms. Patients diagnosed as a case of neuropathic pain attending outpatient department of medicine, Swaroop Rani Nehru Hospital. Patient were enrolled in the study after signing the consent form which were provided in Hindi and English both or any other language patient can understand. Drugs: the drugs which we compare in the study were pregabaln and gabpentin, these two were most commonly used and available at our tertiary care centre where study was conducted.

Table 1: Douleur neuropathique 4 questions (DN4).

Douleur neuropathique 4 questions
Patient interview: Answer the four questions below with yes or no for each item:
Question 1: dose your pain present by one or more of the following characteristics.
Pain feels like burning Sensation of painful cold Pain feels like electric shocks
Question 2: in the same area, is your pain associated to one or more symptoms?
Tingling Pins and needles Numbness Itching
Patient examination
Question 3: is the pain located in an area where the exam unveils?
Hypoesthesia to touch? Hypoesthesia to pinprick?
Question 4: is the pain provoked or increased by?
Brushing?
Yes=1/No= 0 patient's Score: /10
Scores ≥ 4/10 indicate neuropathic pain

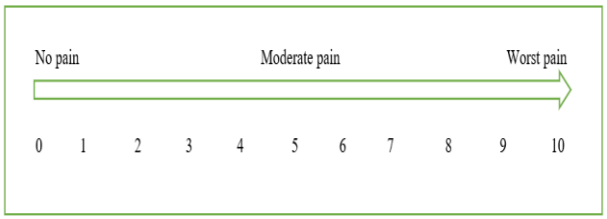


Figure 1: Numeric pain rating scale (NPRS).

Pregabalin: it is a 3-isobutyl derivative of gamma-amino butyric acid (GABA) with anti-convulsant, anti-epileptic, anxiolytic, and analgesic activities. Although the exact mechanism of action is unknown, pregabalin selectively binds to alpha-2-delta (α2σ) subunits of presynaptic voltage-dependent calcium channels (VDCCs) located in the central nervous system (CNS). Binding of pregabalin to VDCC α2σ subunits prevents calcium influx and the subsequent calcium-dependent release of various neurotransmitters, including glutamate, norepinephrine, serotonin, dopamine, and substance P, from the presynaptic nerve terminals of hyper excited neurons; synaptic transmission is inhibited and neuronal excitability is diminished. Pregabalin does not bind directly to GABA-A or GABA-B receptors and does not alter GABA uptake or degradation. Pregabalin is an

inhibitor of neuronal activity used for therapy of painful neuropathy and as an anticonvulsant. Gabapentin: it is a synthetic analogue of the neurotransmitter gamma-aminobutyric acid with anticonvulsant activity. Although its exact mechanism of action is unknown, gabapentin appears to inhibit excitatory neuron activity. This agent also exhibits analgesic properties.

Diagnosis

Neuropathic pain diagnosis is based on Douleur Neuropathique en 4 questions and assessed by numerical pain scoring scale. The Hindi version of DN4 questionaire is validated by an article by Gudala et al in korean journal of pain.[22] Douleur Neuropathique en 4 questions (DN4) has seven items related to symptoms and three related to clinical examination. It is simple to use and has been translated into numerous languages. A sensitivity of 83% and a specificity of 90% have been reported, and the seven sensory descriptors have been used as a self-report tool with similar accuracy.[23,24] DN4 questionnaire for Neuropathic pain assessment is most commonly used screening test in day-to-day practice. DN4 (or neuropathic Pain 4 questions in French) was developed by French neuropathic pain group. It helps in the differentiation of neuropathic pain from non-neuropathic pain.

Interpretation

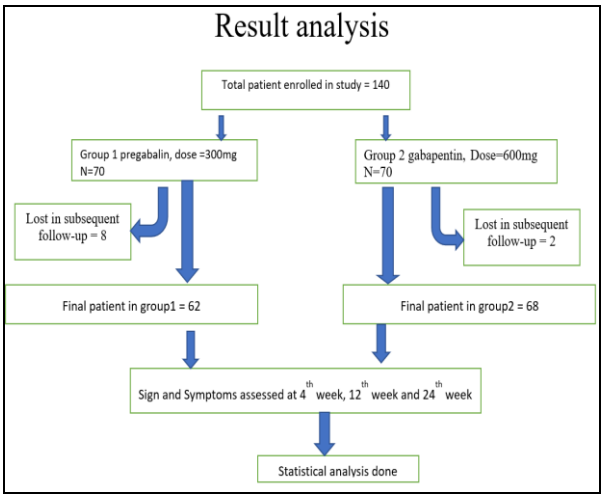
Written informed consent was taken from all the participants and a cut off score of 4 was reported to have a predictive value of 86%, a sensitivity of 82.9%, and a specificity of 89.9%.

Clinical scoring system

Objective signs and subjective symptoms were observed at baseline (before treatment) and at 4th week, 12th week and 24th week after treatment initiation. The Numeric Pain Rating Scale (NPRS) an outcome measure is a unidimensional measure of pain intensity in adults. The NPRS is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0-10 integers) that best reflects the intensity of his/her pain. The common format is a horizontal bar or line. Similar to the VAS, the NPRS is anchored by terms describing pain severity extremes. The 11-point numeric scale ranges from '0' representing one pain extreme (e.g., “no pain”) to '10' representing the other pain extreme (e.g., “pain as bad as you can imagine” or “worst pain imaginable”).

Statistical analysis

Data were summarised as mean±SE (standard error of mean). Groups were compared by independent student’s t test. Groups were also compared by repeated measures analysis of variance (ANOVA). A two tailed p for all statistical value less than 0.05 ($p<0.05$) was considered significant. All statistical analyses were performed using SPSS software version 20.



Figutre 2: Statistical analysis.

RESULTS

Patients attending medicine OPD on particular days with symptoms of neuropathic pain were invited to participate in the study. 140 patients were enrolled, 10 of them did not come for follow up, thus on final 130 patients were included in study fulfilling the inclusion criteria and giving their consent for inclusion in the study were enrolled and were randomly divided into two groups.

Demographic distribution details

In our study, mean age of population is 43.02±16.02, while in group 1 (pregabalin) has average of 42.32±16.03 and group 2 (Gabapentin) has 43.66 16.358, so these groups are comparable in terms of age distribution. Out of 130 patients, total female were 57 (43.8%) and male were 73 (56.2 %), in group 1 (pregabalin) total female were 28 and 34 were male. And in group 2 (gabapentin), females were 29 and male were 39.

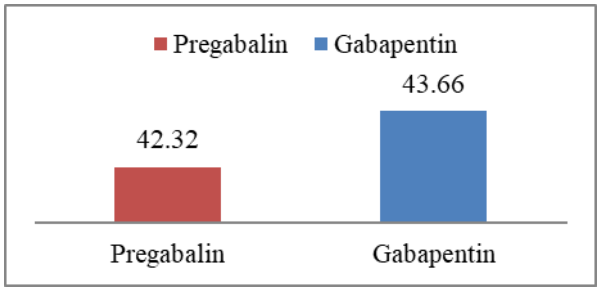


Figure 3: Mean age of drug group pregabalin and gabapentin.

Total patients enrolled in study were 140, 70 patients in each group. Pregabalin group have 70 patients in which 8 patients lost in subsequent follow-up, final count 62 patients. Gabapentin group have 70 patients in which 2

patients lost in subsequent follow-up, final count 68 patients.

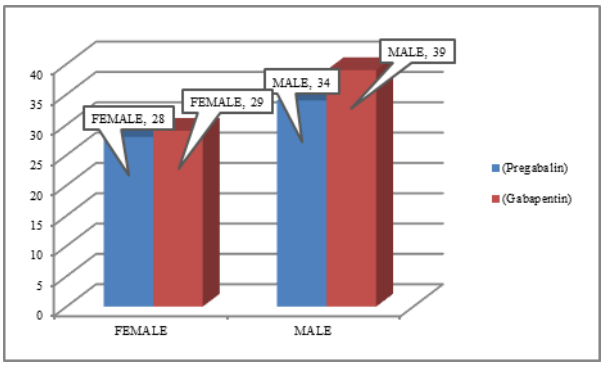


Figure 4: Between group comparison of sex and drug groups.

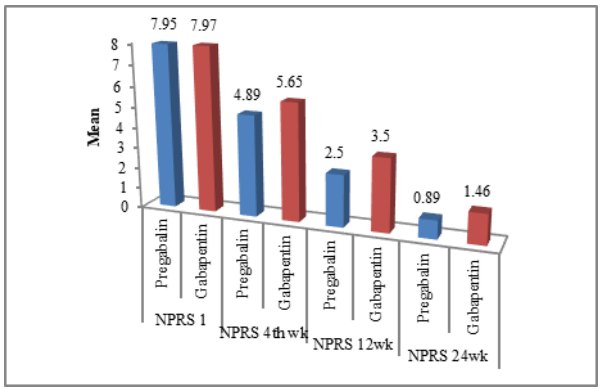


Figure 5: Independent T test for comparing means between two groups at 4th week, 12th week and 24th week.

Table 2: Independent T test for comparing means between two groups at 4th week, 12th week and 24th week.

Variable	Day 1	4th week	12th week	24th week
Significance level of group means between pregabalin and gabapentin	0.913	0.000	0.000	0.000

Sign and symptoms were assessed at 4th,12th and 24th week. Mean age: pregabalin 42.32, gabapentin 43.66 years. Female were 57 (43.8%) and male were 73 (56.2%). There is no significant difference between group 1 and group 2 (gabapentin) as the mean of their pain rating score is 7.95 and 7.97 respectively at first day of OPD (baseline). But at 4th week group 1 is showing difference in pain rating in compare to group 2(Gabapentin) with a significance (2 tailed) 0.001 ($p<0.05$). Similarly at 12th week, group1 (pregabalin) is more effective than group 2 (gabapentin) with a statistical significance level of 0.001 ($p<0.05$). Similarly, at 24th week, group1 (pregabalin) is more effective than group 2 (gabapentin) with a statistical significance level of 0.001 ($p<0.05$).

DISCUSSION

In my present study, a prospective observational trial was carried out collectively at department of medicine, Swaroop Rani Nehru Hospital and department of pharmacology, Moti Lal Nehru medical college, Prayagraj over a period of one year from 2020 to 2021, efficacy of pregabalin and gabapentin which were commonly used in neuropathic pain in outpatient department of medicine (neurology) of above-mentioned hospital was studied. The Patients who were attending outpatient department on specified OPD days in Swaroop Rani Nehru Hospital, Moti Lal Nehru medical college Prayagraj, were diagnosed for neuropathic pain based on the criteria led by the Douleur Neuropathique 4 questionnaire (DN4) which was developed by the French neuropathic pain group. It helps in the differentiation of Neuropathic pain from non-Neuropathic pain. It is a simple and objective tool and consist of interview and examination of patient.

The efficacy of drug was measured on the basis of decrease in neuropathic pain based on numerical pain rating scale measured at particular intervals. The cases were randomly divided in two groups. Group 1 (N=62) received Pregabalin (300 mg). Group 2 (N=68) received Gabapentin (600mg) as a single daily dose for a period of 24 weeks. The observation was made at baseline and after 4th week, 12th week and 24th week. We found that within each group numerical pain rating score (NPRS) decreased significantly ($p<0.05$) at all post periods as compared to respective predecessor periods in both groups. Similarly, for each period, on comparing the mean numerical pain rating score (NPRS) between the groups at 4-week, 12-weeks, 24-weeks, the NPRS score improved significantly more in group prescribed pregabalin as compared to the group prescribed gabapentin. The study found pregabalin is a better drug for treatment of neuropathic pain than gabapentin.

Various studies on efficacy and safety of drugs on neuropathic pain has been done. Attal et al found that pregabalin is more efficacious than gabapentin in case of patients with spinal cord injury having chronic neuropathic pain.[25] A prospective randomized double-blind placebo-controlled study done on 120 patients by Mishra et al for comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain showed that all antineuropathic drugs are effective in relieving cancer-related neuropathic pain.[26] There was statistically and clinically significant morphine sparing effect of pregabaline in relieving neuropathic cancer pain and neuropathic symptoms as compared to other antineuropathic drugs Kiss et al published an article in which he summarises, presents and evaluates national and international guidelines issued in the last five years.[27] The most frequently suggested drugs by all guidelines are

amitriptyline, duloxetine, gabapentin and pregabalin. Pregabalin is the only drug that is recommended first line in all guidelines referred. Robertson et al while comparing efficacy and side effects of pregabalin and gabapentin in treatment of sciatic pain reviewed 11 studies and came to conclusion that pregabalin is more effective than gabapentin.[28] Bruce C M Wang et al had developed a China-localized 12-week simulation model to determine the cost-effectiveness of pregabalin compared to gabapentin in 1000 patients with pNeP and PHN and concluded that pregabalin is an effective treatment for post herpetic neuralgia.[29] Markman et al had collected data from 18 randomized, double-blind, placebo-controlled trials of pregabalin in patients with NeP who were previously treated with gabapentin and come to conclusion that pregabalin may be used successfully to treat patients with NeP who may be refractory, respond inadequately, or are intolerant to gabapentin.[30] Robertson et al has done a randomised, double-blind, cross-over trial (PAGPROS) for pregabalin versus gabapentin in the treatment of sciatica and establish the efficacy of pregabalin compared with gabapentin in reducing pain in people with sciatica and lead to greater understanding of the treatment options available.[31] Kopel et al had published a case report which describe a patient treated for PHN using pregabalin after failure with gabapentin.[32] Pregabalin may be an effective first-line therapy for PHN and other forms of neuropathic and chronic pain. Tong et al had completed a network meta-analysis which shows eight randomized controlled trials that examined four interventions (pregabalin, gabapentin, carbamazepine, and amitriptyline).[33] Based on the average pain intensity after treatment, the efficacy order from highest to lowest was pregabalin, gabapentin, amitriptyline, carbamazepine, and placebo in patients with spinal cord injury-related neuropathic pain.

Limitations

Current study was done over a limited period of 12 months. Some dietary and lifestyle parameter changes might have influenced the study. There may be the question of compliance with the use of study drugs in some subjects. Being on subjective parameter, another limitation of this study might be the individual difference in pain perception for different individuals. Primary outcomes in terms of efficacy and adverse effects should be assessed by conducting long term studies, using different doses of pregabalin and gabapentin and taking recurrence of disease after discontinuation of medication into consideration as recurrence is major factor in present treatment options of neuropathic pain. Because of small sample size, lack of blinding or placebo group, there are chances of statistical error. Larger sample size and multicentric studies can add better outcome. The final limitation is the power of the study and also the duration of the study to ascertain long term effects and safety. Larger groups and longer follow up are needed for acquiring more information.

CONCLUSION

To conclude, on the basis of efficacy pregabalin 300 mg once daily brought better improvement of symptoms and sign than that of gabapentin 600 mg administered once daily dose. The study found pregabalin is a better drug for treatment of neuropathic pain than gabapentin although findings of present study may need further validation on larger sample size.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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