Efficacy of Gabapentin in Neuropathic Pain: A Study at Nobel Medical College and Teaching Hospital, Nepal

Prem K. Gupta1,*, B.D. Paranjape1, Anjali Deka2, Ranjib K. Jha1, Raju Poudel4

1Department of Pharmacology, Nobel Medical College & Teaching Hospital, Biratnagar, Nepal
2Department of Pharmacology, College of Medical Sciences & Teaching Hospital, Bharatpur, Nepal
3Department of Orthopedics, Nobel Medical College & Teaching Hospital, Biratnagar, Nepal
4Department of Neurology, College of Medical Sciences & Teaching Hospital, Bharatpur, Nepal

*Corresponding author: premgupta11@yahoo.com

Abstract

Pain is a common symptom in many diseases. Neuropathic pain is produced by damage to or pathological changes in the peripheral or central nervous systems. Since most neuropathic pain respond poorly to NSAIDs and opioid analgesics, newer anticonvulsant drug, ‘Gabapentin’ having neuromodulatory effect on pain perception mechanisms, has shown promising effects in alleviating such pain. To have an idea of the analgesic efficacy of gabapentin in relieving neuropathic pain, this hospital based observational prospective study was taken up for six months at Nobel Medical College and Teaching Hospital, Biratnagar in the Department of Orthopedics. 100 patients with neuropathic pain were monitored daily for the severity of pain and quality of sleep for 1 week using Visual Analog scale (VAS) and Sleep Quality Scale. The mean baseline pain score on Visual Analog Scale (VAS) for all cases on day 1 was 62.8±13.4mm while it was reduced to 34.8±11.9 mm (p<0.001) on day 7. Similarly, the mean baseline Sleep interference score on Sleep Quality Scale for all cases on day 1 was 3.04 ± 1.77 while on day 7 the score was reduced to 1.92 ± 0.39 (p<0.001). Overall, the mean pain reduction in neuropathic pain was 44.58%, and the mean reduction in sleep interference was 36.84%. The study showed that gabapentin had significant analgesic efficacy in reduction in neuropathic pain with few adverse effects like dizziness and somnolence (drowsiness).

Keywords: Analgesic Efficacy, Gabapentin, Neuropathic Pain, Sleep Quality Scale, Visual Analog Scale (VAS)


1. Introduction

Pain is a commonly experienced and feared symptom in many diseases. Neuropathic pain affects millions of people around the world. Because of non-availability or inadequacy of treatment patients are often forced to experience symptoms, such as pain, paraesthesia, dysesthesia, hyperalgesia and allodynia for many years [1].

The International Association for the Study of Pain (IASP) has defined pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage’. Pain perception does not therefore correlate with the degree of tissue damage, and each patient’s experience and expression of pain are different. Effective pain treatment facilitates recovery from injury or surgery, adds rapid recovery of function, and may minimize chronic pain and disability [2].

Pain can be classified into two main types: nociceptive and neuropathic pain. 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 Aδ and C–fibers which are located in skin, bone, connective tissue, muscle and viscera. Nociceptive pain usually responds to opioids and non-steroidal anti-inflammatory drugs (NSAIDS). Neuropathic pain, in contrast to nociceptive pain, is produced by damage to or pathological changes in the peripheral or central nervous systems. So, most neuropathic pain responds poorly to NSAIDs and opioid analgesics [3]. Neuropathic pain syndromes involve multiple etiologies including metabolic, traumatic, ischemic, toxic, infectious and immune-mediated insults [4].

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 [3]. The common causes of neuropathic pain are diabetes, 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 [3].
For neuropathic pain of any etiology, various drugs have been used. Commonest drugs used for treatment are predominantly tricyclic antidepressants (TCAs), anticonvulsants, serotonin and norepinephrine uptake inhibitors, opioid analgesics etc. [3].

Significant improvement of neuropathic pain on treatment with the newer anticonvulsants has been reported and studies have demonstrated the neuromodulatory effects of these drugs on a hyperexcitable damaged nervous system [1]. Among them newer generation of anticonvulsants, gabapentin (1-[aminomethyl]-Cyclohexaneacetic acid) is probably the most promising and best studied for neuropathic pain [5]. Various studies have been done to see the efficacy of gabapentin in neuropathic pain [5,6].

Previously conducted various studies suggest that most of the neuropathic pain respond only poorly to NSAIDs and opioid analgesics. Opioid analgesics also carry long term risk of habituation with chronic use. TCAs commonly cause troublesome cardiovascular side effects such as arrhythmias and postural hypotension and autonomic side effects such as blurred vision, dry mouth, constipation and urinary retention [7]. Similarly In Philippines Bitanga et al [7] conducted a post-marketing surveillance study of gabapentin usage in Filipino patients with neuropathic pain. Safety, tolerability and analgesic efficacy were assessed on 1214 patients over a minimum of two weeks period with mean age of 54 years. Ninety-two percent of patients were maintained within a dose range of 300mg/day to 1200mg/day. The incidence of adverse events was 6%, and consisted mostly of somnolence and dizziness, with 76% of patients reporting “very good” to “excellent” tolerability. There were 34 documented dropouts (2.9%), of which only seven (0.6%) were thought to be related to an adverse event from gabapentin. Visual analog scale(VAS) pain scores declined significantly from a mean of 67.8 ± 20 mm at baseline, to 16.1 ± 15mm after treatment (p< 0.05). The study concluded that gabapentin at a dose of 300mg/day to 1200mg/day was well tolerated and efficacious among Filipino patients with various neuropathic pain syndromes.

Randomized controlled trial conducted by Bennett et al [8] on pharmacology and clinical effectiveness of gabapentin in the treatment of neuropathic pain have demonstrated its effectiveness in the treatment of a variety of neuropathic pain syndromes. Patients with neuropathic pain can expect a mean reduction in pain score of 2.05 points on an 11 point numerical rating scale compared with a reduction of 0.94 points if they had taken the placebo. Around 30% of patients can expect to achieve more than 50% pain relief and a similar number will also experience minor adverse events, the most common of which are somnolence and dizziness. In patients with neuropathic pain due to cancer, higher response rates might be observed with gabapentin when administered with opioids because of a synergistic interaction.

A double-blind, randomised, placebo-controlled 8-week study conducted by Serpell [9] to evaluate the efficacy and safety of gabapentin in the treatment of neuropathic pain, using doses up to 2400 mg/day. The study used a novel design that was symptom- rather than syndrome-based. Patients were randomised to gabapentin (n=153) or placebo (n=152). Gabapentin was given in three divided doses, initially titrated to 900 mg/day over 3 days, followed by two further increases, to a maximum of 2400 mg/day if required by the end of week 5. Over the 8 week study, the score decreased by 1.5 (21%) in gabapentin treated patients and by 1.0 (14%) in placebo treated patients (p=0.048, rank-based analysis of covariance). Significant differences were shown in favour of gabapentin (p<0.05) for the Clinician and Patient Global Impression of Change, and some domains of the Short Form-McGill Pain Questionnaire (SF-MPQ). The most common adverse events were mild to moderate dizziness and somnolence, most of which were transient and occurred during the titration phase. The study showed that gabapentin reduced pain and improved some quality-of-life measures in patients with a wide range of neuropathic pain syndromes.

Retrospective study done in two tertiary referral teaching hospitals in south-eastern Michigan by Rosenberg et al [10] to evaluate the effects of gabapentin on pain scores and opiate use. Retrospective reviews of patient charts who received gabapentin for at least 30 days was undertaken. Patients were divided into three groups based on their pain diagnosis; low back, neuropathic and myofascial pain and data were collected. The neuropathic group was subdivided into Post Herpetic Neuralgia (PHN), diabetic neuropathy, sympathetically maintained pain and phantom pain. A significant decrease in pain scores with gabapentin was seen in the neuropathic pain group (paired t-test, p=0.0001) but not in the low back pain group. Of the neuropathic pain group, patients with PHN had the greatest decrease in pain scores. Opiate use was unchanged in all groups. Patients who were taking opiates had significantly less benefit with gabapentin use in terms of pain score. Gabapentin may be a useful adjunct for treating neuropathic pain with a minimum of side effects.

Backonja et al [11] conducted randomized controlled studies through a search of PubMed and MEDLINE from 1966 to the present using the search terms gabapentin, randomized, placebo, and pain to review data on the efficacy and tolerability of gabapentin in the treatment of neuropathic pain in adults and to determine the optimal dosing schedule. The study concluded that gabapentin was effective in the treatment of painful diabetic neuropathy, PHN, and other neuropathic pain syndromes. It relieved symptoms of allodynia, burning pain, shooting pain, and hyperesthesia. Adverse effects were typically mild to moderate and usually subsided within 10 days from initiation of treatment. Based on available data, it appears that treatment should be started at a dose of 900 mg/day (300 mg/day on day 1, 600 mg/day on day 2, and 900 mg/day on day 3). The effective dose should be individualized according to patient response and tolerability. At doses of 1800 to 3600 mg/day, gabapentin was effective and well tolerated in the treatment of adults with neuropathic pain.

Moreover in a country like Nepal, different factors play role for the failure in managing the pain. These factors include geographical variation and limited resources, legal restrictions on import of drugs like morphine, lack of proper medical care, fear of drug addiction, drug tolerance and side effects. Neuropathic pain is characterized by both positive (hyperalgesia and allodynia) and negative (sensory deficit) symptoms that are unrelieved by many commonly used analgesics [1]. Therefore, it seems pertinent to evaluate the efficacy of agent like Gabapentin.
for alleviating neuropathic pain of various etiology which is common among the people of Nepal.

2. Aim and Objective

To know the analgesic efficacy of gabapentin in relieving neuropathic pain among patients of Nobel Medical College and Teaching Hospital, Biratnagar, Nepal.

3. Material and Methods

3.1. Study Design

This was hospital based observational prospective study, to find out analgesic efficacy of Gabapentin in relieving neuropathic pain in patients attending at Department of Orthopedics of Nobel Medical College and Teaching Hospital, Biratnagar, Nepal.

3.2. Duration of Study

This study was conducted for duration of six months, starting from November 2014 to April 2015.

3.3. Study Population

Hundred patients of either sex, aged more than 18 years, with neuropathic pain irrespective of the cause admitted in Department of Orthopedics of Nobel Medical College and Teaching Hospital were selected for this study.

3.4. Inclusion Criteria

i. Patients who had neuropathic pain
ii. Patients willing to undergo for study
iii. Patients of both gender above 18 years of age
iv. Patients with pain intensity at rest that could be measured on Visual Analog Scale (VAS) and quality of sleep that could be measured by Sleep Quality Scale.

3.5. Exclusion Criteria

i. Patients allergic to Gabapentin
ii. Pregnant women
iii. Patients with known drug addiction or abuse
iv. Patients with cardiac, hepatic or renal insufficiency
v. Patients unwilling to participate in the study.

3.6. Methodology

Ethical clearance was taken from the institutional ethical committee before commencing of the study, Written consent was taken from each patient prior to the study.

The study was carried out on randomly selected one hundred patients with neuropathic pain. The patients were monitored daily for the severity of pain and quality of sleep for 1 week using Visual Analogue Scale(VAS) [12] and Sleep Quality Scale [13].

VAS is a 10cm line, where the maximum pain is indicated as ‘10’, and no pain is indicated as ‘0’ (0-no pain, 2-mild pain, 4-tolerable pain, 6-distressfull pain, 8-severe pain, 10-totallydisabling pain). The Sleep Quality Scale is assessed to report their quality of their sleep over the past 24 hours on an 11-point numeric rating scale ranging from 0 (“best possible sleep”) to 10 (“worst possible sleep”).

Patients’ socio-demography data and details of history regarding neuropathic pain were recorded in pre-structured questionnaire. Complete clinical assessment and necessary investigation were done for the cause of neuropathic pain.

3.7. Efficacy Criteria

Primary efficacy outcome measures were pain intensity differences (PID) assessed on VAS at different time point intervals and also from the quality of sleep every night using an 11-point numeric rating Sleep Quality Scale started from the day of drug administration with low dose which was increased in daily increment until an effective dose reached.

3.8. Statistical Analysis

Data was recorded on predesigned proforma and statistical analysis (student’s ‘t’ test) was done to carry out the output. Data were expressed in mean, SD, and percentage. The value p<0.05 was considered to be statistically significant. Statistical analysis of the collected data was done with appropriate statistical methods using Statistical Package for Social Sciences (SPSS Ver. 20) program and was compared with International Standard Literature.

4. Results

4.1. Demographic Features of Study Population

There were 100 patients having neuropathic pain with 98% completing minimum 7 days duration of therapy, attending Department of Orthopedic at Nobel Medical College and Teaching Hospital, Biratnagar, Nepal from November 2014 to April 2015.

4.2. Age and Gender

Females were the predominant sex 56% followed by males 44%. The mean age of the study population was 48.2 ± 13.1 years. In this study, maximum number of patients fall under the age of 41-50 years 28%, comprising of 18 females and 10 males. Minimum number of patients were found in age group of less than 30 years. Demographic study on employment status shows that housewife 54% were mostly affected by neuropathic pain in comparison to others like farmer 26%, service 16%, and business 4%.

4.3. Clinical Diagnosis

The most common diagnoses of neuropathic pain treated were radiculopathy 54%, CTS 28%, diabetic neuropathy 4%, Guillain-Barré syndrome 2%, herpetic neuralgia 2%, leprosy neuritis 2%, myalgia 2%, costocondral neuropathic pain 2%, left thalamic pain 2%, trigeminal neuralgia 2% as depicted in Figure 1.

4.4. Concomitant Illness and Medications

The most commonly documented pre existing illness were hypertension and diabetes. So, antihypertensive,
hypoglycemic, vitamins & nutrient supplements were being taken by some patients prior to starting treatment with Gabapentin which is represented in Figure 2.

4.5. Starting Doses of Gabapentin

In the present 7 days study, 100 patients having different neuropathic pain, were treated with different doses of Gabapentin ranging from 300 mg/day to 900 mg/day. Among them 68% (n=68) of them were started with 300 mg/day, 22% (n=22) were started with 600 mg/day and 10% (n=10) with 900 mg/day. The mean starting daily dose was 426 mg/day. In some patients starting with higher doses suggested that upward titration was necessary for analgesic efficacy.

4.6. Efficacy of Gabapentin

From 100 patients who responded, most patients rated their baseline pain on day 1 as distressful 72% or severe 24% on the Visual Analog Scale (VAS). The mean baseline pain-score for all cases on day 1 using sleep quality scale was 3.04 ± 1.77. At the end of one week study mean sleep interference score was 1.92 ± 0.39, which was significantly lower than that compared to baseline score on day 1 (p<0.001) as shown in Table 1.
4.7. Safety of Gabapentin

Of the 100 patients who received at least one dose of the drug under study, 18 patients reported an adverse event which accounts for 18%. Most common adverse effects observed in this study were dizziness followed by somnolence (drowsiness).

5. Discussions

Previously conducted various studies suggest that most of the neuropathic pain respond poorly to NSAIDs and opioid analgesics. Opioid analgesics also carry long term risk of habituation with chronic use. Tricyclic Antidepressants (TCAs) commonly cause troublesome cardiovascular side effects such as arrhythmias and postural hypotension and autonomic side effects such as blurred vision, dry mouth, constipation and urinary retention [7]. Moreover in a country like Nepal, different factors play role for the failure in managing the pain. These factors include geographical variation and limited resources, legal restrictions on import of drugs like morphine, lack of proper medical care, fear of drug addiction, drug tolerance, and side effects [1].

5.1. Age

In the study, Female were the predominant sex (56%) followed by male (44%). The mean age of the study population was 48.2 ± 13.1 years where maximum number of patient fall under the age group of 41-50 years (28%) of which 18% were female and 10% were male. Minimum number of patients was found in the age group of less than 30 years. The most common diagnoses that were treated were; radiculopathy (54%), CTS (28%), diabetic neuropathy (4%), Gullian-Barrè syndrome (2%), herpetic neuralgia (2%), leprosy neuritis (2%), myalgia (2%), costocervical neuralgic pain (2%), left thalamic pain(2%), trigeminal neuralgia (2%). These finding were consistent with studies conducted by Bitanga et al [7]. and Kasimcan et al [14].

5.2. Gender

In the study, most representation was from female (56%) compared to males (44%) which is similar to post-marketing surveillance study conducted by Bitanga et al [7], which had females (54%) and males (46%).

5.3. Efficacy of Gabapentin in Neuropathic Pain Reduction

Study conducted by Bitanga et al [7] showed VAS pain scores declined significantly from a mean of 67.8 ± 20 mm at baseline, to 16.1 ± 15 mm after treatment (p<0.05) with Gabapentin at a dose of 300mg/day to 1200mg/day was well tolerated and efficacious among Filipino patients with various neuropathic pain syndromes.

Study conducted by Bennett et al [8] showed that patients with neuropathic pain can expect a mean reduction in pain score of 2.05 points on an 11 point numerical rating scale compared with a reduction of 0.94 points if they had taken the placebo. Around 30% of patients can expect to achieve more than 50% pain relief.

Study conducted by Serpell [9] showed that the score improved by 1.5 (21%) in gabapentin treated patients and by 1.0 (14%, p<0.05) in placebo treated patients (p=0.048, rank-based analysis of covariance), at gabapentin doses of 900mg/day to 2400mg/day.

Study conducted by Kasimcan et al [14] inferred that patients treated with oral administration of gabapentin, with radicular pain, caused by Lumbar Spinal Stenosis or Lumbar Disk Hernia, and concluded that gabapentin could be an option in the conservative management of acute or chronic radicular pain.

Backonja et al [5] inferred that Gabapentin titrated from 900 mg/day to 3600 mg/day or maximum tolerated dosages or placebo treated patients mean daily pain score at the study end point (baseline, 6.4; end point, 3.9; n=82) was significantly lower compared with placebo treated patients end point score (baseline 6.5; end point 5.1; n=80).

Dallocchio et al [15] showed that Gabapentin produced greater pain reductions than amitriptyline (mean final scores were 1.9 vs. 1.3 points below baseline scores; p=0.026) at doses titrated from 1200mg/day to a maximum of 2400 mg/day.

In a study conducted by Rice et al [16] showed that Gabapentin at a dose of 1800 mg/day or 2400 mg/day for treating Post Herpetic Neuralgia(PHN), pain scores showed a significantly greater improvement with gabapentin from week 1, the final difference between baseline was −34.5% for the 1800 mg dose, −34.4% for the 2400 mg dose compared with −15.7% for the placebo group. There was significant differences in favor of gabapentin for number of patients reporting >50% reduction in their pain intensity in the VAS of pain.

Similarly, Pandey et al [17] in a study showed that the numeric pain score decreased from 7.22 ± 0.83 to 2.33 ± 1.67 on the second day after initiation of gabapentin therapy and remained low during the period of gabapentin therapy (2.06 ± 0.63) (p< 0.001), at Gabapentin dose of 15 mg/kg/day in 3 divided doses or matching placebo as initial medication for 7 days.

The result of the current study matches with that of the above mentioned studies. The patients having different neuropathic pain, who were treated with different doses of gabapentin ranging from 300 mg/day to 900 mg/day, included patients who started with: 300 mg/day, 68%(n=68); 600 mg/day, 22%(n=22) and 900 mg/day, 10%(n=10). The mean starting daily dose was 426 mg/day. However in contrary to the studies done earlier which have titrated the doses of gabapentin up to 3600 mg/day depending on the evaluation of patient condition over a longer duration, the dose of gabapentin in this study was titrated only up to 900 mg/day due to shorter duration (1 week) of study.

The mean baseline pain score for all cases on day 1 using the 100 mm VAS was 62.8±13.4mm. At the end of one week study period, the percentage of patients who reported with mild pain increased to 28% and 64% rated their pain as tolerable pain. Overall, mean pain score for all cases on day 7 on VAS (34.8 ± 11.9 mm), which was significantly lower than that compared to the baseline score on day 1(62.8 ± 13.4mm, p=0.001). VAS shows 44.58% reduction in mean pain score for all cases from day 1 to day 7. The reduction in mean pain score on the VAS has been comparable to some studies whereas it has shown little reduction when compared to other studies,
which probably could be due to a shorter duration of study and smaller titrated dose of gabapentin.

5.4. Sleep Interference

Backonja et al [5] study to evaluate the effect of Gabapentin monotherapy on pain associated with diabetic peripheral neuropathy showed that Gabapentin monotherapy appeared to be efficacious for the treatment of pain and sleep interference associated with diabetic peripheral neuropathy.

Rowbotham et al [18] study to determine the efficacy and safety of the anticonvulsant drug, gabapentin in reducing PHN pain over a 4-week titration period to a maximum dosage of 3600 mg/day of gabapentin or matching placebo showed that secondary measures of pain as well as changes in pain and sleep interference improved with gabapentin (p < 0.001).

Rice et al [16] study to evaluate the efficacy and safety of gabapentin at a dose of 1800 mg/day or 2400 mg/day in treating PHN, showed significantly greater improvement with gabapentin in sleep interference diaries from week one.

In another study conducted by Singh et al [19] in which gabapentin was used for the treatment of PHN, demonstrated the effectiveness of gabapentin at doses of up to 3600 mg/day to significantly improve sleep (p< 0.01).

Bone et al [20] study on analgesic efficacy of gabapentin in post-amputation phantom limb pain (PLP) with daily dose of gabapentin titrated in increments from 300 mg to 2,400 mg or the maximum tolerated dose showed that was no significant difference between placebo and gabapentin therapy in sleep interference.

The results in this study are comparable or similar to the studies mentioned earlier, with the mean baseline Sleep interference score for all cases on day 1, using Sleep Quality Scale was 3.04 ± 1.77, and at the end of one week study it was 1.92 ± 0.39, which was significantly lower than that compared to baseline score on day 1 (p< 0.001). Thus, there was a significant improvement in the sleep interference score.

5.5. Adverse Effect

In studies conducted by Bitanga et al [7], Bennett et al [8], Serpell [9], Backonja et al [5], Hui et al [21], Rice et al [16] showed that the most commonly occurring side effects with Gabapentin were somnolence and dizziness which was also seen in the present study in 18% (n=9) of the patients while Rowbotham et al [18] also showed, ataxia, peripheral edema, and infection and Gilron et al [22] reported the most common adverse effect as dry mouth, which were not reported in the present study. Other studies conducted by Rosenberg et al [10], Backonja et al [11], Erdemoglu [23], Pandey et al [17] showed mild to minimal side effects.

6. Conclusion

The study showed that Gabapentin had significant analgesic effect in reduction of neuropathic pain with few adverse effects like dizziness and somnolence (drowsiness).

Acknowledgement

The authors wish to thank Mr Nitendra Chaurasiya, Dr. Asis De, Mr. Naresh Manandhar, Dr. Lekh Jung Thapa, Dr. Baburam Pokhrel, Dr. Lokeshwar Chaurasia, Dr. Pukar Thapa, Dr. Prakash Kaffe and colleagues for their support and cooperation throughout the study period.

Declaration of Conflicting Interests

The authors declare that there is no potential conflicts of interest with respect to the research, authorship and /or publication of this article.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

References


