IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 6 Ser.14 (June. 2023), PP 25-31
www.iosrjournals.org

Efficacy and Safety of Pregabalin Compare to Duloxetine in Neuropathic Pain among Patients with Prolapsed Inter Vertebral Disc: A comparative study

Parendra Debbarma[1], Kaushik Chakraborty[2], Satyabrata Nath[3], Debasis Ray[4]
[1](Post Graduate Trainee, Pharmacology Department, Agartala Govt Medical College, India)
[2](Asstt. Professor, Pharmacology Department, Agartala Govt Medical College, India)
[3](Asstt. Professor, PMR Department, Agartala Govt Medical College, India)
[4](Professor, Pharmacology Department, Agartala Govt Medical College, India)

Abstract:
Background*: Prolapsed Inter Vertebral Disc (PIVD)Is Commonly Encounter Clinical Entity Which 5-20 Cases Per 1000 Adults Annually And Is Most Common In People In 3rd To 5th Decade Of Life. Pregabalin And Duloxetine Are The Commonly Prescribed Medicine For Controlling Neuropathic Pain In Many Circumstances. But There Is A Limited Number Of Studies Comparing The Efficacy And Safety Of Pregabalin And Duloxetine.*
Materials & Methods: *An Comparative Study Conducted In The Department Of PMR At AGMC And GBP Hospital Between July, 2021 To April, 2022 Among Those Patients Attending The OPD Among 100 Participants Each Treatment Group Of Pregabalin And Duloxetine In PIVD With Neuropathic Pain Due To PIVD. The Efficacy Was Assessed By VAS, DN4 And LANSS Assessment. Both Descriptive And Inferential Statistics Were Used To Analyze The Data.*
Result: *The Results Have Shown A Significant Improvement In The Mean Difference Of VAS Score, DN4 Score And LANSS Score Of Both Pregabalin (P= <0.001) And Duloxetine (P= <0.001) Before And After The Therapy, The Pregabalin Dominates Over Duloxetine In Both. The Proportion Of Pain Reduction Is Higher In Pregabalin (67%) Compare To Duloxetine (56%). Adverse Events Were Developed More In Duloxetine Therapy (25%) Compare To Pregabalin Treatment (16%).*
Conclusion: *Both Medications Was Found To Be Highly Effective Where Pregabalin Is Comparatively More. The Safety Assessment Also Better In Pregabalin Therapy In Neuropathic Pain Due To PIVD. However, More Clinical Study Is Required Controlling Confounding Factors.*
Keywords: *PIVD, Neuropathic Pain, Pregabalin, Duloxetine, Efficacy, Adverse Effects.*

Date of Submission: 19-06-2023 Date of Acceptance: 29-06-2023

I. Introduction

According to The International Association for the Study of Pain (IASP) the revised definition of Pain as follows: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[1] Prolapsed inter vertebral disc (PIVD) or Spinal disc herniation or sciatica, slipped disc, nerve cramps disc protrusion, herniated nucleus pulposus or extruded intervertebral disc is a commonly encounter clinical entity.[2] It may be in lumbar, lumbosacral or cervical. Due to compression of nerve patients obtained complained of neuropathic pain like numbness, tingling, loss of motor power, difficulty in bending, loss of bladder and bowel sensation.[2,3] The most common symptom is low back pain and the pain radiates down the back of leg called sciatica or sciatic pain in case of Lumbar PIVD and pain in upper limbs and neck in case of cervical PIVD. It is a spinal condition that occasionally produces symptoms such as back or neck pain, as well as pain, numbness, tingling and weakness in the muscle in the extremities.[2-4] Every 5-20 cases per 1000 adults annually and is most common in people in 3rd to 5th decade of life. More in males than female ratio of 2:1.[3,5-11] Neuropathic pain is frequently encountered in clinical practice because it affects 6.9-10% of the population with PIVD accounting for 40% cases. Due to its severity, chronicity, co-morbidities, and impact on the individual and society, neuropathic pain is particularly challenging.[11-15] Furthermore, patients with neuropathic pain often receive suboptimal treatment (i.e., Inappropriate drug therapy and/or use of sub therapeutic doses), which increases the disease burden.[12-21] Two agents Pregabalin and Dulexetine have been approved by the U.S food and drugs administration (FDA) for a first-line treatment for certain types of NeP e.g. painful diabetic peripheral neuropathy (pDPN), postherpetic neuralgia (PHN), neuropathic pain due to spinal cord injury (SCI-NeP), fibromyalgia, and as adjunct therapy for partial onset seizures.[21,22] Pregabalin is an analogue of inhibitory neurotransmitter gamma- aminobutyric acid (GABA), though it does not bind directly to

either G_ABA_A or $GABA_B$ receptors Pregabalin does, however, bind to the alpha-2-delta (α2δ) subunit of voltage-gated presynaptic Ca++ channels and reduce the Ca++ ion influx.[23] Through this mechanism, pregabalin suppresses ectopic neuronal impulses and could, as a result, be efficacious in patients with lumbar and cervical NeP.[22-26] Duloxetine inhibits the reuptake of serotonin and norepinephrine (NE) in the central nervous system. Duloxetine increases dopamine (DA) specifically in the prefrontal cortex, where there are few DA reuptake pumps, via the inhibition of NE reuptake pumps (NET), which is believed to mediate reuptake of DA and NE. Duloxetine has no significant affinity for dopaminergic, cholinergic, histaminergic, opioid, glutamate, and GABA reuptake transporters, however, and can therefore be considered to be a selective reuptake inhibitor at the 5-HT and NE transporters.[23-25] Duloxetine actually works by helping serotonin and noradrenaline to continue to circulate within the brain and not be reabsorbed into the nerve cells that are in the brain. In short, this helps patients to feel better for longer. There are no major side effects of taking duloxetine, however, there are a number of side effects that many patients experience, to varying degrees: these include feeling nauseous, constipation, light-headedness or being too drowsy or even too wide awake and being unable to sleep.[24,25] Although there are several treatments available for the management of neuropathic pain, in this study, we will focus on Pregabalin an anticonvulsant and calcium channel α2-δ ligands and SNRIs Duloxetine. The efficacy and safety of Pregabalin and Duloxetine have been proved individually in neuropathic pain due to PIVD. However, there is a limited number of studies comparing the efficacy and safety of Pregabalin and Duloxetine in this condition in Indian population specially in Northeastern state, it is thought that it is worthy to do this study to determine the efficacy as well as safety of Pregabalin in comparison with Duloxetine in out-patients department of PMR of a tertiary care Hospital in Agartala.

II. Material And Methods

A comparative cross-sectional study was conducted in the Department of Pharmacology, AGMC and GBP Hospital for a period of 1 (one) year from July, 2021 July to June, 2022 among the patients with neuropathic pain due to PIVD and attending the OPD of PMR Department of AGMC & GBP Hospital, Agartala, West Tripura. Total 200 sample size (100 in each arm) size was calculated with 80% power at 95% significance level two sided α with 10% drop out rate.[27,28] All clinically confirmed cases of neuropathic pain due to PIVD who were prescribed either Pregabalin or Duloxetine during study period were taken up for the study till the sample size was achieved. Study participants were advised to take one month treatment course in orally on daily basis and requested to complete the course. 18 years and above, all clinically diagnosed cases of neuropathic pain due to PIVD and who were prescribed either Pregabalin or Duloxetine and fulfilled the criteria such patients whose visual analogue scale (VAS) score >4, patients having DN4 questionnaires score >4 and Leeds assessment of neuropathic symptoms and sign (LANSS) score >12. Neuropathic pain due to other co-morbidities e.g. (Peripheral Neuropathy, Alcoholic, Cancer, Pregnancy and lactation, Mental disorder) were excluded. Those who are receiving herbal medicine and homeopathy or any other medicine having pain modulator properties except NSAIDS and those who taken Pregabalin or Duloxetine prior to the study were also excluded. After obtaining permission from dept. of PMR and by Institutional ethical committee, AGMC, those who were diagnosed by consultant physician as having neuropathic pain due to PIVD and who were prescribed either Pregabalin (75mg) or Duloxetine (20mg) at bed time for pain relief. The patients included in the study were explained regarding the study technique and who were willing to participants and follow up was enrolled according to inclusion and exclusion criteria. Efficacy was assessed by using VAS for severity of pain and DN4 questionaries' LANSS for neuropathic pain. Co- medication like NSAID, PPI/ H2 blocker, muscle relaxant and other was recorded accordingly. They were followed up for 1 month on three occasions after 1 weeks and 2 weeks and 4 weeks interval. Assessment of LANSS, VAS, and DN4 questionaries was done in every visit i.e., Baseline at 1-, 2- and 4-weeks interval. On the revisit patients was evaluated and as per response if required dose of test drug was increased or NSAIDS were prescribed as rescue medication. Safety of the drug was assessed by the incidence of treatment emergent adverse events as they report. Details of ADRs like their appearance, temporal relationship with the drug, Causality and severity was also recorded by using WHO UMC scale and Modified Hartwig and Siegel severity assessment scale. Data was recorded in a case record form and entered and analyzed by using computer SPSS version 21.0 software. Descriptive statistics like mean, SD, frequency and percentage were used. To assess the significant difference between the groups, for continuous variable student's t-test and for categorical variable chi-square test were used. A p value of<0.05 was taken as statistically significant.

III. Result

Total 200 patients with diagnosed as a case of PIVD having neuropathic pain participated in the study. 100 each treatment group were included in the study. Participants were followed up to 4 weeks and retained 90% and 80% in

pregabalin and duloxetine treatment group respectively. The mean age of the participants was 58.33 ± 6.98 years ranges from 28 to 60 years. The mean age of the participants 59.01 ± 7.21 years and 57.21 ± 4.67 years in pregabalin and duloxetine treatment group respectively. It is comparable in both group (p value 0.14). In duloxetine group male were 64% and female were 36% and in pregabalin group male were 68% and 32% were female. It is comparable in both group (p value 0.89) (table 1).

Table 1: Demographic characteristics of the study participants.

Demographic characteristics	Study group		P value
	Pregabalin (N=100)	Duloxetine (N=100)	
Educational qualification (%)			
Illiterate	12	10	0.61
Primary	23	32	
Secondary	36	29	
Graduate	21	12	
Above graduate	8	17	
Occupation			
Self employed	71	63	0.07
Employed	29	37	

The distribution of the educational status also comparable in both groups. In pregabalin group secondary education is higher and duloxetine group primary educated people were higher. In pregabalin group self-employed were more (71%) and in Duloxetine group employed person were more (37%). However, this distribution is comparable in both group (table 1).

Table 2: Changes and comparison of different efficacy assessment scale

Different scale		Baseline	1st Week	2nd Week	4th Week	Mean Difference (at 4th week from baseline)
Visual Analogue scale (VAS) score	Treatment A	7.84 ± 1.04	4.78 ± 1.98	3.23 ± 1.9	2.23 ± 0.1	4.23 ± 2.1 (p - 0.001)**
	Treatment B	8.28 ± 2.64	5.01 ± 2.45	3.98 ± 0.04	3.23 ± 1.6	5. 06 ± 1.08 (p - 0.001)**
	p value	0.23	0.07	0.01*	0.02*	0.04*
DN4 questionnaire scale score	Treatment A	6.86 ± 1.98	5.78 ± 2.12	3.72 ± 1.39	2.56 ± 1.01	4.03 ± 1.50 (p- 0.04)
	Treatment B	5.92 ± 3.28	4.02 ± 1.34	4.02 ± 1.34	3.01 ± 0.71	2.67 ± 1.01 (p- 0.007)**
	p value	0.58	0.08	0.04*	0.001**	0.001**
LANSS score	Treatment A	16.24 ± 0.46	13.56 ± 4.2	9.93 ± 1.2	6.41 ± 1.76	9.03 ± 2.75 (p- 0.001)**
	Treatment B	13.86 ± 0.12	10.41 ± 4.0	9.12 ± 0.51	7.01 ± 2.04	5.85 ± 3.29 (p- 0.01)
	p value	0.67	0.06	0.02*	0.003**	0.000**
*Treatment A: Pregabalin, Treatment B: Duloxetine, * significant, ** highly significant*						

There is significance difference of VAS score either group 4.23 and 5.06 in pregabalin and duloxetine group after 4 weeks of followed up. From Baseline to 4 weeks period, the VAS score of both groups reduced significantly from 7.84 ± 1.04 to 2.23 ± 0.1 in pregabalin group and from 8.28 ± 2.64 to 3.23 ± 1.60 in duloxetine group (table 2). There is no significant difference in pain score between base line and after 1st week by both the therapy but at the end of 2nd and 4th week of treatment there is significant difference between two intervention group with a p value of 0.01 and 0.01 respectively (table 2). DN4 questionnaire scale score was better in the treatment group by pregabalin 4.03 ± 1.50 than duloxetine 2.67 ± 1.01 and their mean difference were found significant after 2nd week and 4th week therapy with a p value of 0.04 and 0.001 respectively. LANSS score was found significance change from baseline upto 4th week's therapy in both group (p value 0.001 and 0.01). significance difference also observed in 2nd and 4th week in between the group with a p value of 0.02 and 0.003 in group A and group B respectively (table 2). Figure 3 shows therapy by pregabalin medication was found significant reduction rate in pain intensity, at baseline 100% having pain but subsequent visit percentage having pain reduces gradually like in week 1 - 70%, week 2- 25% and at 4th week only 2.8% having pain which are comparatively higher in duloxetine group. Group A (pregabalin) is found better – 16% efficacy to developed side effects compare to group B (Duloxetine) – 25% out of total enrolled participants.

The duration of illness was ranges from 15 days to 5 months or more. However, the distribution of duration of illness was comparable in both group as it is showing almost equal distribution irrespective of the duration in both group (figure 1).

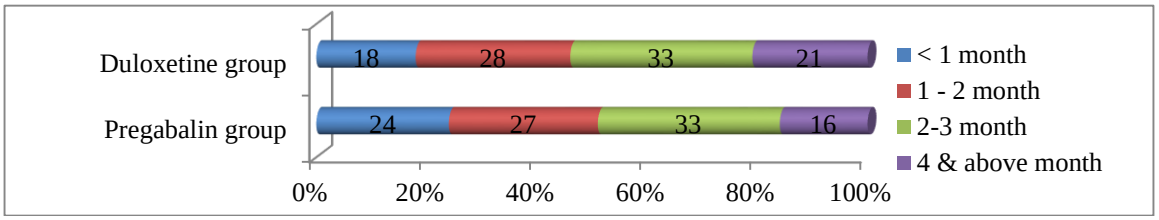

Fig 1: Comparison of duration of illness (PIVD-Neuropathic pain)

The study finding also shows that there is drastically reduction of PIVD pain by both medication in follow up at week1, week 2 and after 4 week but the rate of reduction of pain more incase of pregabalin medication (40%) than doluxetine (25%) of the participants at the end of week 2.

It was found that dryness was present in 5% of the pregabalin group and somnolence was present in 12% of the doluxetine group. Drowsiness was seen in pregabalin group (4 cases) and nausea was seen in duloxetine group (5 cases) (table 3).

Table 3: Different side effects comparison in between the study group (N=100 each)

Pregabalin Group (N=90)		Duloxetine Group (N=80)	
Side effects	Frequency	Side effects	Frequency
Dryness of mouth	5	Somnolence	12
Drowsy	4	Nausea	5
Dizziness	2	Giddiness	6
Somnolence	2	Insomnia	2
Numbness at legs	2		
Insomnia	1		

Table 4: Drug prescribing pattern as co-therapy in neuropathic pain due to PIVD

Drugs / Medications	Pregabalin group N(%)	Duloxetine N(%)	Total N(%)
Etodolac	30	50	40
Etoroxib	18	12	15
Tramadol	12	18	15
Aceclofenac	5	15	10
Paracetamol	8	12	10
Trypsin / chymotrypsin	60	100	80
Methylcobalamin	75	95	85
PPIs	96	98	97

As anti-inflammatory and /or analgesics, etodolac (40%), etoroxib (15%), Tramadol (15%), aceclofenac (10%), paracetamol (10%) and combination medicine (10%) were used. As adjuvant or supplement, trypsin and chymotrypsin (80%), methyl cobalamin (85%) and PPIs (97%) (shown in table 4).

IV. Discussion

The present study was carried out for a period of 1 month for each patient with a follow up at 2nd and 4th week to compare the efficacy and tolerability of pregabalin and duloxetine in chronic low backache with neuropathic pain. In the current study more than 50% of the patients belonged to more than 50 years of age and this is similar to an observation in a previous study done in India by Kalita et al[40,44] whereas 40.8% of the participants belonged to the same age range. This observation indicates that chronic low backache with neuropathic pain is more common among near elderly age groups. Both the study groups showed similar percentage of patients having age comparable. It was also observed in the present study that 75% of patients in pregabalin group reported reduction from severe to mild pain at the end of 2 weeks, 97.2% at the end of 4 weeks. These findings are incorporated with a few of previous literature.[44-46] The mean age of the participants was 58.33 ± 6.98 years ranges from 28 to 60 years. The mean age of the participants 59.01 ± 7.21 years and 57.21 ± 4.67 years in pregabalin and duloxetine treatment group respectively. It was more or less than that found in the studies done by Toelle et al[48] (61 years), Banerjee et al[49] (53.5 years), Padmini et al[50] (57 years), Tanenberg et al[51] (61.9 years) etc. There is significance difference of VAS score either group 4.23 and 5.06 in pregabalin and duloxetine group after 4 weeks of followed up. From Baseline to 4 weeks period, the VAS score of both groups reduced significantly from 7.84 ± 1.04 to 2.23 ± 0.1 in pregabalin group and from 8.28 ± 2.64 to 3.23 ± 1.60. The mean difference in baseline and 1st week after therapy shows insignificant in both group but 2nd week and 4th weeks after therapy shows significance difference with a p value of 0.01 and 0.01 respectively.

Many previous literatures are similar to this study and one of the studies conducted by Kiran MD et al[29] found that pregabalin has better efficacy than placebo group where the mean of VAS score was 7.87 at baseline, 5.6 at day 7 and 3.42 at day 21. 46.4% at day 7 and 84.6% at 21 had a reduction of pain; however, Vijayalakshmi A et al[30] found that in duloxetine, there was a reduction in the VAS pain score in the patients from 6.46 (baseline) to 2.96 (Review 2) respectively. Similar findings were observed by Digambar P. Nawani et al[31.] Similar observation was seen by Toshihiko Taguchi et al[32] favouring pregabalin than duloxetine showing least-squares mean change in PRSIS from baseline to week 8 favoured Pregabalin (–1.167 vs –0.269; treatment difference –0.898 [95% CI –1.262, –0.535], P<0.001). One of the studies[56] which is reported that, at the end of the single blind pregabalin treatment phase with a flexible-dose of 150-600 mg/day, the pain score had decreased from mean baseline pain of 6.4 to a mean of 2.3. 57.9% patients experienced >30% reduction in pain and 34% of patients reported >50% of less pain which is similar to the present study findings. DN4 questionnaire scale score was better in the treatment group by pregabalin 4.03±1.50 than duloxetine 2.67±1.01 and their mean difference were found significant after 2nd week and 4th week therapy with a p value of 0.04 and 0.001 respectively. LANSS score was found significance change from baseline upto 4th weeks therapy in both group (p value 0.001 and 0.01) significance difference also observes in 2nd and 4th week in between the group with a p value of 0.02 and 0.003 in group A and group B respectively. In present study, only 16% of the participants treated with pregabalin developed minor to mild form side effects but duloxetine group developed 25% side effects. All adverse events are due to possible cause as WHO UMC system of causality assessment. Previous literatures have shown that both pregabalin and duloxetine is known to be associated with undesirable side effects, such as sedation, dizziness, visual disturbance.[28,29,30,56] A fewer studies only conducted in the past comparing duloxetine and pregabalin. The findings are varied. The present study findings are incorporated with the study findings conducted by Hiroaki Nakashima et al[28,] Kiran MD et al[29], Vijayalakshmi A et al[30] where pregabalin efficacy shows higher with less proportion of side effects where Kiran MD et al reported that only 4% has dizziness 15% has sedation and 3% has dry mouth and constipation.[29]

The present study is a unicentric study. When comparing to multicentric trial, the benefits multicentric include a larger number of participants, different geographic locations, the possibility of a wider range of population groups, the ability to compare results among center, all of which increase the generalizability of the study. In many cases, efficacy will vary significantly between population groups with different genetic, environmental, and ethnic or cultural background; normally only geographically dispersed trials can properly evaluate this. Sample size reflects the population. The present study was conducted only on 200 sample (100 in each group). There are some key factors including confidence levels and margins of error, power, and effect sizes. All of these are affected by how large a sample is. The present study was conducted only 1 year 2 month and 10 days periods, where each patient is followed up only for 28 days. As the duration of study was short thus this study is inefficient for rare outcomes with long induction or latency periods. Cost effectiveness of the present study was not analyzed. Blinding was not done hence a chance of selection biases were there.

V. CONCLUSION:

Each medication is effective against neuropathic pain but it was observed that proportion of reduction was more on treatment group by pregabalin. Comparatively minor side effects were more in duloxetine group than pregabalin group. All side effects are of possible cause and all are of mild form of severity. The present study demonstrated that pregabalin has higher safety and efficacy than duloxetine group to control or reducing the neuropathic pain due to Prolapsed Inter Vertebral Disc (PIVD). However, randomized control trails is recommended involving higher number of participants controlling the confounding factors.

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