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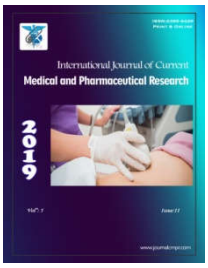

Research Article

COMPARATIVE STUDY OF SAFETY AND EFFICACY OF GABAPENTIN, PREGABALIN AND AMITRIPTYLINE IN MANAGEMENT OF NEUROPATHIC PAIN

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ABSTRACT

Background: 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 270 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.

INTRODUCTION

Neuropathic pain (NeP) is triggered by a lesion or a disease affecting the somatosensory nervous system that alters its structure and function, so that pain occurs spontaneously and responses to noxious and innocuous stimuli are pathologically amplified. [1] Peripheral causes of NeP are for example, polyneuropathy, postherpetic neuralgia, postoperative pain, and posttraumatic neuralgia, while causes of central NeP are spinal cord injuries, stroke, and so on. [2]

Neuropathic pain is often difficult to treat because it is resistant to many medications and/or because of the adverse effects associated with effective medications. Pain and anxiety symptoms are subjective with wide variation in reported prevalence. [3] No single drug works for all neuropathic pain, and given the diversity of pain mechanisms, patients' responses and diseases, treatment must be individualised. [4] Other than analgesia, factors to consider when individualising therapy include tolerability; other benefits (e.g. improved sleep, mood, and quality of life); co-morbidities; concomitant therapies and contra-indications; low likelihood of serious adverse events and cost effectiveness to the patient and the health economy. [5-7]

Tricyclic antidepressants and gabapentin constitute the first line drugs recommended by various guidelines for the management of neuropathic pain. Indian market survey data (sales data) suggested that low dose unit packs of amitriptyline, pregabalin, and gabapentin were preferred to

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(had higher sales than) the high dose unit packs. [8-12] This suggests that these drugs may be prescribed at a lower dose than what is actually recommended.

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: - Present study was prospective, comparative, open label, single centre, three arm study.

Study Centre: - Study conducted at outpatient Orthopaedics department in collaboration with Department of Pharmacology, NC Medical college & Hospital.

Study Design: Total patients were 270 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

Pain intensity was measured at the baseline, after 1 months and after 2 months with the help of Numeric pain rating Scale (NPRS).

Inclusion criteria: - Either sex with age group of 18-65 years. Diagnosed cases of chronic lumbar radiculopathy based on symptoms, clinical examination, X-ray and MRI scan of lumbosacral spine. Patient willing to participate in the study and give written and informed consent.

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

Study conduct: - Brief description of procedure in the study: Consenting patients were initially screened for the diagnosis and eligibility. After getting enrolled and prior to the commencement of the treatment, the following were recorded in the case record form

- Physical examination
- Systemic examination
- Vital signs
- Past medical history
- Concomitant medications if any
- Clinical tests for chronic lumbar radiculopathy
- X-ray of lumbosacral spine-AP & Lateral views (Digital-AGFA x-ray machine)
- MRI scans of lumbosacral spine (GE made MRI scan machine -1.5 Tesla) Pain assessment was done using numeric pain rating scale (NPRS) at the start of the study (0 day), at 1 months and at 2 months.

ADR Reporting

Adverse drug reaction reported by the patient or observed by the clinician during the study was reported using ADR reporting form.

Statistical Analysis

The collected data was compiled in EXCEL sheet and Master sheet was prepared. For analysis of this data SPSS (Statistical package for social Sciences) software version 20th was used. Data was also presented by visual impression like Bar-Diagram. Qualitative data was represented in form values & percentages. Quantitative was represented in form of mean & 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

The present study conducted in Outpatient department of Orthopaedics in collaboration with Department of Pharmacology at NC Medical college & Hospital.

Table 1 Distribution of patients according to Gender

Gender	Group A	Group B	Group C
Male	51 (56.66 %)	49 (54.44 %)	53 (58.88 %)
Female	39 (43.33 %)	41 (45.55 %)	37 (41.11 %)
Total	90 (100 %)	90 (100%)	90 (100%)

In each group total 90 patients were there. In Group A: 51 (56.66 %) were males and 39 (43.33 %) were females. In Group B: 49 were males (54.44 %) and 41 (45.55 %) were females. In Group C: 53 were males (58.88 %) and 37 (41.11 %) were females. total patients were

Table 2 Distribution of Patients according to Age group

Age-group	Group A	Group B	Group C
18-40	16	13	17
41-60	37	38	33
>61	36	39	40
Total	90 (100 %)	90 (100 %)	90 (100 %)
Mean SD	43.44 ± 9.39	44.01 ± 8.19	43.21 ± 9.01
F-value	0.213		
p-value	0.731^{ns}		

In Group A: Mean age of patients was 43.44± 9.39 years. In group B: Mean age of patients 44.01±8.19 years. In group C: Mean age of patients was 43.21±9.01. The F-value was 0.213 and p-value 0.731 which was statistically not significant.

Table 3 Comparison of Numeric pain rating scale (NPRS) score in all three groups at baseline after 1 months and after 2 months (ANOVA)

		Mean±SD	F-value	p-value
Baseline	Group A	8.31 ± 1.65	0.921	0.631^{ns}
	Group B	8.42 ± 1.44		
	Group C	8.29 ± 1.93		
After 1 month	Group A	6.21 ± 1.35	1.87	0.059^{ns}
	Group B	6.83 ± 2.01		
	Group C	7.11 ± 2.49		
After 2 months	Group A	3.72 ± 2.65	6.63	0.001^{s}
	Group B	3.63 ± 2.65		
	Group C	5.21 ± 2.65		

(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 8.31±1.65 in Group B and Group C were 8.42± 1.44 and 8.29±1.93 respectively with F-value of 0.921 and p-value of 0.631 which was not statistically significant. At 1 month, the Mean±SD of NPRS score in Group A was 6.21 ± 1.35, in Group B and Group C were 6.83±2.01 and 7.1l±2.49 respectively with F-value of 1.87 and p-value of 0.059 which was not statistically significant. 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.

Table 4 Comparison of NPRS score in tow groups at baseline, 1 month and 2 months [Tukey Post Hoc Test]

		Mean± SD	p-value
Baseline	Group A Vs Group B	0.11	0.751 ns
	Group A Vs Group C	0.02	0.813 ns
	Group B Vs Group C	0.13	0.632 ns
After 3 months	Group A Vs Group B	0.62	0.361 ns
	Group A Vs Group C	0.90	0.043 s
	Group B Vs Group C	0.28	0.329 ns
After 6 months	Group A Vs Group B	0.09	0.523 ns
	Group A Vs Group C	1.49	0.006 s
	Group B Vs Group C	1.58	0.007 s

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

Table 5 Comparison of percent reduction of NPRS (Numeric Pain Rating Scale) score baseline vs after 2 months in all three groups

Group	Mean reduction
Group A at baseline Vs Group A at 6 months	4.59
Group B at baseline Vs Group B at 6 months	4.79
Group C at baseline Vs Group C at 6 months	3.08

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	11	12.22	21	23.33	4	4.44	5.93	0.041
Sedation	23	25.55	28	31.11	22	24.44	7.32	0.036
Constipation	0	00	0	00	8	8.88	9.31	0.019
Dry mouth	0	00	0	00	11	12.22	14.22	0.000

In present study, 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]. The occurrence of constipation was seen in 8 patients of group C (8.88%) which was significantly more than in Group A and B with 0 patients (0%) [p=0.019]. The occurrence of dryness of mouth was significantly more in group C with 11 patients (12.22%) 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].

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. The occurrence of Dizziness was more with pregabalin (23.33%) as compared to gabapentin (12.22%) and amitriptyline (4.44%). The incidence of sedation was also high with pregabalin (31.11%) than gabapentin (25.55%) and amitriptyline (24.44%). In addition to this, some subjects treated with amitriptyline also showed anticholinergic side effects such as dry mouth and constipation.

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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