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Original research article

Comparative Study of Efficacy and Safety of Gabapentin and Amitriptyline in Treatment of Neuropathic Pain Associated with Chronic Lumbar Radiculopathy. An Open Label, Prospective Randomized Clinical Study.

Dr Shaikh Huzaif[1], Dr Syed Maaz Hussain [2], Dr Shadab Munawar Moosa[3], Dr Imran Nawaz Khan[4], Dr Afshan Kausar*[5], Dr Quazi Zubair[6]

[1] Assistant Professor Department of Pharmacology JIIU's Indian Institute of Medical Science and Research and Noor Hospital, Jalna.

[2] Associate Professor Department of Pharmacology JIIU's Indian Institute of Medical Science and Research and Noor Hospital, Jalna.

[3] Associate Professor Department of Physiology JIIU's Indian Institute of Medical Science and Research and Noor Hospital, Jalna.

[4] Professor Department of Pharmacology JIIU's Indian Institute of Medical Science and Research and Noor Hospital, Jalna.

[5] Associate Professor Department of Physiology JIIU's Indian Institute of Medical Science and Research and Noor Hospital, Jalna.

[6] Assistant Professor Department of Pharmacology JIIU's Indian Institute of Medical Science and Research and Noor Hospital, Jalna.

Corresponding Author: Dr. Afshan Kausar
Email ID: dr.afshankausar@gmail.com

Abstract

Title: Comparative study of efficacy and safety of gabapentin and amitriptyline in treatment of neuropathic pain associated with chronic lumbar radiculopathy. An open label, prospective randomized clinical study.

Background: Chronic lumbar radiculopathy is a clinical condition characterized by back and leg pain associated with sensory, reflex, or motor deficits in the area of nerve root distribution lasting for more than 12 weeks. The lifetime prevalence of lumbar radiculopathy has been reported to be 5.3% in men and 3.7% in women.

Objective: To evaluate the efficacy and safety of gabapentin and amitriptyline in patients with chronic lumbar radiculopathy by measuring the change in NPRS score.

Material and Methods: The present study was conducted in the outpatient department (OPD) of orthopedics in collaboration with department of pharmacology. It was a 12 weeks randomized comparative open label single centre two arm prospective study. Total patients were randomized equally into 2 groups. Patients in Group 'A' received Tablet Gabapentin 300 mg two times in a day and Patients in Group 'B' received Tablet Amitriptyline 10 mg. Pain intensity was assessed at baseline (0 week), at 6 weeks and at 12 weeks of starting the treatment using Numeric pain rating scale (NPRS).

Results: 75 subjects in each group who completed the 12 weeks study. In present study mean NPRS score in Gabapentin group was 8.27 at baseline which reduced to 3.89 after the 12 weeks of treatment and mean NPRS score in amitriptyline group was 8.03 at baseline which reduced to 5.64 after the 12 weeks of treatment. The difference in mean NPRS among both groups was 1.74 at 12 week which was statistically significant.
Conclusion: Gabapentin having better efficacy and safety as compared to amitriptyline in treatment of neuropathic pain associated with chronic lumbar radiculopathy.
Keywords: Neuropathic pain, chronic lumbar radiculopathy, gabapentin, amitriptyline.

Introduction

Chronic lumbar radiculopathy is a clinical condition characterized by back and leg pain associated with sensory, reflex, or motor deficits in the area of nerve root distribution lasting for more than 12 weeks. [1, 2]The lifetime prevalence of lumbar radiculopathy has been reported to be 5.3% in men and 3.7% in women.[3]Lumbar radiculopathy due to a prolapsed disc resolves spontaneously in 23-48% of patients, but up to 30% will still have pronounced symptoms after one year, 20% will be out of work, and 5-15% will undergo surgery.[4, 5]

In patients where the primary symptom is leg pain, conservative management like physical therapy, use of pain reducing medications and epidural steroid injections, as well as surgical intervention such as lumbar discectomy have been shown to be helpful.[6-11]Regardless of the introduction of new treatments, the management of patients with neuropathic pain remains a challenge.[12] In clinical practice, patients with neuropathic pain including those with spinal pain, often receive suboptimal treatment. In this context, the most widely used pharmacological treatments in these patients are non-steroidal anti-inflammatory drugs, which are not totally effective in treating pain with a neuropathic element such as the one seen in various radiculopathies.[13, 14]Such suboptimal treatment of neuropathic pain contributes substantially to the patient disease burden.[15] Although, various therapies are available for neuropathic pain, including antidepressants, opioids, and different antiepileptic drugs, the results of a recent systematic review suggest that, in view of their balance between efficacy and tolerability, gabapentin and pregabalin can be regarded as first line treatments for neuropathic pain.[12]In addition, these antiepileptic drugs, together with antidepressants, offer the advantage of acting not only on pain but also on the associated symptoms of depression.[12]The presence of psychological disorders in these subjects may exacerbate pain intensity and disability. Therefore, treatment with anticonvulsive drugs or antidepressants could optimize treatment effectiveness and reduce the occurrence of adverse events.[16]

Gabapentin which fit in to a new category of drugs called as alpha-2-delta ($\alpha_2\delta$) modulators, have been discovered to be effective in the treatment of neuropathic pain related with multiple conditions.[17-21] Gabapentin is effective in multiple types of neuropathic pain and it is likely to be effective in neuropathic pain related with nerve root compression.Gabapentin have agonistic action on a subset of $GABA_B$ receptors,which may negatively regulate voltage gated Ca^{2+} channelsand activate inwardly rectifying K^+ channels. In addition, gabapentin is capable of blocking Ca^{2+} and Na^+ channels as well as open K^+ channels, consequently inhibiting the abnormal unprompted activity and hyper-excitability of sensory neurons, thus reducing pain.[22-24]

As a member of tricyclic antidepressants (TCAs), amitriptyline is known to inhibit the pre-synaptic reuptake of serotonin (5-HT) and nor epinephrine (NE) and consequently increase the concentrations of both neurotransmitters at the synaptic cleft. 5-HT and NE are significant neurotransmitters of pain modulation system, which can augment the descending inhibitory system for painand provides a supra-spinal analgesic effect. [25]So we planned this study to compare the effect of Gabapentin andamitriptyline in patients suffering from chronic lumbar radiculopathy associated with neuropathic pain.

Material and Methods:

The present study was conducted in the outpatient department (OPD) of orthopedics in collaboration with department of pharmacology at tertiary care hospital Aurangabad from 11 December 2015 till 18 August 2017. It was a 12 weeks randomized comparative open label single centre two arm prospective study, conducted after the approval of the Institutional Ethics Committee and as per ICH-GCP guidelines. Patients presenting in the orthopaedics OPD with chronic lumbar radiculopathy symptoms were screened and clinical examination was performed by the orthopaedic surgeons. Clinically diagnosed cases were then subjected to radiological investigations for confirming the diagnosis.

Patient of either sex, age range between 18 to 65 years, diagnosed with chronic lumbar radiculopathy (confirmed by clinical and radiological examination) and willing to participate in the study and give written informed consent were included in the study.

Patients with history of diabetes, tuberculosis and hypertension were not considered for the study. Patients with history of cardiac, renal and liver diseases were excluded from the study. Patients taking anticholinergic, antipsychotic drugs or patients who have taken the study drugs previously within past one month were not included in the study. Patients having neuro-deficit disorder in lower limbs or having bowel and bladder incontinence, radiculopathy secondary to tumours or immunocompromised state were excluded from the study. Pregnant and lactating women and patients with known hypersensitivity to the study drugs were not considered for study.

Sample size calculated according to the below mentioned formula was 73. Randomization of the patients in two groups was done using chit method.

Sample size (n) for the study was calculated by the formula given below

$$n = \frac{Z^2 p \times (1-p)}{d^2}$$

Methodology:

Patients fulfilling the inclusion criteria were enrolled in the study. Written informed consent in patients own vernacular language was obtained. Total patients were randomized equally into 2 groups. Patients in Group ‘A’ received Tablet Gabapentin 300 mg two times in a day for 12 weeks and Patients in Group ‘B’ received Tablet Amitriptyline 10 mg before sleep for 12 weeks.

Pain intensity was assessed at the start of study i.e. at baseline (0 week), at 6 weeks and at 12 weeks of starting the treatment using Numeric pain rating scale (NPRS).For each patient enrolled, all clinical and radiological observations are recorded on case record form. If the patient has withdrawn from the study, the reason for withdrawal was recorded in the case record form. The investigator has complied with GCP regulatory requirements to protect the right of the subject and to ensure the regulatory validity of data.

Primary objective of the study was to evaluate the efficacy of gabapentin and amitriptyline in patients with chronic lumbar radiculopathy by measuring the change in NPRS score from baseline to 12 weeks. Secondary objective of the study was to evaluate the safety and tolerability of the study drugs.

Statistical Analysis:
The collected data was compiled in MS-EXCEL sheet and Master sheet was prepared. For analysis of this data software 'Graph pad prism' was used. Qualitative data was represented in form values & percentages. Quantitative was represented in form of mean & SD. For comparison of mean pain on numerical pain rating scale between two groups Student's unpaired 't' test was used. Fisher's exact test was used to evaluate adverse drug reactions between two study groups. P-value <0.05 considered as statistical significant.

Results:
Out of 1176 patients screened, 160 patients who were fulfilling the eligibility criteria and willing to participate in the study were randomized into 2 groups of 80 each. Out of 160 patients 150 patients completed the 12 weeks study. Total 6 subjects were lost to follow up, due to severe dizziness and sedation caused by study drugs which was confirmed telephonically with the patients (2 in group A, 4 in group B). 4 subjects (3 in group A, 1 in group B) who developed neuro-deficit in lower limbs during the course of study were excluded and referred for immediate surgical intervention. Therefore 75 subjects in each group who completed the 12 weeks study were evaluated and analyzed.Both groups were similar in demographic profile at baseline as shown in (Table 1). Mean age in group A and B was 37.64 ± 9.26 years and 37.13 ± 9.66 respectively (Table 1). Mean NPRS score was 8.27±1.18 and 8.03±1.17 at baseline which was reduced to 3.89±2.99 and 5.64±3.24 in group A and B respectively after 12 weeks of treatment (Table 2). In group A ADRs were seen in 12 patients and in group B ADRs were seen in 26 patients and sedation was the most common adverse effect seen in both groups (Table 5).

Table 1: Demographic details of patients in group A and group B

Parameter	Group A (n=75)	Group B (n=75)	'P' value
Age in years			
21-30	20 (26.66%)	20 (26.66%)	0.7723†
31-40	27 (36.0%)	26 (34.66%)	
41-50	22 (29.33%)	25 (33.33%)	
51-60	06 (8.0%)	04 (5.33%)	
Mean ± SD	37.64 ± 9.26	37.13 ± 9.66	
Gender			
Men (n)	47	50	0.7328‡
Women(n)	28	25	

*(n: Numbers; SD: Standard deviation; Values: Mean ± SD (otherwise mentioned); *: Statistically significant, †: Using 2-tailed unpaired t-test, ‡: Using Fisher's exact test.*

Table 2: Comparison of NPRS (Numeric Pain Rating Scale) in score group A and group B

Sr. No	Parameter	Group A (Mean ± SD)	Group B (Mean ± SD)	*P value inter group*†
1	Mean NPRS score Baseline 6 weeks 12 weeks	 8.27±1.18 6.76±1.56 3.89±2.99	 8.03±1.17 7.01±1.80 5.64±3.24	 0.2133 0.3590 0.0008*
	P value intragroup§	< 0.0001*	< 0.0001*	

*(n: Numbers; Values: Mean ± SD (otherwise mentioned); *: Statistically significant, †: Using 2-tailed unpaired t-test,* §: *Repeated measure ANOVA.)*

Table 3: Comparison of mean difference of NPRS (Numeric Pain Rating Scale) score in two groups at baseline, 6 weeks and 12 weeks.

Time	Study groups	Mean Difference	*P value inter group*$
Baseline	Group A vs. Group B	0.240	0.459
At 6 weeks	Group A vs. Group B	0.253	0.663
At 12 weeks	Group A vs. Group B	1.74	0.002*

**: Statistically significant, $: Using Tukey Post Hoc test*

Table 4: Comparison of percent reduction of NPRS (Numeric Pain Rating Scale) score after 12 weeks in two groups

Groups	Mean reduction in NPRS	% Mean reduction
Group A at baseline vs. group A at 12 weeks	4.38	52.96%
Group B at baseline vs. group B at 12 weeks	2.39	29.76%

Table 5: Adverse Drug Reactions in group A and group B

Sr No	Adverse Effect	Group A (n=75)	Group B (n=75)	*P value inter group*‡
1	Sedation	7	12	0.3263
2	Dizziness	5	1	0.2092
3	Dry mouth	0	9	0.0030*
4	Constipation	0	4	0.1200

*(n: Numbers; *: Statistically significant; ‡: Using Fisher's exact test.)*

Discussion:

There are many different modalities of pharmacotherapies are available for chronic lumbar radiculopathy pain such as NSAIDS, antidepressants, opioids, and different antiepileptic drugs. The antiepileptic drugs along with antidepressants offer the benefits of acting not only on pain but also on the associated symptoms of depression.[12]

In present study mean NPRS score in Gabapentin group was 8.27 at baseline which reduced to 3.89 after the 12 weeks of treatment and mean NPRS score in amitriptyline group was 8.03 at baseline which reduced to 5.64 after the 12 weeks of treatment. The difference in mean NPRS among both groups was 1.74 at 12 week which was statistically significant. When we compared the individual drugs, it showed that the pain reduction in patients treated with gabapentin was 52.96 % and with amitriptyline it was 29.76 % at the end of 12 weeks. Hence, gabapentin showed more pain reduction as compare to amitriptyline [52.96% vs. 29.76%] at the end of 12 weeks study in patients suffering from chronic lumbar radiculopathy pain.

Kasimcan et al.[26]evaluate the efficacy of Gabapentin for the pain relief in patients with lumbar radiculopathy. In their study visual analogue scale for pain was 7.00 at baseline which significantly reduced to 2.13 after 12 week of treatment with gabapentin (p=0.001).
Dallocchio C et al[27] compared the efficacy and tolerability of gabapentin and amitriptyline in painful diabetic neuropathy. They found that Gabapentin produced significant pain reductions than amitriptyline (P= 0.026). They observed that paresthesia scores also significantly decrease in patients receiving gabapentin (P= 0.004).

Keskinbora K et al[28]conducted a randomized clinical trial on forty six patients with neuropathic pain which was burning, stabbing and shooting in quality. Patients received gabapentin (group GBP) and amitriptyline (group AMI) monotherapy. The assessment were done on visual analog scale (VAS; 0: no pain, 10: worst pain imaginable). They found that shooting pain was significantly improved in patients received Gabapentin. They observed that gabapentin was well tolerated than amitriptyline.So findings of our study was in accordance with the previous studies.

The efficacy of gabapentin can be due to the agonistic action on a subset of $GABA_B$ receptors which negatively regulates the α2δ-1 subunit of voltage gated Ca^{2+} channels,activate inwardly rectifying K^+ channels, blocks Ca^{2+} and Na^+ channels and open K^+ channels which leads to inhibition of the abnormal activity and hyper-excitability of sensory neurons, thereby reducing pain.

During the course of the study it was found that the adverse drug reactions were found more in amitriptyline treated groups as compared to gabapentin group. The occurrence of sedation was more with amitriptyline (16.0%) as compared to gabapentin (9.3%). The incidence of dizziness was also high with gabapentin (6.7%) than amitriptyline (1.3%). In addition to this, some subjects treated with amitriptyline also showed anticholinergic side effects such as dry mouth and constipation. In a study of Dallocchio C et al[27] adverse events were more frequent in the amitriptyline group than in the gabapentin group. They were reported by 11/12 (92%) patients in amitriptyline and 4/13 (31%) patients in the gabapentin group (P= 0.003). These findings were also in accordance with our study.

Conclusion:
Gabapentin having better efficacy and safety as compared to amitriptyline in treatment of neuropathic pain associated with chronic lumbar radiculopathy.

Limitation:
It was a single center study and subjects were not followed up after 12 weeks which could have been helpful in finding out long term implications and effects of the study drugs.

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