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Comparative Study of Efficacy of Pregabalin and Lacosamide in Neuropathic Pain

Authors
Vishnu.R. Nair[1], Maneesha Dominic[1*], Fathima Sharin[1], Mariya P Chacko[1], Chrismol Devassy[1], Rajeev. P. Thomas[1], Dr. P. Abdurahiman[2]
[1]Department of Pharmacy Practice, National College of Pharmacy, Kozhikode, 673602 (Kerala)
[2]Professor and HOD, Department of Neurology, KMCT Medical College Hospital, Kozhikode, Kerala, India
[*]Corresponding Author
Maneesha Dominic
Department of Pharmacy Practice, National College of Pharmacy, Kozhikode, 673602, Kerala, India

Abstract
Introduction: *Lacosamide is a noval anti-epileptic drug, which is being evaluated for the treatment of Neuropathic Pain. The role of pregabalin in neuropathic pain is already well-established. So, the scope of the study is to compare the effectiveness of lacosamide (a newer molecule), with a well-established pregabalin.*
Methods: *107 patients, who met the inclusion criteria, were enrolled in the study. Patients are randomly arranged into 2 groups, each group receiving either lacosamide or pregabalin. Comparison is done among both the groups, to assess the Efficacy, and Quality of Life, using Visual Analog Scale (VAS) and SF-36 Questionnaire respectively. Patients are assessed during the first visit, and follow up is done after one month of initial treatment and subsequent reviews done in 2 months interval, up to 6 months.*
Results: *After analysis it was found that out of 107 patients, 54 patients were enrolled into the lacosamide treatment group and the remaining 53 into the pregabalin treatment group.Severity of pain was significantly reduced in patients treated with lacosamide, compared to that of pregabalin. Quality of life of the patients treated with lacosamide showed greater improvement compared to that of pregabalin.*
Conclusion: *Based on study results, it was concluded that lacosamide has greater efficacy compared to that of pregabalin. Patients treated with lacosamide had significant improvement in quality of life compared to that of pregabalin. Consequently, this study supports the use of lacosamide for neuropathic pain over pregabalin.*
Keywords: *Lacosamide, Pregabalin, SF-36 Questionnaire, Quality of life.*

Introduction

Understanding pain is an essential aspect to achieve both these goals. Since pain is universally understood as a signal of disease, it is the most common symptom that brings a patient to a physician's attention. The pain sensory system aims to protect the body from further damage and maintain homeostasis. It achieves this objective by detecting, localizing and identifying tissue-damaging processes. Different diseases produce characteristic patterns of tissue damage. So the quality, time course, and location of a patient's pain complaint provide important diagnostic clues, which can be used to evaluate the patient's

response to treatment. Once this information is obtained, it is the obligation of the physician to provide rapid and effective pain relief[1]. Pain is an unpleasant sensory and emotional experience that can have a significant impact on a person's quality of life, general health, psychological health, and social and economic well-being. The International Association for the Study of Pain (IASP, 2011) defines Neuropathic Pain, as "Pain caused by a lesion, or disease of the somatosensory nervous system". Central Neuropathic Pain is defined as "Pain, caused by a lesion or disease of the central somatosensory nervous system", and Peripheral Neuropathic Pain is defined as "Pain, caused by a lesion or disease of the peripheral somatosensory nervous system". Acute pain is usually associated with behavioural arousal and a stress response, tantamounting to increased blood pressure, heart rate and pupil diameter. In addition, local muscle contraction (e.g., limb flexion, abdominal wall rigidity) is often present[1].Regular recording of formal pain assessment and patient-rated pain scores improves pain management and reduces the time taken to achieve pain control. Presently a mechanism-based classification of neuropathic pain is not possible, because the detailed pain mechanisms in each individual case are extremely difficult to find out. Moreover, one mechanism can be accountable for various symptoms, and the same symptom in two patients can be caused via different mechanisms.[2] Neuropathic pain is characterized by spontaneous and provoked pain by other positive symptoms such as paresthesias and dysesthesias, and by negative signs (sensory deficits) reflecting the neural damage. It is not possible to determine the etiology of neuropathic pain from the clinical characteristics of the pain[3].Neuropathic pain is very challenging to manage, because of the heterogeneity of its etiologies, symptoms and underlying mechanisms[1]. Assessment of a pain patient with suspected neuropathic pain aims at:

(i) Recognizing neuropathic pain
(ii) Localizing the lesion (whether it is peripheral or central and whether it is in the brain, brainstem, spinal cord, nerve root, plexus, or the peripheral nerve or its branch).
(iii) Diagnosing the causative disease or event
(iv) Assessing the functional limitations that result from pain. In addition, assessment of psychosocial aspects is necessary for an individually tailored management strategy. Possible comorbidities should be taken into account, such as impaired sleep, anxiety, depression, and disability, as well as secondary impairment in work, family, and social life[6].

Evidence-based symptomatic pharmacotherapy is the mainstay of the treatment of neuropathic pain, and it should be titrated individually according to the efficacy and possible contraindications or side effects.[4, 5]Pregabalin blocks VGCC (voltage gated calcium channel) and hence decrease glutamate and sensory neuropeptides (substance P and CGRP (Calcitonin gene related peptide)) release at the synapse by decreasing Ca2+ influx. EAATs (Excitatory amino acid transporters) activity is increased by pregabalin which caused more decrease in synaptic availability of glutamate. Decreased glutamate levels further inhibited the activation of NMDA (N- methyl-D-aspartate receptor) and decreased the neuronal firing. Additionally, pregabalin also activates the KATP (ATP -sensitive potassium) channels, which also contribute inhibition of neuronal excitation. Pregabalin through all these pathways ultimately provides significant pain relief in various neuropathic pain state.[13]Lacosamide has dual action. It augments the gradual inactivation of voltage-gated sodium channels without altering the fast inactivation of voltage-gated sodium channels. This inactivation stops the channel from opening, helping end the action potential. Slow inactivation does not produce complete blockade of voltage-gated sodium channels, with both activation and inactivation occurring over hundreds of milliseconds or more. Lacosamide makes this inactivation happen at less depolarized membrane potentials.[17] It also modulates collapsin

response mediator protein 2 (CRMP-2 (Collapsin response mediator protein family)), a phosphoprotein, involved in the down regulation of NMDA (N- methyl-D-aspartate receptor) receptor, which is a key modulator of pain transmission, preventing the formation of abnormal neuronal connections in the brain.[18] Lacosamide is a newer anti-epileptic drug, which is being evaluated for the treatment of Neuropathic Pain. The role of pregabalin in neuropathic pain is already well-established. So, the scope of the study is to compare the effectiveness of lacosamide (a newer molecule), with a well-established pregabalin.

Objectives

- To compare the efficacy of lacosamide and pregabalin in the treatment of neuropathic pain.
- To compare the quality of life of patients, taking lacosamide and pregabalin, respectively, in the treatment of neuropathic pain.

Methodology

A prospective observational study, entitled "Comparative study of efficacy of pregabalin and lacosamide in Neuropathic Pain" is conducted on 107 patients of age 18 years or above, with a clinical diagnosis of Neuropathic Pain. Patients are randomly arranged into 2 groups. Group 1 received Pregabalin, whereas the other received Lacosamide. The comparison is done among both the groups to assess efficacy, using VAS (Visual Analog Scale). Visual Analog Scale is a unidimensional measure of pain intensity, which is a single 11-point numeric scale. Score ranges from 0-10, in which the score "0" resembles "No pain", and that of "10" resembles "worst pain imaginable". Respondent is asked to indicate the scale that best describes their pain intensity, after which, the corresponding percentage is calculated (0-100%; 0 signifying "No pain", and 100 signifying "Worst pain"). Quality of Life is assessed using the SF-36 Questionnaire, developed by RAND. It consists of a set of generic, coherent & easily administered Quality of life measures. All of the surveys from RAND Health are public documents, available without charge. Includes 8 health surveys (Physical functioning, Role limitation due to health problems, Role limitation due to emotional problems, emotional well-being, social functioning, energy/fatigue, pain, general health)[10]. In the first visit, clinical history of the patient, along with an assessment of pain (using VAS scale) and Quality of life is done. After one month, during the first review, assessment of pain and Quality of life is assessed, followed by a second review after 3 months, during which patients are telephoned and assessed for drug efficacy along with Quality of life estimation.

Subject Selection

The patients were selected during the time period from November 2017 to June 2018. From the 650 patients who visited Neurology department, 107 patients who satisfied the inclusion, as well as exclusion criteria, were allotted to study. The sample population are requested to answer at the time of their first review and relevant information are collected.

Sources of Data

Patient interview and patients case records which contain the patient's demographics, history, laboratory investigation reports and prescribed drugs

Inclusion Criteria

- Patients those who signed the Informed Consent Document.
- All patients, having clinical diagnosis of Neuropathic Pain.
- Age category between 18-65 years.
- Patients of both sexes.

Exclusion Criteria

- Patient less than 18 years of age and more than 65 years of age.
- Pregnant women and lactating mother.
- Psychiatric patients.

- Patients, who are unwilling to take part in the study.
- Patients taking pain medications other than lacosamide and pregabalin.

Statistical Analysis: Data are analyzed using SPSS (Statistical package for Social Sciences). Analysis is done using paired t test. A p value of ≤.05 is considered statistically significant.

Results

Table No. 1: Categorization based on age

Age (Years)	Frequency	
	Lacosamide	Pregabalin
20-30	1	3
30-40	8	4
40-50	21	12
50-60	19	22
>60	5	12

Majority of the study population belonged to the age group (40-50) and (50-60) [Table No. 1].

Table No:2 Categorization Based On Gender

Gender	Frequency	
	Lacosamide	Pregabalin
Female	25	24
Male	29	29

In the entire study population male constituted a majority among both groups .i.e. 58/107 and 49/107, respectively (Table No. 2)

Comparison of Pain Response

Table No:3 Comparison of pain response in two treatment groups

Pain	Scale Average Value	
	Lacosamide	Pregabalin
Before	8.54	8.29
After	1.09	6.8

In the entire study population, patients treated with lacosamide showed a significant reduction in the pain. Patients treated with pregabalin showed a less significant reduction in pain (Table No. 3).

Table no: 4 Association of Pain (Paired Samples Test)

	Mean	S. D	P-Value
Lacosamide	7.44630	1.13764	.000
Pregabalin	1.4925	.71813	.0011

Comparison of pain in lacosamide and pregabalin groups showed significance as the p-value is <.05 (Table No.4)

Table No.5: Comparison of the Quality of life of patients in the Lacosamide and Pregabalin treatment groups

QOL	LACOSAMIDE		PREGABALIN	
	I	II	I	II
Physical functioning	27.41	82.14	16.31	30.94
Physical health limitations	46.29	97.63	16.088	34.27
Emotional problems	96.57	99.03	97.36	98
Fatigue	50.98	87.11	44.19	49.37
Emotional well being	54.73	86.56	47.38	54.62
Social functioning	62.29	88.09	57.49	65.17
Pain	42.99	88.74	27.34	41.87
General health	39.57	71.12	22.17	30.17

QOL has significantly increased in the patients treated with Lacosamide. While patients treated with Pregabalin showed significantly less betterment in the quality of life (Table No.5).

Table No: 6 Analysis of Quality of life: Paired Sample Test

	MEAN	S. D	P VALUE
Lacosamide	.0817	.134	.03908
Pregabalin	1.33	.685	.0407

Comparison of the quality of life of patients treated by lacosamide and pregabalin showed significance as the p value is < .05 (Table No. 6).

Discussion

In this study the patients in the Lacosamide treatment group showed major reduction in the pain score i.e. average pain score before the study was 5.31 and 1.23 after the study. Pregabalin treatment group showed only less reduction in the pain score compared to that of lacosamide i.e. 7.66 was the average pain score before the study and 6.801 after the study. The statistical analysis by paired t test generated a p value that was <.05. Thus, it shows the significance in the comparison of pain severity between lacosamide and pregabalin. So, by considering the reduction in the average pain score, lacosamide has more efficacy in pain reduction over pregabalin. Though similar studies were not found to compare the present study, **Richard.L.Rauck. *et al.*,** 2007, study states that lacosamide monotherapy significantly

attenuates the pain of diabetic peripheral neuropathy compared with placebo[11]. Also, **Brett. R. Stacey.*et al.***, 2008, study states that Pregabalin was associated with improvement in pain at the end of the first 3-month treatment period. Pain quickly returned to pretreatment levels soon after cessation of pregabalin treatment. This pattern of relief on remarkably consistent throughout the five 3-month pregabalin treatment periods and four pregabalin drug holidays; these mean changes in pain scores (34%) were statistically significant[12].

In this study the quality of life of the patients in the Lacosamide treatment group showed significant improvement compared to Pregabalin treatment group. Statistical analysis of the association was done by paired t test which generated a statistically significant p value .i.e. p value <.05. Considering the significant improvement in the quality of life of patients in the lacosamide group over pregabalin group, it can be stated that lacosamide has more effectiveness compared to pregabalin. To the best of our knowledge there has been no other study based on the comparison of lacosamide and pregabalin in the treatment of neuropathic pain. So this study has its relevance.

Conclusion

From the study results, we conclude that lacosamide has more efficacy compared to pregabalin, as severity of pain has significant reduction in lacosamide treatment group compared to that of pregabalin. Patients treated with lacosamide had significant improvement in the quality of life compared to pregabalin. Thus this study supports the use of lacosamide for neuropathic pain, over pregabalin.

Limitation

The present study has its own limitations. The study was done for a short interval of a period of only 6 months and the number of study participants was limited to 107. Potentially large sample size was required for the study so as to get more significant results. Study is based on a tertiary center, and thus the results may not be generalizable to all patients in the community.

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