

## Comparative study of efficacy and safety of pregabalin and gabapentin in neuropathic pain.

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### Abstract:

Neuropathic pain differs from nociceptive pain by their causation, character and also mode of treatment. Most neuropathic pain responds poorly to non steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics. Pregabalin and gabapentin have been extensively studied in the treatment of neuropathic pain but there is no evidence to indicate superiority of one of these drugs above the other. So, in this study our aim was to compare their efficacy and safety in neuropathic pain.

A randomized assessor blind unicentric fixed dose study of pregabalin and gabapentin in treatment of neuropathic pain was conducted in 100 patients attending Neurology OPD of R.G.Kar Medical College, Kolkata. These 100 patients were divided in 2 groups, 50 patients were received pregabalin 75 mg twice daily and other group of 50 patients were received gabapentin 300 mg twice daily for consecutive 8 weeks.

Both the groups of patients were followed up at 2, 4 and 8 weeks after starting study drugs and reduction in quantity and quality of pain were assessed by - Visual analogue scale (VAS) and pain quality assessment scale (PQAS). Friedman's test was applied followed by Dunn's multiple comparison test and it showed that both the drugs reduce VAS score similarly but for PQAS score, Pregabalin has resulted superiority earlier than gabapentin. Also, total reduction of PQAS score from 0 to 8 weeks in pregabalin group is highly significant ( $p = .0146$ ) in comparison to reduction in gabapentin group, measured by unpaired t test. So, pregabalin has significant better result in reduction of pain quality than gabapentin after 8 weeks of treatment. No similar result was obtained while comparing their reduction in pain intensity.

**Keywords** : Neuropathic pain, Pregabalin, Gabapentin, VAS score.

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### Introduction:

According to the definition of the International Association for the Study of Pain (IASP) the term neuropathic pains refers to all pains initiated or caused by a primary lesion or dysfunction of the nervous system. Sensations that characterize neuropathic pain are often multiple, like burning, gnawing, aching, shooting or lancinating qualities. There is almost invariable association with one or more symptoms of neuropathic pain with a sensory deficit and local autonomic dysfunction. As much as 7% to 8% of the population is affected by neuropathic pain and in 5% cases

it may be severe enough that the patients seek medical help. Neuropathic pain may result from disorders of the peripheral nervous system or they may arise from the central nervous system (brain and spinal cord) (1).

The common causes of neuropathic pain are diabetes and other metabolic conditions like porphyria, other causes of painful peripheral neuropathies are herpes zoster infection, HIV-related neuropathies, nutritional deficiencies, drug induced (paclitaxel, vinca alkaloids), uremia, chronic liver diseases, remote manifestations of malignancies, genetic, and immune mediated disorders or physical trauma to a nerve trunk. Neuropathic pain is common in cancer as a direct result of cancer on peripheral nerves (e.g., compression by a tumor), or as a side effect of chemotherapy, radiation injury or surgery.

Nociceptive and neuropathic pains are caused by different neuro-physiological processes, and therefore they respond to different modalities of treatment. Nociceptive pain is mediated by receptors on A-delta and C-fibers which are located in skin, bone, connective tissue, muscle and viscera. Nociceptive pain usually responds to opioids and non-steroidal anti-inflammatories (NSAIDs).

Neuropathic pain, in contrast to nociceptive pain, is produced by damage to or pathological changes in the peripheral or central nervous systems (2). So, most neuropathic pain responds poorly to NSAIDs and opioid analgesics. The mainstay of treatment are predominantly the tricyclic antidepressants (TCA's), the anticonvulsants, serotonin and nor epinephrine uptake inhibitors, tramadol (3).

Pregabalin is a novel, centrally acting neuromodulating agent that was approved by the US Food and Drug Administration (FDA) in 2004 for the treatment of painful diabetic peripheral neuropathy and post-herpetic neuralgia. Pregabalin is approved by the European Medicines Agency for the treatment of peripheral and central neuropathic pain in adults (4). Gabapentin, also initially approved only for use in partial seizure but soon showed promise in the treatment of chronic pain syndromes, especially neuropathic pain (5).

Gabapentin and pregabalin bind to  $\alpha_2\text{-}\delta$  subunit of voltage dependent calcium channels and may modulate neurotransmitter (e.g.- substance P, glutamate) release from primary afferent terminals, via an action on interneurons in the dorsal horn of spinal cord (6). Both drugs have been extensively studied in painful diabetic neuropathy and post herpetic neuralgia in large. According to preclinical studies, pregabalin has an increased binding affinity for the  $\alpha_2\text{-}\delta$  protein subunit of voltage-gated calcium channels, which is associated with analgesic and anticonvulsant activity, and has shown greater analgesic activity compared with gabapentin (7).

Despite these preclinical data, it is unclear whether pregabalin has a clinical advantage over gabapentin, as the two drugs have not been adequately compared in clinical trials. So in this study, their comparative safety and efficacy were looked upon.

**Materials and methods:**

A randomized, assessor-blind, unicentric, fixed-dose study of Pregabalin versus Gabapentin in treatment of neuropathic pain has been conducted. Patients attending the Neurology out-patient department (OPD) of R.G.Kar Medical College & Hospital, Kolkata, with the diagnosis of neuropathic pain as clinically diagnosed by the Visiting Physician of Neuromedicine OPD and by electrophysiological evidence from Nerve Conduction Velocity (NCV) study. For recruited subjects, the screening assessment was considered as baseline. The informed consent was obtained from the patient or their legally acceptable representative. Patients were randomized by using computer generated random number in block of 10 at 1:1 ratio into 2 groups.

Group 1- Patient receiving gabapentin 300 mg twice daily.

Group 2- Patients receiving pregabalin 75 mg twice daily.

There were followed up at 2 weeks intervals after starting the study drugs up to 8 weeks; i.e at the end-of-study period. However, for tolerability assessment any adverse event reported spontaneously by subjects up to 4 weeks after last intake of study medication were recorded. During the first visit, patients were assessed by application of Visual Analogue Scale and Quality of Pain Assessment Scale. At each follow-up visit, the clinical history was taken and assessment of the patients with the help of various scales as well as searching for any adverse effects was done. The patient and their accompanying family members were also questioned for treatment-emergent adverse events. Finally, compliance with study medication was accessed through the traditional pill-count method, the patient having been asked to bring all used and unused medication strips. In addition to the above assessments, the end-of-trial certification was given by the Principal Investigator.

**Assessment parameters**

The following parameters were assessed at the visits specified:

**Effectiveness parameters:**

**Primary outcome measure-** Visual Analogue Scale (VAS) score at 1<sup>st</sup> visit and follow up visits at 2, 4 and 8 weeks.

**Secondary outcome measures-** Pain Quality Assessment Scale. (PQAS) (it includes 20 criteria for assessing pain quality like burning, tingling, numbness, cramping, radiating nature of pain and how much it affects daily activity etc.)

**Safety and tolerability parameters--** Hemoglobin, total leukocyte count, Serum creatinine , ECG– screening cum baseline and end of study.

After calculating VAS score and total scores in pain quality assessment scale at 0, 2<sup>nd</sup>, 4<sup>th</sup>, 8<sup>th</sup> week visits of each patient, statistical measures were applied.

For VAS score, as the scores of 50 patients of each group did not pass normality test, Friedman's test (non-parametric repeated measure ANOVA) was applied, followed by Dunn's multiple comparison test. Reduction of VAS score and PQAS scores from 0 wk to 8 wks between pregabalin and gabapentin group was measured by unpaired t test.

## Results

Total 100 patients were followed up, among them 64 were male and 36 were female. Age range varied from 23 years to 68 years with mean age 42.62 years. Both groups were comparable in VAS score and PQAS score at baseline visit.

### Change of VAS score

**Table-I**

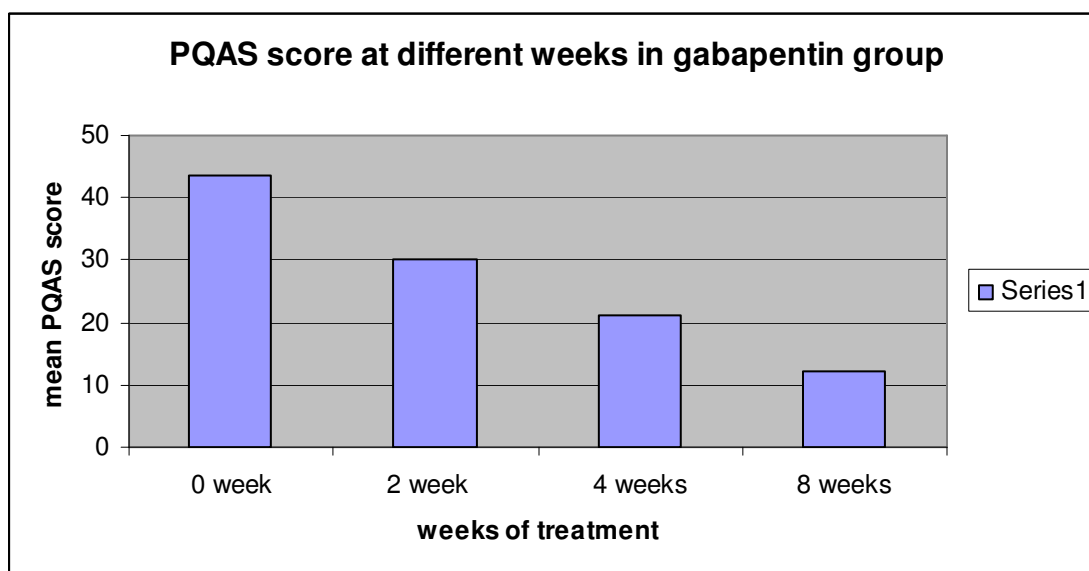
<b>Week of treatment</b>	<b>Gabapentin group (mean +/- Standard deviation)</b>	<b>Pregabalin group (mean +/- Standard deviation)</b>
<b>0 week</b>	<b>7.48 +/- 1.88</b>	<b>7.30+/-2.88</b>
<b>2 weeks</b>	<b>3.91+/- 1.76</b>	<b>4.00+/-2.00</b>
<b>4 weeks</b>	<b>2.48+/- 1.67</b>	<b>2.30+/- 1.29</b>
<b>8 weeks</b>	<b>1.17+/-1.19</b>	<b>1.13+/-1.01</b>

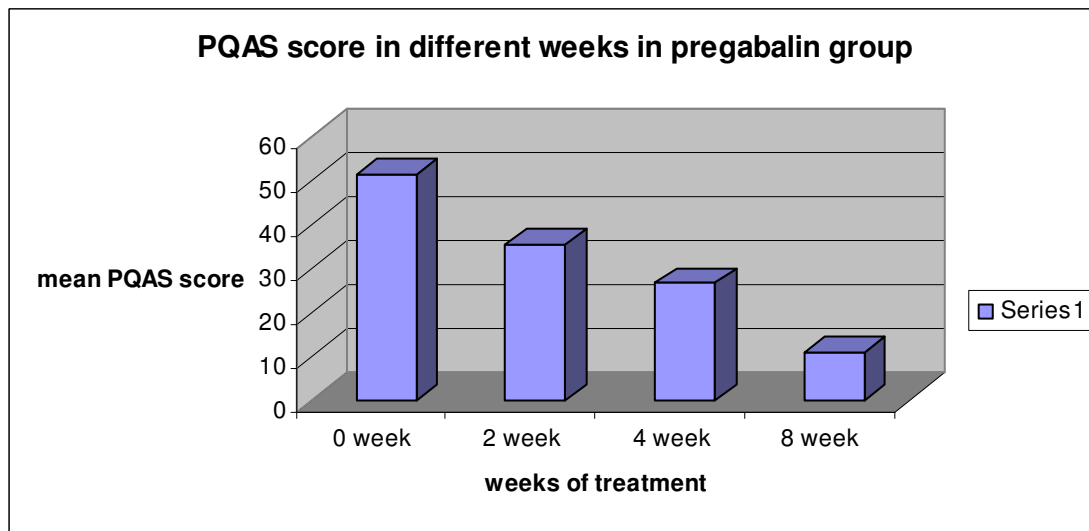
Very significant differences were seen when calculating VAS score in between gabapentin groups as well as pregabalin groups in between 0 and 4 weeks ( $p < 0.001$ ), in between 0 and 8 weeks ( $p < 0.001$ ) and in between 2 weeks and 8 weeks ( $p < 0.001$ ), but non significant results between 0 and 2 weeks, 2 weeks and 4 weeks or 4 weeks and 8 weeks groups. Importantly, there were no significant inter group differences ( $p > 0.05$ ) in VAS scores between gabapentin and pregabalin groups after similar duration of treatment.

**Change of PQAS score****Table II**

<b>Week of treatment</b>	<b>Gabapentin group (mean +/- Standard deviation)</b>	<b>Pregabalin group (mean +/- Standard deviation)</b>
<b>0 week</b>	<b>43.48 +/- 19.9</b>	<b>51.32 +/- 24.84</b>
<b>2 week</b>	<b>30.22 +/- 13.24</b>	<b>35.40 +/- 15.45</b>
<b>4 week</b>	<b>21.02 +/- 9.08</b>	<b>26.58 +/- 13.05</b>
<b>8 week</b>	<b>12.16 +/- 6.20</b>	<b>10.76 +/- 10.37</b>

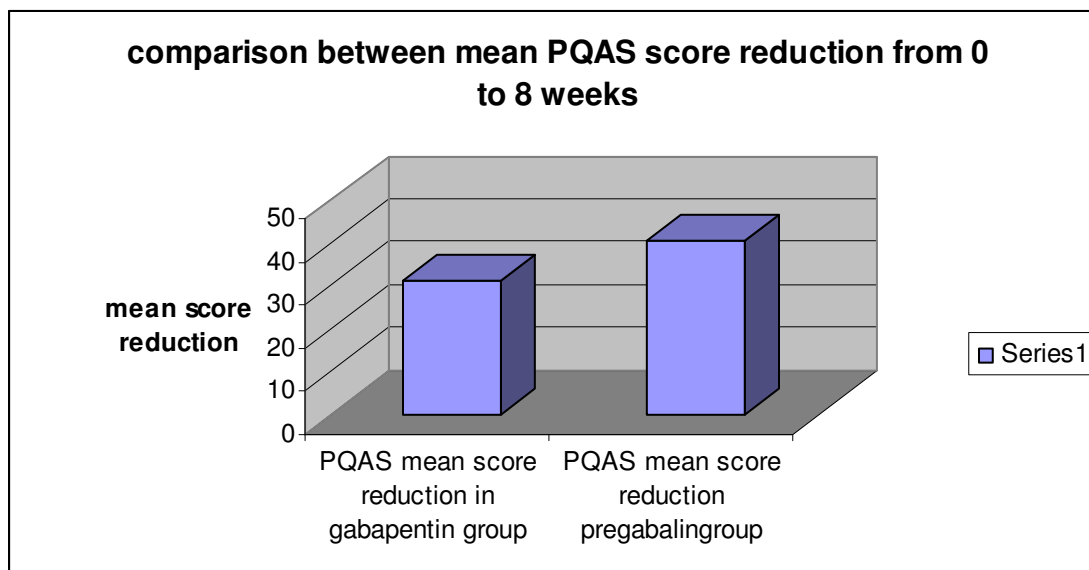
Similarly, PQAS scores were calculated and Friedman's test (non-parametric repeated measure ANOVA) was applied, followed by Dunn's multiple comparison test. It showed very significant result in both gabapentin & pregabalin group at 0 and 4 weeks ( $p < 0.001$ ), at 0 and 8 weeks ( $p < 0.001$ ), at 2 weeks and 8 weeks ( $p < 0.001$ ), and only significant results between 0 and 2 weeks, 2 weeks and 4 weeks and 4 weeks and 8 weeks group. ( $p < 0.05$ ). (diagram 1 & diagram 2)

**Diagram I (Change of PQAS score after gabapentin therapy)**



**Diagram-II (Change of PQAS score after pegabalin therapy)**

But while comparing the total reduction of PQAS scores from 0 wk to 8 wks between pregabalin and gabapentin group, mean reduction in pregabalin group is highly significant ( $p < 0.01$ ) in comparison to mean reduction in gabapentin group, measured by unpaired t test. For gabapentin group, mean reduction in PQAS score from 0 to 8 weeks is 31.32 with 95% confidence limit is from 26.849 to 35.691, and for pregabalin group, the mean reduction from 0 to 8 weeks is 40.56 with 95% confidence limit is from 34.569 to 46.551.



Regarding cost effectiveness, pregabalin 75 mg twice daily costs Rs. 15-16 per day whereas gabapentin 300 mg twice daily costs Rs. 22 per day. So for similar or better result, pregabalin is definitely more cost effective than gabapentin.

Also, in study subjects in both the groups there were no adverse effect noted apart from drowsiness in some and there is no significant difference in the safety between these 2 drugs.

### **Discussion:**

In our study, there is no significant difference in final PQAS and VAS scores between pregabalin and gabapentin group on 8<sup>th</sup> week but reduction of PQAS score at 8 weeks is more significant in pregabalin group than gabapentin group, no such similar result has been found in reduction of VAS score.

Also, pregabalin can affect the pain quality very significantly quicker than gabapentin, as evidenced in this study because, gabapentin has taken 8 weeks to make the result for PQAS score very significant, whereas pregabalin has taken just 4 weeks to reach that result. Pregabalin's increased binding affinity for the  $\alpha_2\text{-}\delta$  protein subunit of voltage-gated calcium channel and more linear pharmacokinetics may be the reason for this difference.

Unlike gabapentin, pregabalin exhibits linear pharmacokinetics after oral administration, with low inter subject variability. This provides a more predictable dose- response relationship (7). In another study, substitution of gabapentin therapy with pregabalin in neuropathic pain due to peripheral neuropathy has shown that pregabalin may provide additional pain relief and possible improvement in quality of life above that received by gabapentin use. Another study showed that pregabalin may provide better analgesic outcomes than gabapentin over a 12-weeks period (8).

Cost-effectiveness analysis of pregabalin versus gabapentin in the management of neuropathic pain due to diabetic polyneuropathy or post-herpetic neuralgia has shown that pregabalin is more cost-effective than gabapentin(9).

### **Conclusion :**

So, we can conclude that pregabalin has significant better result in mean reduction of pain quality than gabapentin after 8weeks of treatment but no similar differences was obtained while comparing their reduction of pain intensity.

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