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A PROSPECTIVE OBSERVATIONAL STUDY TO COMPARE THE CLINICAL OUTCOME OF PREGABALIN AND AMITRIPTYLINE IN NEUROPATHIC PAIN

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ABSTRACT

Background

Neuropathic pain has a significant negative impact on the patients' quality of life. Antidepressants like Amitriptyline and newer anticonvulsants such as Pregabalin have been proven beneficial in patients with peripheral neuropathic pain. Studies comparing the real-world effectiveness and safety of drugs for neuropathic pain are scarce.

Aims and objectives

The aim of the study was to compare the efficacy and safety of Pregabalin and Amitriptyline in relieving neuropathic pain.

Methods

After ethics committee approval and informed consent, 200 outpatients (100 each) prescribed any one of the drugs were consecutively recruited in a prospective observational study. Drug effectiveness was assessed by comparing difference in visual analogue scale (VAS) score from baseline, obtained from pain diary. The quality of pain was assessed by using the Short Form Mc Gill Pain Questionnaire (SF-MPQ). Safety was assessed by comparing frequency of adverse drug reactions (ADRs).

Results

The difference in mean VAS score at 12 weeks showed that Amitriptyline group had a greater reduction in pain compared to Pregabalin. Patients in Amitriptyline group also had a greater reduction in Mc Gill sensory, affective and total scores after 12 weeks. Adverse reactions like sedation, dizziness, lack of concentration, fatigue, dry mouth occurred in both groups, but Amitriptyline group had higher incidence of sedation, dizziness and dry mouth.

Conclusion

Amitriptyline was more effective in relieving neuropathic pain compared to Pregabalin. Higher incidence of sedation, dry mouth and dizziness was observed in Amitriptyline treated group compared to Pregabalin.

KEY Words: Amitriptyline, Pregabalin, Neuropathic Pain, Visual Analogue Scale, Short Form Mc Gill Pain Questionnaire.

INTRODUCTION

IASP (International Association for the Study of Pain) approved definition for neuropathic pain as 'pain arising as a direct consequence of a lesion or a disease affecting the somatosensory system'.[1,2] It is an abnormal activation of pain pathway and can occur as a result of injury to peripheral nerves and posterior roots (peripheral neuropathic pain) or spinal cord and brain (central pain).

The prevalence of neuropathic pain is found to be 6% to 8%.[3] Most of the patients present with post-herpetic neuralgia, diabetic neuropathy and phantom limb. Other causes of neuropathic pain include mononeuropathies like trauma, connective tissue disorders, malignant plexopathy and polyneuropathies like metabolic (alcoholic, pellagra), drug induced Isoniazid((INH), Vincristine, Cisplatin), infective (HIV, Guillain Barre Syndrome) and dorsal root ganglion neuropathies like trigeminal neuralgia, prolapsed disc.[4]

Pain can be assessed by various factors like periodicity, intensity, modifying factors, effects of treatment, functional impact and impact on the patient. Pain rating scales can be used to quantify the intensity of pain. Examples are visual analogue scale[5] and verbal rating scale. Questionnaires are also available to assess the impact of pain on general activity, mood, work, relations, sleep and enjoyment of life. Sometimes, the clinical features may itself suggest a diagnosis (example- post herpetic neuralgia). X-ray, CT and MRI may also aid in diagnosis. Nerve conduction studies can confirm neuropathy. But they can assess only the large fiber neuropathies. Other methods like microneurography, functioning neuroimaging and laser evoked potentials are under development.[6]

Treatment of neuropathic pain is still a challenge because many patients do not experience sufficient pain relief. Many of them require more than one drug for pain relief. In case of diabetes or nerve root compression, the treatment of the underlying cause might result in partial or complete pain relief. Adequate control of the underlying disease will prevent the progression of nerve damage. The treatment of neuropathic pain is a multi-disciplinary approach including pharmacological and non-pharmacological treatment regimen such as cognitive, behavioral, physical and occupational therapy.[7,8]

Antidepressants (tricyclic antidepressants, SSRIs and atypical antidepressants (Venlafaxine, Duloxetine)[1,9] anticonvulsants (Pregabalin, Gabapentin, Carbamazepine, Phenytoin, Lamotrigine, Topiramate, Zonisamide and Levetiracetam)[1,10] and topical Lidocaine are the first line medications. Recommended second line drugs are opioids like Tramadol, Oxycodone, Methadone and Morphine.[11,12] Other medications that would be used as third line treatment are Baclofen, Phentolamine, topical Capsaicin, Mexiletine and NMDA Receptor antagonists (Ketamine and Dextromethorphan).

Even though many drugs are available, only a few high-quality studies comparing these drugs are available. Majority of the studies comparing the clinical effectiveness of these drugs have been carried out in Western countries. Only a few studies comparing the effectiveness and safety of Pregabalin and Amitriptyline have been done in India. This study was formulated to compare the efficacy and safety of Pregabalin and Amitriptyline in neuropathic pain which could generate more data relevant to the physicians.

MATERIALS AND METHODS

This prospective observational study was approved by the Institutional Ethics Committee (IEC) [15/132/12/2014 dated January 17, 2012]. It was carried out in the Outpatient Department of Physical Medicine and Rehabilitation, Govt. Medical College, Thiruvananthapuram, Kerala, India from February 2012 to January 2013. Two hundred patients in the age group 18-65 years presenting with neuropathic pain of duration less than one month, and who were prescribed either Pregabalin (PGN) or Amitriptyline (AMY) by their treating physicians were included in the study. Patients with history of heart disease, epilepsy, peripheral occlusive vascular disease, spinal cord injury with signs of upper motor neuron lesion, pregnant and lactating mothers were excluded from the study. A

sample size of 100 in each group was determined sample size was calculated using the data obtained from a similar study[13] by the formula,

$$n = \frac{(Z\alpha + Z_{1-\beta})^2 \times [P_1 (1-P_1) + P_2 (1-P_2)]}{(P_1-P_2)^2}$$

Patient recruitment stopped when 100 patients each had accrued into the two treatment observation groups.

Information regarding patient demographics, past history, concomitant diseases and medications, symptoms, diagnosis, drug received (either PGN or AMY) were collected and recorded in the proforma. Tools used to compare the effectiveness of the drugs were the Visual Analogue Scale for pain (VAS) and the Short Form Mc Gill Pain questionnaire (SF-MPQ). At first the patient's pain status was determined using the Visual Analogue Scale for pain.[5] The VAS is usually a horizontal line, 10 centimeters in length, anchored by word descriptors at each end like 0 which represents no pain and 10 which represents maximum pain. The patient was asked to mark on the line, the point that he/she feels represents the pain perception at that time. The VAS score was determined by measuring in centimeters from the lefthand end of the line to the point marked by the patient.

The Short Form Mc Gill Pain Questionnaire (SF-MPQ) is a modified version of the Mc Gill Pain Questionnaire and was developed by Melzack to provide a useful measure of pain. It has 15 descriptors (11 sensory and 4 affective) which are rated on an intensity scale as 0=none, 1=mild, 2=moderate and 3=severe. The patient was asked to check the column to indicate the level of his/her pain for each word or leave the column blank if it did not describe the pain. Three pain scores were derived from the sum of the intensity rank values of the words chosen for sensory (maximum is 33), affective (maximum is 12) and total (maximum is 45) descriptors.

Patients were followed up after 6 weeks and 12 weeks. The details of adverse events like dizziness, dry mouth, blurred vision, nausea, vomiting, constipation, and peripheral edema were recorded.

Comparability of the two groups at baseline was assessed using either unpaired t test or chi square according to the variable. Comparison of outcome measures between the two groups was done using unpaired t test. Paired t test was done to assess the Improvement from baseline at each visit. Safety variables in each group were expressed as frequencies and Percentage. Data were analyzed using SPSS 16 for windows.

RESULTS

Two hundred patients receiving AMY and PGN were recruited in this study (100 in each group) of which 110 were females and 90 males. Majority of the patients were more than 50 years of age. The patients in the two treatment groups were similar in baseline characteristics as shown in Table 1.

Baseline characteristics	**Baseline values: Mean ±SD or n (%)**		
	PGN(n=100)	**AMY(n=100)**	**P Value**
Gender			0.776
Male (n)	44	46	
Female(n)	56	54	
Age (years)	48±9	47±9	0.451
Co-morbidities			0.679
Diabetes (%)	38	37	
Hypertension (%)	19	17	
Hyperlipidemia (%)	12	15	
Thyroid disorders (%)	3	4	
COPD (%)	3	3	

History of trauma (%)	16	14	0.692
History of numbness (%)	86	84	0.547
History of pin and needle sensation (%)	65	71	0.363
History of sleep disturbances (%)	85	89	0.400
Presence of neurological deficit (%)	2	2	1.000
Presence of radiological evidence (%)	55	56	0.887
Diagnosis			0.973
Cervical radiculopathy (%)	34	33	
Lumbar radiculopathy (%)	29	32	
Diabetic neuropathy (%)	28	29	
Traumatic neuropathy (%)	4	3	
CTS (%)	3	2	
RSD (%)	2	1	

Table 1: Baseline characteristics

As shown in table 2 the mean VAS score of PGN treated group reduced to 3.17 from 7.82 after 12 weeks of therapy and the difference between the mean VAS scores at day 0 and 12 weeks was statistically significant (p value <0.001). After 12 weeks of therapy with AMY, the mean VAS score reduced to 2.76 from 7.90 and this difference was statistically significant (p value=0.000). After 6 weeks of therapy, 77% of patients in the PGN group and 89% in the AMY group showed 25-50% of reduction in pain score. After 12 weeks of therapy, >50% reduction in pain score was observed in 81% of patients in the PGN group and 95% in the AMY group.

Pregabalin(n=100)					
		Mean	**SD**	**T**	**p**
Vas score	At the time of diagnosis	7.82	1.10	32.710	.000
	After 6 weeks	5.26	1.19		
Vas score	At the time of diagnosis	7.82	1.10	59.360	.000
	After 12 weeks	3.17	1.21		
Amitriptyline (n=100)					
		Mean	**SD**	**T**	**P**
Vas score	At the time of diagnosis	7.90	1.11	66.746	.000
	After 6 weeks	4.90	1.18		
Vas score	At the time of diagnosis	7.90	1.11	80.823	.000
	After 12 weeks	2.76	1.08		

Table 2: Assessment of effectiveness of PGN and AMY using VAS score

The mean VAS score of PGN group after 6 and 12 weeks of therapy was 5.26 and 3.17 as compared to AMY group which 4.90 and 2.76 respectively and it was statistically significant(p<0.001). AMY group had a greater percentage of pain relief after 6 weeks and 12 weeks (38.76% and 66.05% respectively) compared to PGN (33.06% and 60.40% respectively) (p value=0.000).

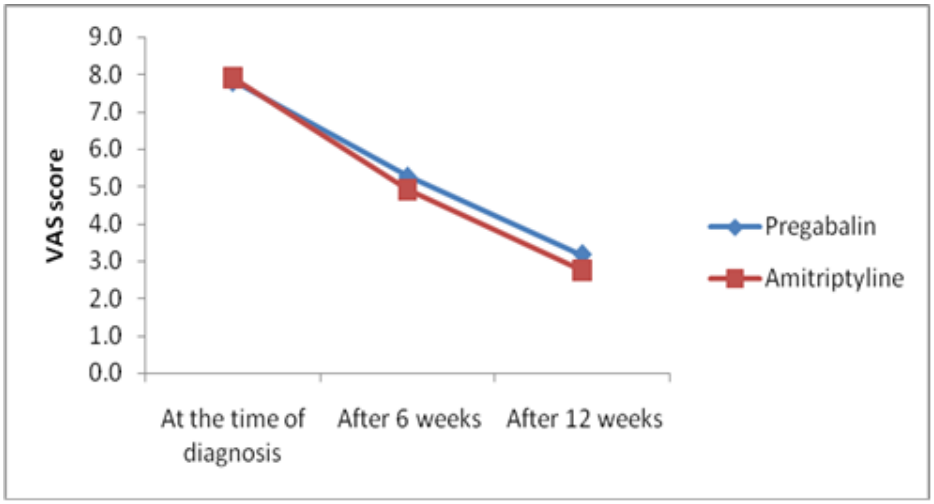

Figure 1: Comparison of mean reduction in VAS

As shown in table 3 & 4, before treatment, the mean sensory, affective and total SF-MPQ scores of PGN group were 10.88, 5.15 and 16.03 respectively. After 12 weeks of treatment, the sensory, affective and total scores reduced to 8.90, 3.35 and 12.25 respectively (p value=0.000). In AMY group, the mean McGill sensory, affective and total scores before treatment were 10.79, 4.89 and 15.68 respectively. The mean sensory, affective and total scores after 12 weeks of therapy reduced to 7.15, 2.63 and 9.78 respectively (p value=0.000).

	Category	Mean	SD	t	P
Mc Gill sensory before treatment	Pregabalin	10.88	1.60	.386	.700
	Amitriptyline	10.79	1.70		
Mc Gill sensory after treatment	Pregabalin	8.90	2.83	4.160	.000
	Amitriptyline	7.15	3.12		
Difference in Mc Gill sensory score	Pregabalin	1.98	2.59	-4.369	.000
	Amitriptyline	3.64	2.78		
Table 3: Comparison of effectiveness using SF-MPQ Sensory score					

	Category	Mean	SD	t	p
Mc Gill affective score before treatment	Pregabalin	5.15	1.45	1.302	.194
	Amitriptyline	4.89	1.38		
Mc Gill affective score after treatment	Pregabalin	3.35	1.89	3.022	.003
	Amitriptyline	2.63	1.45		
Difference in Mc Gill affective score	Pregabalin	1.80	1.79	-2.086	.003
	Amitriptyline	2.26	1.29		
Table 4: Comparison of effectiveness using SF-MPQ Affective score					

The mean Mc Gill sensory and affective scores after 12 weeks of therapy in PGN group was 8.90 and 3.35 respectively and that in AMY group was 7.15 and 2.63 respectively. AMY showed a greater difference in affective score compared to PGN and this difference was statistically significant (p value-0.003). After 12 weeks, the mean Mc Gill total score in PGN group was 12.25 and that in AMY group was 9.78 which was statistically significant (p value=0.000).

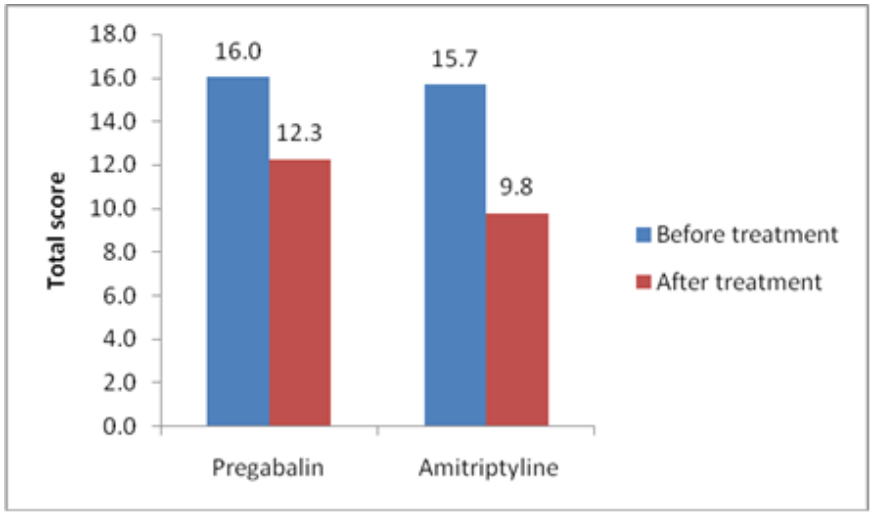

Figure 2: Comparison of effectiveness using SF-MPQ total score

Safety assessment

On comparing the individual ADRs, the incidence of ADRs like sedation (p value<0.001), dizziness (p value-0.041), dry mouth (p value<0.001), constipation (p value<0.001) was higher in AMY group. Though the incidence of urinary retention, lack of concentration and weight gain were also high in AMY group compared to PGN group, the difference between the two groups was not statistically significant. Distribution of patients with peripheral edema was high in PGN group compared to AMY group, but this difference was not statistically significant.

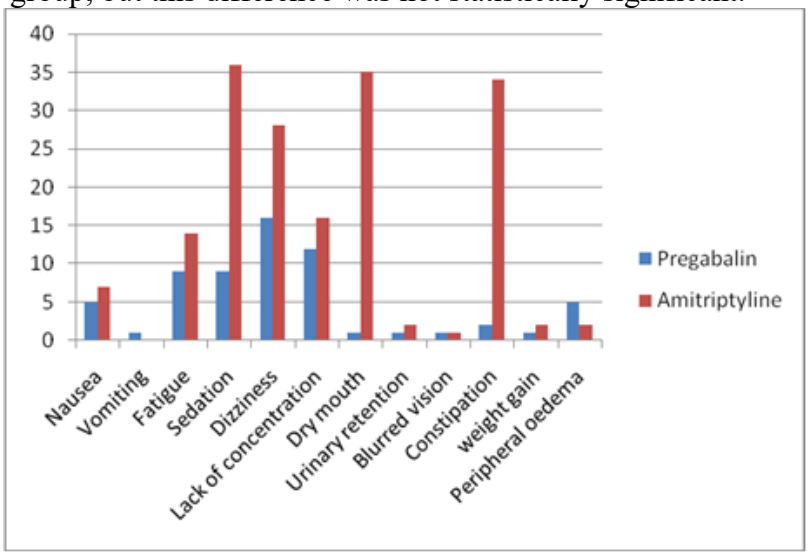

Figure 3: Distribution of patients based on the presence of ADRs

DISCUSSION

The present study showed that PGN and AMY prescribed by the treating physicians were effective for the symptomatic treatment of pain in patients suffering from neuropathic pain over 3 months. The primary objective of this study was to compare the real-world effectiveness of the two drugs in reducing pain severity in patients with neuropathic pain. The two drugs achieved comparable reduction in pain severity over 3 months. The assessment of pain based on VAS showed a statistically significant reduction in the two treatment groups. AMY produced a greater reduction of mean VAS score compared to PGN and thus AMY was found to be more efficacious in reducing pain.

In the present study, 89% of patients in the AMY group and 77% in the PGN group showed 25-50% reduction in pain score after 6 weeks of therapy. This was comparable with earlier studies. In a

study comparing AMY and DUL in painful diabetic neuropathy, Kaur H et al[14] observed that 55%, 24% and 15% of patients on AMY produced good, moderate and mild pain relief respectively.
Study by Sumedhan et al[1] AMY, DUL and PGN produced similar reductions in subjective pain perception in patients as evidenced by comparable improvement in VAS score. In study by Arvinth et al,[15] PGN is found to be more efficacious when compared to Gabapentin among Type 2 diabetes mellitus patients with painful peripheral neuropathy.
In a study done by Guler N et al,[16] AMY produced a statistically significant reduction in VAS scores (from 9.6 at day 0 to 0.3 after 12 months of therapy) in atypical facial pain. The results were also supported by the study done by Watson CP et al[17] which showed that AMY produced excellent pain relief in 66% of patients with post herpetic neuralgia. Other studies[18,19] proved PGN to be more effective compared to placebo.
Quality of pain assessment: In the PGN group, the mean Mc Gill sensory score of patients was reduced from the initial score of 10.88 to 8.90 after therapy and in the AMY group, a reduction from 10.79 to 7.15 was observed. The mean affective score decreased from 5.15 to 3.35 in the PGN group and from 4.89 to 2.63 in the AMY group. In the PGN group a reduction from 16.03 to 12.25 was observed in the total score and in the AMY group, the score reduced from 15.68 to 9.78. The two treatment groups demonstrated significant reductions from baseline scores after 12 weeks of therapy. There was also a significant difference in the reduction of mean scores between the two groups after therapy. AMY was found to be more effective in the present study based on SF-MPQ scores.
In a similar study done by Rosenstock et al[20] in diabetic neuropathy, PGN showed significant reduction in total SF-MPQ scores ($p<0.01$). This was supported by the results obtained from the study done by Guan Y et al[21] in peripheral neuropathic pain. Majority of the patients experienced significant reduction in SF-MPQ score after treatment with PGN. Kaur H et al[14] observed that AMY produced significant reduction in pain on SF-MPQ (p value<0.001) after 6 weeks of treatment in diabetic neuropathy.
In the present study, the most common adverse reaction produced by Pregabalin was dizziness (16%) followed by lack of concentration (12%), fatigue (9%) and sedation (9%). Peripheral oedema (5%) and nausea (5%) were the other side effects observed. All ADRs were found to be related to the mechanism of action of the drugs and no unexpected or serious ADRs occurred in our study. This was similar to study by Sumedhan et al[1] where sedation (4%) and dizziness (36%) were the most common ADRs observed. The results also correlate with the findings obtained from the study done by Anastassiou et al[22] in which dizziness (15.2%) was the most common side effect. Others were somnolence (9.1%), nausea (3.2%), peripheral oedema (1.7%) and fatigue (1.6%). This is also supported by another study done by Seventer et al[23] in which dizziness and somnolence were the most frequent adverse reactions.
Sedation (36%), dry mouth (35%) and constipation (34%) were the most common adverse reactions produced by AMY in the present study followed by dizziness (28%), lack of concentration (16%) and fatigue (14%). This is also consistent with the data obtained from the study done by Sumedhan SV et al[1] in which patients treated with AMY developed dry mouth, fatigue sedation and dizziness. Study done by Max MB et al[24] showed that patients treated with AMY developed dry mouth, fatigue and constipation.
On comparing the individual ADRs in the study, the incidence of sedation in the AMY group (36) was found to be significantly high compared to PGN group (9). The difference in incidence of dry mouth and constipation between AMY group (35 and 34 respectively) and PGN group (1 and 2 respectively) was also statistically significant on analysis. Dizziness (28 in AMY group and 16 in PGN group) also showed statistically significant difference between the two treatment groups.
As patients with prostatic enlargement and spinal cord injury with signs of upper motor neuron lesion were excluded from the study, the ADRs of PGN and AMY on this group could not be assessed properly. This could be the reason why the anticholinergic effects of AMY were not as evident as expected. In another similar study done by Boyle J et al[21] PGN had a significantly

higher number of adverse reactions compared to AMY and DUL. This could be due to the differences in genetic constitution and tolerability to drugs among different populations.
The strength of our study was that it was conducted in real world clinical scenario to assess the effectiveness and safety of the two drugs. However, its limitations included being an observational study of relatively small sample size and short follow-up. Other factors contributing to neuropathy such as uremia, vitamin deficiencies, smoking, and hereditary factors were also not assessed in this study.

CONCLUSION

PGN and AMY are effective as first line drugs for symptomatic treatment of pain in patients with neuropathic pain. However, AMY significantly reduced pain compared to PGN in neuropathic pain. The incidence of dizziness and anticholinergic side effects were significantly higher in AMY group compared to PGN group. Further studies with larger sample size and longer follow-up are required in Indian population to fully assess the effectiveness and safety of drugs for neuropathic pain.

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