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Original Research Article

A Comparative Study on Efficacy and Safety for Management of Neuropathic Pain with Gabapentin, Pregabalin and Amitriptyline

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Abstract

Introduction: Current treatment for neuropathic pain (NeP) are tricyclic antidepressants (TCA), gabapentin and pregabalin as first-line treatment for the most common NeP conditions. Current therapy for the treatment of neuropathic pain is often unsatisfactory. Considerable variation in treatment pattern still exists in spite of availability of sufficient literature from various guidelines. Recent Indian market data suggested that the utilization (sale) of drugs such as amitriptyline, pregabalin, and gabapentin is actually recommended in the guidelines.

Methods: It is a prospective, comparative, open label, single centre, three arm study. A total of 300 patients diagnosed with cases of chronic lumbar radiculopathy based on symptoms, clinical examination, X-ray and MRI scan of lumbosacral spine, were randomized into three groups to receive Group A patients received Gabapentine 300 mg, Group B patients received Pregabaline 75 mg, Group C patients received Amitriptyline 10 mg. Patients were assessed for pain relief by using visual analogue scale and an overall improvement in their general condition by patient's global impression of change scale. Adverse drug reactions were recorded on each follow up.

Results: All patients had significant improvement in pain relief in three treatment groups. The mean Numeric pain rating scale (NPRS) score At 2 months, the Mean±SD of NPRS score in Group A was 3.72±2.65, in Group B and Group C were 3.63±2.65 and 5.21±2.65 respectively with F-value of 6.63 and p-value of 0.001 which was statistically significant. Intergroup comparison shows significant differences among three the treatment groups. The adverse effects reported occurrence of dizziness was significantly more in group B with 21 patients (23.33%) as compared to group A with 11 patients (12.22%) and group C with 4 patients (4.44%), [p=0.041). The sedation occurred in 28 patients of group B (31.11%), which was significantly more than group A i,e, in 23 patients (25.55%) and group C i.e. 22 patients (24.44%), [P=0.036].

Conclusions: In patients with NeP Thus, in conclusion three groups Gabapentine, Pregabaline and Amitriptyline are equally efficacious in relieving pain in NeP. Pregabalin has the advantages in terms of Numeric pain rating scale (NPRS) score over the Gabapentine and Amitriptyline. Gabapentine has fewer reported adverse effects and hence a better patient compliance on long term use.

Keywords: Gabapentine, Amitriptyline, Pregabalin, Neuropathic pain

Introduction

Neuropathic pain is caused by a lesion or disease of the somatosensory system, including peripheral fibres (Aβ, Aδ and C fibres) and central neurons, and affects 7–10% of the general population. [1] Multiple causes of neuropathic pain have been described and its incidence is likely to increase owing to the ageing global population, increased incidence of diabetes mellitus and improved survival from cancer after chemotherapy. Indeed, imbalances between excitatory and inhibitory somatosensory signalling, alterations in ion channels and variability in the way that pain messages are modulated in the central nervous system all have been implicated in neuropathic pain.[2] The burden of chronic neuropathic pain seems to be related to the complexity of neuropathic symptoms, poor outcomes and difficult treatment decisions. Importantly, quality of life is impaired in patients with neuropathic pain owing to increased drug prescriptions and visits to health care providers, as well as the morbidity from the pain itself and the inciting disease.[3] In a systematic review of the epidemiology of chronic pain, a prevalence between 3% and 17% was found, while the incidence was calculated in 3.9–42.0/100,000 person-years for post-herpetic neuralgia; 12.6–28.9/100,000 person-years for trigeminal neuralgia; 15.3–72.3/100,000 person-years for PDN, and 0.2–0.4/100,000 person-years for glossopharyngeal neuralgia. Moreover, neuropathic pain was more prevalent among women (60.5% of patients), reached a peak at 50–64 years of age, and was more frequently reported by manual workers, as well as among people from rural areas. [4] Despite challenges, progress in the understanding of the pathophysiology of neuropathic pain is spurring the development of new diagnostic procedures and personalized interventions, which emphasize the need for a multidisciplinary approach to the management of neuropathic pain.[5] Pregabalin is a well-established anticonvulsant and analgesic agent. Pregabalin is the first drug to receive approved labelling from Food and Drug Association (FDA) for the treatment of neuropathic pain and post-herpetic neuralgia.[6] Preclinical and clinical studies have shown the effectiveness of pregabalin in managing the neuropathic pain. Animal based studies have helped to describe the mechanisms for its anti-hyperalgesia and anti-allodynia action.[7] Clinical studies have also shown the efficacy and dose dependent effects of pregabalin either as monotherapy or in combination with analgesics in relieving pain and related symptoms. The major advantage of pregabalin is its relative reliability, easy use and high tolerance in patients with neuropathic pain.[8] Gabapentin (GBP) is a commonly used for post-herpetic neuralgia (PHN). The mechanism of action for GBP relates to its ability to bind with high-affinity to the alpha-2-delta subunit of voltage-gated calcium channels located throughout the peripheral and central nervous system; thus, modifies the release of neurotransmitters and reduces excitability of nerve cells.[9] It is this mechanism of action that may produce analgesic effect in patients experiencing neuropathic pain.[10] Amitriptyline is a tricyclic antidepressant that is widely used to treat chronic neuropathic pain. The mechanism of action of amitriptyline in the treatment of neuropathic pain remains uncertain, although it is known to inhibit both serotonin and noradrenaline reuptake.[11] The mechanism is likely to differ from that in depression since analgesia with antidepressants is often achieved at a lower dosage than the onset of any antidepressant effect; adverse events associated with amitriptyline often wane after two or three weeks, when the benefits of the drug become apparent.[12] In addition, there is no correlation between the effect of antidepressants on mood and pain, and antidepressants produce analgesia in

people with and without depression.[13] To test this hypothesis, we evaluated the prescription pattern of these first line drugs (amitriptyline, pregabalin, and gabapentin) for the management of neuropathic pain amongst caregivers. Other classes of first-line drugs used for the management of neuropathic pain are not included in this survey.

Material and Methods:

Study Design: The present study conducted in Outpatient department of Dept.of Neurology, GSVM Medical College, Kanpur.

Inclusion criteria: Patients with either sex with age group of more than 18 years. Diagnosed cases of neuropathic pain due to diabetic peripheral neuropathy, low back pain, post herpetic neuroglia, fibromyalgia and spinal cord injury.

Exclusion criteria: Patients with history of liver diseases, cardiac illness, renal disease, diabetes, tuberculosis. Pregnant and lactating women. Patients who are immunocompromised. Patients with known hypersensitivity to the study drugs.

Study Design: Total 300 patients were diagnosed neuropathic pain and were randomized into 3 groups.
Group A patients received Gabapentine 300 mg
Group B patients received Pregabalin 75 mg
Group C patients received Amitriptyline 10 mg

Statistical Analysis:

The collected data was compiled in EXCEL sheet and Master chart was prepared. For analysis of this data SPSS (Statistical package for social Sciences) software version 20th was used. Qualitative data was represented in form values and percentages. Quantitative was represented in form of mean and SD. For comparison between three groups mean pain on numerical pain rating scale ANOVA was used. Also for comparison between two groups at different time intervals Tukey Post Hoc test was used. Chi square test was used to evaluate adverse drug reactions in all the three study groups. p-value was checked at 5 % level of significance

Results:

Table 1: Distribution of patients according to Gender

Gender	Group A	Group B	Group C
Male	42 (60 %)	39 (55.7 %)	41 (58.5 %)
Female	28 (40 %)	31 (44.28 %)	29 (41.42 %)
Total	70 (100 %)	70 (100%)	70 (100%)

In each group total 90 patients were there. In Group A: 42 (60%) were males and 28 (40%) were females. In Group B: 39 were males (55.7%) and 31 (44.28%) were females. In Group C: 41 were males (58.5%) and 29 (41.42%) were females.

Table 2: Distribution of Patients according to Age group

Age-group	Group A	Group B	Group C
18-40	16	14	11
41-60	23	27	26
>61	31	29	33
Total	70 (100 %)	70 (100 %)	70 (100 %)
Mean SD	54.38 ± 6.38	53.24 ± 6.48	54.48 ± 6.33
F-value	0.326		
p-value	0.635^{ns}		

In Group A: Mean age of patients was 54.38 ± 6.38 years. In group B: Mean age of patients 53.24 ± 6.48 years. In group C: Mean age of patients was 54.48 ± 6.33. The F-value was 0.326 and p-value 0.635 which was statistically not significant.

Table 3: Clinical Diagnosis of the patients

Clinical Diagnosis	**Group A**	**Group B**	**Group C**
Peripheral neuropathy	29	32	30
Diabetic peripheral neuropathy	13	16	14
Trigeminal neuralgia	9	8	9
Central pain after stroke	7	6	8
Post herpetic neuralgia	3	3	2
Myelopathy pain	2	1	2
Central neurogenic pain	2	2	1
Reflex sympathetic dystrophy	1	1	2
Others	3	1	2

Table 4: Comparison of Numeric pain rating scale (NPRS) score in all three groups at baseline after 15 days and after 30 days (ANOVA).

		Mean±SD	**p-value**
Baseline	**Group A**	7.84 ± 1.53	0.435[ns]
	Group B	7.96 ± 1.62	
	Group C	7.96 ± 1.62	
After 15 days	**Group A**	5.12 ± 1.42	0.061 [ns]
	Group B	5.23 ± 1.32	
	Group C	6.23 ± 1.43	
After 30 days	**Group A**	3.11 ± 1.04	0.001 [s]
	Group B	3.63 ± 1.02	
	Group C	4.25 ± 1.03	

(P<0.05 is statistically significant, S-significant, NS-not significant, NPRS-Numeric Pain Rating Scale)

At baseline, the Mean±SD of NPRS score in Group A was 7.84±1.53 in Group B and Group C were 7.96 ± 1.62 and 7.96 ± 1.62 respectively and p-value of 0.435 which was not statistically significant. At 15 days, the Mean±SD of NPRS score in Group A was 5.12 ± 1.42, in Group B and Group C were 5.23±1.32 and 6.23±1.43 respectively and p-value of 0.061 which was not statistically significant. At 30 days, the Mean±SD of NPRS score in Group A was 3.11 ± 1.04, in Group B and Group C were 3.63 ± 1.02 and 4.25±1.03 respectively and p-value of 0.001 which was statistically significant.

Table 5: Comparison of NPRS score in tow groups at baseline, 15 days and 30 days [Tukey Post Hoc Test]

		Mean± SD	**p-value**
Baseline	Group A Vs Group B	0.12	0.632[ns]
	Group A Vs Group C	0.11	0.538 [ns]
	Group B Vs Group C	0.23	0.502 [ns]
After 15 days	Group A Vs Group B	0.11	0.438 [ns]
	Group A Vs Group C	1.11	0.023 [s]
	Group B Vs Group C	1.00	0.481 [ns]
After 30 days	Group A Vs Group B	0.52	0.432 [ns]
	Group A Vs Group C	1.14	0.007 [s]
	Group B Vs Group C	0.62	0.004 [s]

(p<0.05 is statistically significant. S-significant. NS-not significant. NPRS-Numeric Pain Rating Scale)

Table 6: Comparison of percent reduction of NPRS (Numeric Pain Rating Scale) score baseline vs after 30 days in all three groups

Group	Mean reduction
Group A at baseline Vs Group A at 30 days	**4.73**
Group B at baseline Vs Group B at 30 days	**4.33**
Group C at baseline Vs Group C at 30 days	**3.48**

Table 6: Adverse drug reaction in patients in all three groups

	Group A		Group B		Group C		Chi-square	p-value
	n	%	n	%	n	%		
Dizziness	9	12.8	17	24.2	2	2.85	4.39	0.036
Sedation	17	24.2	23	32.8	17	24.2	6.58	0.021
Constipation	0	00	0	00	6	8.5	8.58	0.000
Dry mouth	0	00	0	00	7	10.	11.39	0.000

In present study, occurrence of dizziness was significantly more in group B with 17 patients (24.2%) as compared to group A with 9 patients (12.8%) and group C with 2 patients (2.85%), [p=0.036). The sedation occurred in 23 patients of group B (32.8%), which was significantly more than group A i,e, in 9 patients (12.8%) and group C i.e. 17 patients (24.2%), [P=0.021]. The occurrence of constipation was seen in 6 patients of group C (8.58%) which was significantly more than in Group A and B with 0 patients (0%) [p=0.000]. The occurrence of dryness of mouth was significantly more in group C with 7 patients (11.39%) as compared to that of Group A and B with 0 patients (0%) [p=0.000].

Discussion:

Neuropathic pain is defined as "Pain caused by a lesion or disease of the somatosensory nervous system". It is commonly associated with back pain (e.g., lumbar or cervical radiculopathy), diabetes (painful diabetic neuropathy), post-surgical pain, HIV-AIDS, and herpes zoster (post-herpetic neuralgia), but can also arise through many other diseases or injuries. [13] Specific clinical features include symptoms such as paraesthesia, burning or shooting pains, altered sensation (numbness, allodynia or hyperalgesia), and locally altered autonomic function. [14] In the absence of a 'gold standard' for defining cases and a clinical code for routine healthcare use, it is impossible to identify the precise prevalence of neuropathic pain, for example through the Global Burden of Disease 2013 study. [15] However, a recent systematic review found that between 7 and 10% of the adult population are affected by pain with neuropathic characteristics (identified through validated questionnaires). [16] With a global population of approximately 7.4 billion people, this means that some 518 to 740 million individuals are estimated to currently be affected by neuropathic pain. [17] In this present study, there was significant reduction of mean pain scores in all three groups at the end of 2 months. In patients treated with gabapentin, the mean pain score reduced significantly to 3.72 from 8.31. This finding was similar to the study conducted by Gilron et al. [18] The mean pain score in patients treated with pregabalin reduced significantly to 3.63 from 8.42. This finding was similar to the study conducted by Holbech et al [2%]. [19] In patients treated with amitriptyline, the mean pain score reduced significantly to 5.21 from 8.29. We could not find any study that showed same results as that of amitriptyline in this study in reduction of chronic lumbar radiculopathy pain. When we analysed the pain scores at the completion of 2 months and compared between all three groups, there was no significant difference in pain scores

comparison of Group A and Group B with mean difference of 0.09 [p-value 0.523], significant difference in pain scores comparison of Group A and Group C with mean difference of 1.49 [p-value of 0.006] and significant difference in pain scores comparison of Group B and Group C with mean difference of 1.58 [p-value of 0.007]. [20] During the course of the study it was found that the adverse drug reactions were found more in Pregabalin and amitriptyline treated groups as compared to Gabapentin group. In present study, occurrence of dizziness was significantly more in group B with 17 patients (24.2%) as compared to group A with 9 patients (12.8%) and group C with 2 patients (2.85%), [p=0.036). The sedation occurred in 23 patients of group B (32.8%), which was significantly more than group A i,e, in 9 patients (12.8%) and group C i.e. 17 patients (24.2%), [P=0.021]. The occurrence of constipation was seen in 6 patients of group C (8.58%) which was significantly more than in Group A and B with 0 patients (0%) [p=0.000]. The occurrence of dryness of mouth was significantly more in group C with 7 patients (11.39%) as compared to that of Group A and B with 0 patients (0%) [p=0.000]. Strength of the present study is, standard validated scales and scores for the diagnosis of neuropathic pain and for assessing the primary outcome measure pain relief. Authors have applied percentage reduction in the primary efficacy parameter to analyse the difference between the two groups. To the best of our knowledge, not many studies have used percentage reduction, which is more sensitive to less number of patients than the simple absolute values. There have been a few limitations in this study. This was an open label study without any blinding. The follow-up of patients was only for 2 months and therefore, the long-term efficacy and safety of the study drugs could not be assessed.

Conclusion:

Thus, in conclusion three groups Gabapentine, Pregabaline and Amitriptyline are equally efficacious in relieving pain in NeP. Pregabalin has the advantages in terms of Numeric pain rating scale (NPRS) score over the Gabapentine and Amitriptyline. Gabapentine has fewer reported adverse effects and hence a better patient compliance on long term use. Amitriptyline is more cost effective than pregabalin which is an important factor to keep in mind while treating patients.

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