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Original Research Article

Evaluation of the Safety and Efficacy of Pregabalin, Gabapentin, and Amitriptyline for Neuropathic Pain

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Abstract:

Background: The existing treatment options for managing neuropathic pain frequently fall short of providing satisfactory relief. Despite the abundance of literature available in various guidelines, there remains notable inconsistency in treatment approaches. This study is designed to assess the safety and effectiveness of gabapentin, amitriptyline, and pregabalin in individuals experiencing severe neuropathic pain that hasn't responded to basic analgesics.

Methods: After the selection of the cases a thorough physical examination, comprehensive systemic assessment, monitoring of vital signs, review of past medical history, assessment of concurrent medications, clinical evaluations for chronic lumbar radiculopathy, lumbosacral spine x-rays (both anterior-posterior and lateral views utilizing a digital x-ray machine), and nerve conduction studies. The study included a total of 150 cases, evenly distributed across three groups: Group (P) received pregabalin 75 mg, Group (G) received Gabapentin 300 mg, and Group (A) received Amitriptyline 10 mg.

Results: At baseline, there was no significant difference in NPRS scores between any of the three groups. This suggests that the groups were well-matched at the start of the study. At the 1-month follow-up, there was still no significant difference in NPRS scores between any of the three groups. This suggests that all three treatments were equally effective in reducing neuropathic pain intensity at this early stage. At the 3-month follow-up, there was a significant difference in NPRS scores between Group P (pregabalin) and the other two groups (gabapentin and amitriptyline), with Group P having the lowest mean NPRS score. This suggests that pregabalin may be more effective in reducing neuropathic pain intensity over the long term.

Conclusion: In summary, this study reveals that gabapentin, pregabalin, and amitriptyline all prove effective in mitigating neuropathic pain (NeP). Notably, pregabalin demonstrates a noteworthy advantage by significantly reducing the NPRS score compared to gabapentin and amitriptyline after 3 months of therapy. Gabapentin, on the other hand, is linked to a lower incidence of reported adverse effects, promoting improved adherence during extended usage. Amitriptyline, being more cost-effective than pregabalin, is a crucial factor to weigh when making treatment decisions for patients.

Keywords: Pregabalin, Gabapentin, Amitriptyline, Neuropathic Pain (NeP).

Introduction

Neuropathic pain (NeP) arises from damage or disease affecting the somatosensory nervous system, resulting in spontaneous pain and exaggerated responses to both harmful and non-harmful stimuli due to altered structure and function. [1] Peripheral causes include polyneuropathy, post-herpetic neuralgia, postoperative pain, and post-traumatic neuralgia, while central causes encompass spinal cord injuries and stroke. [2] The treatment of neuropathic pain poses a significant challenge due to its diverse origins, symptoms, and underlying mechanisms. [3, 4] Ambiguity regarding the lesion's nature and precise location, particularly in non-specialist settings, exacerbates this challenge. Numerous pharmacological options exist for addressing neuropathic pain outside of specialized pain clinics. Guidelines from various pain societies and working groups offer extensive literature to assist caregivers in the optimal use of available drugs for neuropathic pain management. [5-7] Recently, recommendations for NeP pharmacotherapy were updated, emphasizing tricyclic antidepressants (TCA), serotonin and norepinephrine reuptake

inhibitors (SNRIs), pregabalin, and gabapentin as first-line treatments based on strong GRADE recommendations. [8] Pregabalin, an established anticonvulsant and analgesic, was the first drug FDA-approved for neuropathic pain and postherpetic neuralgia. [9] Both preclinical and clinical studies confirm pregabalin's efficacy in managing neuropathic pain, showcasing its reliability, ease of use, and high patient tolerance. [10, 11]

Gabapentin (GBP) is commonly used for post-herpetic neuralgia (PHN), exerting its effects by binding to the alpha-2-delta subunit of voltage-gated calcium channels in the nervous system, modulating neurotransmitter release, and reducing nerve cell excitability. [12] This mechanism accounts for its analgesic effects in neuropathic pain patients. [13] Amitriptyline, a tricyclic antidepressant widely used for chronic neuropathic pain, works by inhibiting the reuptake of serotonin and noradrenaline. [14] Although the precise mechanism remains unclear, it's distinct from its action in depression, as analgesia often occurs at lower dosages and is not correlated with mood improvement. Adverse effects tend to subside after a few weeks, revealing the drug's pain-relieving benefits. Importantly, antidepressants demonstrate analgesic properties irrespective of the presence of depression. [15] However, a notable discrepancy remains in how caregivers initiate, maintain, and administer dosages for different medicines. [16] Variability is also evident among caregivers regarding the sequence in which drugs are introduced for neuropathic pain therapy. Literature documents cases of deviating from treatment guidelines and recommended doses for pain management. [17] The objective of the current study is to assess the safety and effectiveness of gabapentin, amitriptyline, and pregabalin in individuals experiencing severe neuropathic pain that has not responded to basic analgesics.

Material and Methods

This prospective study was conducted in the Department of Orthopedics in collaboration with the Department of Pharmacology, Kakatiya Medical College, and MGM Hospital, Warangal, Telangana State. Institutional Ethical approval was obtained for the study. Written consent was obtained for the study after explaining the nature of the study to the participants in the vernacular language.

Inclusion Criteria

1. Patients diagnosed with Chronic Lumbar radiculopathy based on symptoms, clinical examination, X-rays, and Nerve Conduction studies.
2. Aged 20 to 60 years.
3. Males and Females.
4. Available for follow-up assessments.
5. Voluntarily willing to participate in the study.

Exclusion Criteria

1. Patients with a history of chronic diseases such as TB, Renal Diseases, and Liver diseases.
2. Radiculopathy secondary to tumors.
3. Immunocompromised patients.
4. Patients with a history of allergy to medications used.

Upon enrollment and before commencing the treatment, the following details were documented in the case record: physical examination, systemic evaluation, vital signs, past medical history, any concurrent medications, clinical assessments for chronic lumbar radiculopathy, lumbosacral spine x-rays (anterior-posterior and lateral views using digital x-ray machine) and nerve conduction studies. Pain assessment was conducted using the Numeric Pain Rating Scale (NPRS) at the onset of the study (day 0), at 1 month, and 2 months. A total of 150 cases were equally divided into 3 groups. Group (P) received pregabalin 75 mg. Group (G) received Gabapentin 300mg and Group (A) received Amitriptyline 10mg. Adverse drug reactions, whether reported by the patient or observed by the clinician throughout the study, were recorded utilizing the Adverse Drug Reaction (ADR) reporting form.

Statistical analysis: The data was collected and uploaded on an MS Excel spreadsheet and analyzed by SPSS version 22 (Chicago, IL, USA). Quantitative variables were expressed on mean and standard deviations and qualitative variables were expressed in proportions and percentages. ANOVA analysis was used to find the differences between proportions.

Results

Table 1 shows the distribution of neuropathic pain cases based on the age groups for three different treatment groups: pregabalin (Group P), gabapentin (Group G), and amitriptyline (Group A). The mean age of patients in Group P was 45.55 years, in Group G was 43.25 years, and in Group A was 47.68 years. The majority of patients in all three groups were between the ages of 41 and 50 years old (Group P: 68%, Group G: 56%, Group A: 56%).

Gender distribution: There were more male than female patients in all three groups (Group P: 65% male, 35% female; Group G: 64% male, 36% female; Group A: 64% male, 36% female). There was no significant difference in the age or gender distribution between the three groups (p values >0.05). The age and gender distribution of patients with neuropathic pain in this study are similar to what has been reported in other studies. The majority of patients are between the ages of 41 and 50 years old, and there are more male than female patients.

Table 1: Distribution of Neuropathic pain cases based on the age groups

Age group	Group P (Pregabalin)		Group G (Gabapentin)		Group A (Amitriptyline)	
	Male	Female	Male	Female	Male	Female
21 – 30	1	0	0	0	0	0
31 – 40	3	1	4	3	3	2
41 – 50	17	9	15	8	14	8
51 – 60	12	7	14	6	13	10
Mean ± SD	45.55 ± 5.87		43.25 ± 4.50		47.68 ± 5.12	
P value	0.226		0.554		0.387	

Table 2 shows the distribution of neuropathic pain numeric pain rating scale (NPRS) at different intervals in the age groups for three different treatment groups: pregabalin (Group P), gabapentin (Group G), and amitriptyline (Group A).

Baseline scores: The mean baseline NPRS score was similar in all three groups (Group P: 8.22, Group G: 8.02, Group A: 8.11).

1-month follow-up: At the 1-month follow-up, the mean NPRS score decreased in all three groups, but there was no significant difference between the groups (Group P: 7.16, Group G: 7.06, Group A: 7.55).

3-month follow-up: At the 3-month follow-up, the mean NPRS score continued to decrease in all three groups. However, there was a significant difference between the groups, with Group P having the lowest mean NPRS score (Group P: 3.32, Group G: 4.18, Group A: 5.18). All three treatment groups resulted in a decrease in neuropathic pain intensity at the 1-month and 3-month follow-ups. However, Group P (pregabalin) had the lowest mean NPRS score at the 3-month follow-up, suggesting that it may be more effective in reducing neuropathic pain intensity over the long term.

Table 2: Distribution of Neuropathic pain numeric pain rating scale (NPRS) at different intervals in the age groups

Age group	Group P (Pregabalin)	Group G (Gabapentin)	Group A (Amitriptyline)	P value
Baseline scores	8.22 ± 1.55	8.02 ± 1.65	8.11 ± 1.71	0.315
1-month follow-up	7.16 ± 1.04	7.06 ± 1.00	7.55 ± 1.10	0.084
3-month follow-up	3.32 ± 2.22	4.18 ± 1.98	5.18 ± 1.85	0.0121*

* Significant

Table 3 shows the results of a statistical test comparing the NPRS scores of the three treatment groups (pregabalin, gabapentin, and amitriptyline) at different intervals (baseline, 1-month follow-up, and 3-month follow-up).

Baseline: At baseline, there was no significant difference in NPRS scores between any of the three groups. This suggests that the groups were well-matched at the start of the study.

1-month follow-up: At the 1-month follow-up, there was still no significant difference in NPRS scores between any of the three groups. This suggests that all three treatments were equally effective in reducing neuropathic pain intensity at this early stage.

3-month follow-up: At the 3-month follow-up, there was a significant difference in NPRS scores between Group P (pregabalin) and the other two groups (gabapentin and amitriptyline), with Group P having the lowest mean NPRS score. This suggests that pregabalin may be more effective in reducing neuropathic pain intensity over the long term.

Table 3: Intergroup comparison of NPRS scores at different intervals

	Group versus Group		Mean ± SD	P value
Baseline	Group P	Group G	0.21	0.554
	Group P	Group A	0.18	0.358
	Group G	Group A	0.22	0.667
After 1 month	Group P	Group G	0.88	0.128
	Group P	Group A	0.99	0.041*
	Group G	Group A	0.36	0.179
After 3 months	Group P	Group G	011	0.361
	Group P	Group A	1.55	0.002*
	Group G	Group A	1.66	0.004*

* Significant

Table 4 shows the adverse drug reactions (ADRs) in patients in all three groups of neuropathic pain: pregabalin (Group P), gabapentin (Group G), and amitriptyline (Group A). The table also shows the results of an ANOVA test to compare the three groups. The most common ADRs in all three groups were dizziness and sedation. However, the rates of constipation and dry mouth were significantly higher in the amitriptyline group than in the other two groups. *Dizziness***:** The rate of dizziness was slightly higher in the gabapentin group than in the pregabalin group, but the difference was not statistically significant. The rate of dizziness was also slightly lower in the amitriptyline group than in the other two groups, but again the difference was not statistically significant. *Sedation***:** The rates of sedation were similar in the pregabalin and gabapentin groups. However, the rate of sedation was significantly higher in the amitriptyline group than in the other two groups. *Constipation***:** The rate of constipation was significantly higher in the amitriptyline group than in the other two groups. *Dry mouth:* The rate of dry mouth was significantly higher in the amitriptyline group than in the other two groups. Overall, the table shows that amitriptyline is associated with a higher risk of certain ADRs, such as constipation and dry mouth, than pregabalin or gabapentin.

Table 4: Adverse drug reaction in patients in all three groups of Neuropathic pain.

	Group P (Pregabalin)	Group G (Gabapentin)	Group A (Amitriptyline)	ANOVA P value
Dizziness	8 (16%)	12 (24%)	6 (12%)	0.071
Sedation	14 (28%)	13 (26%)	15 (30%)	0.0352*
Constipation	0 (0.00%)	0 (0.00%)	6 (12%)	0.012*
Dry Mouth	0 (0.00%)	0 (0.00%)	7 (14%)	0.001*

* Significant

Discussion

Neuropathic pain (NP) is thought to result from a multitude of mechanisms. These encompass abnormalities in spinothalamic function altering sensitivity to temperature and pinprick, heightened excitability of neurons, increased firing of pain-related nerve cells, and an inadequate presence of inhibitory circuits, both segmental and non-segmental. [18-20] The outcome is an abnormal perception of pain manifesting as clinical symptoms like burning, stabbing, and stinging, akin to an electric shock. [21] Diverse pharmaceutical interventions have been suggested, including opioids, antidepressants, anticonvulsants, baclofen, non-opioid analgesics, alpha-adrenergic agonists, and ketamine. However, the efficacy of these treatments remains suboptimal, and the extensive utilization of many of these agents is often curtailed due to notable side effects. [22] In this study, we found male preponderance in the treatment groups. Other similar studies in this field have reported similar observations. [23] Although females tend to have lower pain thresholds, the etiological factors causing neuropathic pain are far more common in males as compared to females this could be the reason for increased prevalence among males. Patients administered amitriptyline experienced an anticipated decrease in pain scores, with noticeable pain relief within 5-6 days of initiating the treatment. Similarly, individuals receiving pregabalin exhibited a substantial reduction in pain scores, consistent with findings from other studies, [24, 25], and reported pain relief starting from the fourth day of treatment. Additionally, amitriptyline demonstrated good adherence. A study by Bansal et al. [26] also highlighted that pregabalin provides faster and more effective pain relief compared to gabapentin. Several placebo-controlled studies involving pregabalin over five to eight weeks indicated a significant reduction in pain compared to the placebo ($p<0.001$). [27] Pregabalin, is an anti-convulsant with excellent bioavailability and a well-established safety profile, demonstrating minimal drug interactions. Recent randomized clinical trials have highlighted its efficacy in managing post-herpetic neuralgia and diabetic peripheral neuropathy [23]. Preclinical research indicates that pregabalin effectively decreases neurotransmitter release in hyperexcited neurons. Moreover, two clinical studies have confirmed its effectiveness in treating neuropathic pain associated with spinal cord injury (SCI). [28]

Kaur et al. [29] conducted a study on amitriptyline for neuropathic pain within a dose range of 10 mg to 100 mg per day. Some guidelines propose commencing amitriptyline at 10 mg and gradually increasing it up to 150 mg at bedtime for neuropathic pain treatment. [30] In our current study, the amitriptyline dose was 10 mg at bedtime (HS), aligning with similar investigations previously carried out in India. This underscores that Indian patients typically require a dose of amitriptyline ranging from 10 mg to 50 mg for treating neuropathic pain. Ghosh et al. [31] assessed the efficacy and safety of pregabalin in treating neuropathic pain using standard pregabalin capsules. These studies consistently recommend a daily dose of pregabalin between 300 mg to 600 mg, administered in two or three divided doses. In our study, we initiated pregabalin at 75 mg at

bedtime (HS), allowing for upward titration based on the patient's requirements. This represents a significant advantage of sustained-release preparations, offering once-daily dosing that potentially reduces adverse effects and improves patient compliance. Notably, two other Indian studies employed standard pregabalin capsules at doses ranging from 75 mg to 150 mg per day for the effective treatment of neuropathic pain, demonstrating positive outcomes. [32] Furthermore, a recent multicenter study in India using sustained-release pregabalin and methylcobalamin showcased the efficacy of pregabalin-SR (75-150 mg) in significantly alleviating neuropathic pain at lower doses (150-600 mg), highlighting reduced adverse effects in Indian patients. [33] The observed dose variation is challenging to elucidate and warrants further extensive studies involving a larger patient population. Recent research indicates that Indian patients, and possibly Asians more broadly, may require lower doses of sustained-release pregabalin to attain the desired therapeutic effects with minimized adverse effects. [34]

The reduction in pain for patients treated with pregabalin was 53.74%, while for gabapentin and amitriptyline, it was 51.57% and 33.39%, respectively, after the 2-month study period. Consequently, pregabalin demonstrated a pain reduction similar to gabapentin (53.74% versus 51.57%) by the end of the study. In contrast to our results, Dongre et al. reported from randomized trials that pregabalin's efficacy exceeded that of gabapentin. [35] Pregabalin exhibited greater effectiveness than amitriptyline (53.74% versus 51.57%) in reducing pain at the 2-month mark. This efficacy is attributed to its agonistic action on specific GABAB receptors, which negatively regulate the alpha-2-delta subunit of voltage-gated Ca^{2+} channels. This action activates inwardly rectifying K+ channels, blocks Ca^{2+} and Na^{+} channels, and opens K^{+} channels, ultimately inhibiting abnormal activity and hyper-excitability of sensory neurons, thereby reducing pain. [36] The safety and tolerability assessments in this study did not reveal any unusual or severe adverse events. Dose-limiting adverse effects remain a significant concern for patients with neuropathic pain. The tolerability profile observed in this study generally matched previous research. [37] Amitriptyline users primarily reported dry mouth and drowsiness, with a higher incidence among those taking 50 mg at bedtime (HS). Conversely, a minimal number of pregabalin users reported drowsiness and only two out of forty patients reported dizziness. Pregabalin SR exhibited a lower reported count of adverse events in this study. A strength of the present study lies in the use of standard validated scales and scores for diagnosing neuropathic pain and assessing the primary outcome measure—pain relief. The authors utilized percentage reduction in the primary efficacy parameter to analyze the difference between the two groups. To the best of our knowledge, not many studies have employed percentage reduction, which is more sensitive to a smaller number of patients than simple absolute values. However, this study had a few limitations. It was an open-label study without blinding. Additionally, the follow-up period for patients was only 2 months, and therefore, the long-term efficacy and safety of the study drugs could not be evaluated.

Conclusion

In conclusion, this study found all three groups—gabapentin, pregabalin, and amitriptyline demonstrated efficacy in alleviating neuropathic pain (NeP). Although Pregabalin exhibits an advantage in terms of a significant decrease of NPRS score compared to gabapentin and amitriptyline at the end of 3 months of therapy. Gabapentin is associated with fewer reported adverse effects, enhancing patient compliance with long-term use. Amitriptyline, being more cost-effective than pregabalin, holds significant importance to consider when treating patients.

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