Effectiveness of Pregabalin Compared to Duloxetine in Diabetic Peripheral Neuropathic Pain: An Observational Study

Sujeet Jha¹, Om Prakash Sahani¹, Samreen Siddiqui¹, Manoj Kumar Verma¹, Avijit Mazumder², Swati Waghdhare¹

Abstract

Introduction: Neuropathy is a comorbid complication of diabetes and Pregabalin and Duloxetine are the two most common drugs used for the treatment of neuropathic pain.

Aim: To determine the effectiveness and side effects of Pregabalin and Duloxetine in patients with diabetic peripheral neuropathic pain.

Materials and Methods: This prospective observational study was conducted at Max Super Speciality Hospital. Patients attending the endocrinology department, above 18 years of age who were prescribed with Pregabalin or Duloxetine were screened and included in this study. The data was collected for all study participants using a specially designed case record form by conducting personal interviews. SF-MPQ, Mc-Gill, NRS and DN-4 questionnaires were used to assess the extent of pain and the side-effects associated with the drugs.

Results: Based on the responses from the Numerical Rating Scale and McGill Pain Questionnaire, Pregabalin was seen to be less effective compared to Duloxetine. The only side effect observed with Pregabalin was drowsiness, which was observed in 4% cases at 50 mg dose whereas those reported with Duloxetine were drowsiness (22.2% at 20 mg and 33.3% at 30 mg), vomiting (11.1% at 20mg and 30mg), headache (11.1% at 20 mg and 30 mg), and dizziness (0% at 20mg and 11.1% at 30 mg).

Conclusions: Pregabalin has a better safety profile and tolerability compared to Duloxetine but the latter is more effective in treating Diabetic Peripheral Neuropathic Pain. However, further studies with a larger sample size and longer duration are required to be conducted for finding the effectiveness of these drugs, specifically in the Indian population.

Introduction

Peripheral Neuropathy is the most common complication associated with diabetes.¹,² It affects nearly 30–60% of the diabetic population.³ Around 10–20% of these individuals experience neuropathic pain, which is characterized by hyperalgesia (abnormally increased sensitivity to pain), allodynia (pain resulting from a stimulus that normally would not provoke such pain), and paresthesia (sensation of pricking or tingling without any objective cause) accompanying the continuous aching or burning pain.³

Neuropathic pain is defined as pain caused by a primary lesion or dysfunction in the nervous system.⁴ It may result from damage to the central nervous systems (cerebrovascular accident, multiple sclerosis or injury to the spinal cord) or peripheral nervous system (peripheral neuropathy associated with diabetes, post herpetic neuralgia or surgical intervention).³ It has an insidious onset and usually a symmetrical pattern of ‘Gloving and Stocking’ characterizes the pain.⁶ The main symptom observed in diabetic peripheral neuropathic pain (DPNP) is shooting or burning pain in the feet and lower limbs occurring for more than three months.⁴ The pharmacological response among individuals with this condition is varied and most treatments are not very effective in more than half of the cases. The commonly used drugs for the management of pain are antidepressants, antiepileptics, opioids, analgesics, topical lidocaine, and topical capsaicin.³ Pregabalin is an anticonvulsant which was approved by US in 2005 for the treatment of DPNP and post herpetic neuralgia pain whereas Duloxetine is a reuptake inhibitor of serotonin and norepinephrine used for the management of DPNP.⁴

This study was undertaken to primarily observe the effectiveness of Pregabalin and Duloxetine for the treatment of diabetic peripheral neuropathy pain in patients attending the outpatient department at a tertiary care hospital in New Delhi. We also assessed the side effects associated with these two drugs.

Materials and Methods

Study design, sample size determination, and subjects

This prospective observational study was conducted at Max Super Speciality Hospital, Saket, New Delhi from December 2014–October 2015 to observe the effectiveness of Pregabalin and Duloxetine in patients with diabetic peripheral neuropathy pain (DPNP). According to the study conducted by Freeman R et al. in 2008, Pregabalin was reported to have an efficacy of 47%.⁷ Assuming a power of 80% for detecting a difference of 20% in efficacy, the sample size was calculated to be 47 in each group. However, this sample size was not possible in our study because of the unwillingness of participants,
short duration of the study, as well as discontinuation of Duloxetine during the study period due to observable side effects associated with its usage.

Individuals were eligible for the study if they were more than 18 years of age, experiencing pain for greater than two weeks, having diabetic peripheral neuropathy pain (Neuropathic Pain Diagnostic Questionnaire- DN4 score >4 or Numerical Rating Scale value >5) associated with Type 2 diabetes, and willing to participate in the study. Patients with a previous history of trauma, those having severe osteoarthritis or advised joint surgery, pregnant or breast feeding females, and unwilling individuals were excluded from the study. Written informed consent was obtained from all the study subjects prior to participation. The study was approved by the Scientific and Institutional Ethics Committee of Max Super Specialty Hospital, Saket, New Delhi. The primary objective was to observe the effectiveness of Pregabalin and Duloxetine for the treatment of diabetic peripheral neuropathy in patients attending the outpatient department, which was assessed through Short Form-McGill Pain Questionnaire and Numeric Pain Rating Scale. The secondary objective was to determine the side effects associated with Pregabalin and Duloxetine.

Methods

Various screening questionnaires have been used in the past to assess the neuropathic pain associated with diabetes. Frequency and severity of pain has been assessed using simple scales like Visual Analog Scale, Numeric Rating Scale, or Likert Scale. Some questionnaires such as the DN4 and McGill Pain Questionnaire in its shortened format have also been used previously for identification of neuropathic pain and determination of its intensity.8-11 Hence, these validated questionnaires and rating scales were used in our study. Two questionnaires and two pain rating scales were used to record patient responses. These questionnaires were used for evaluating the qualities of pain (Short form of the McGill Pain Questionnaire- SF-MPQ) and to determine if the pain was neuropathic in nature (Neuropathic Pain Diagnostic Questionnaire- DN4).

The SF-MPQ has four components. The main component of SF-MPQ comprises of 11 sensory and 4 affective descriptors, which are rated on an intensity scale as either none (0), mild (1), moderate (2), or severe (3). It includes two other scales, the Present Pain Intensity (PPI) scale and the Visual Analogue Scale (VAS), which provide information on the intensity but not the quality of pain.12 The fourth component is a figure, where the patient is supposed to mark the region where pain is felt. The DN4 questionnaire (DN4 stands for ‘douleur neuropathique 4 questions’ which means neuropathic pain four questions in French) includes descriptors of pain along with items based on clinical examination.13

The two rating scales used for assessment of pain intensity were Numerical Pain Rating Scale (NRS) and the Faces Rating Scale (FRS) by Wong Baker. The NRS may be an 11, 21, or 101 point scale where the end points represent extremes of pain i.e. no pain or worst possible pain.14,15 We used the graphical scale utilizing a straight line with divisions at specified intervals depicting numbers from 0–10 to assess the pain for each patient, where the lowest number ‘0’ represented no pain and highest number ‘10’ indicated the worst possible pain experienced by the patient.16 Each participant was asked to circle or record the number that best represented their level of pain intensity.

The Wong Baker Faces Pain Scale is based on the concept of image projection technique. The study participants were asked to choose from among the six faces based on their pain experience which best represented them. The first face was a very happy smiling face whereas the last one was a sad tearful face. All faces in between these two faces expressed different levels of sadness.16,17

Starting dose of Pregabalin was 50 mg, which was titrated up to 150 mg, if required, by the clinician. Similarly, for Duloxetine, starting dose was 20 mg, which was titrated up to 90 mg, if required. Additionally, all these patients were receiving Paracetamol 4g/day for not more than three consecutive days for pain relief. These patients were observed for a period of six months to identify the side effects linked with the use of Pregabalin and Duloxetine and determine their effectiveness in the treatment of diabetic peripheral neuropathic pain. The data was collected for all study participants using a specially designed case record form (CRF) by conducting personal interviews. The safety profile of the two drugs was evaluated by measuring the discontinuation rates and adverse events associated with each drug.

Statistical analysis

Continuous data was presented as mean ± SD and categorical data as frequencies. The data obtained was statistically analyzed using Chi Square test and Student t-test. The software used to analyze the data was SPSS Inc. (2007) Version 16.

Results

A total of 420 patients reporting at the Outpatient Department of Endocrinology, Max Super Speciality Hospital, Saket, New Delhi were screened. Out of these, 83 had symptoms of classical neuropathic pain. Due to the unwillingness to participate in the study, 34 patients (Duloxetine: n=9; Pregabalin: n=25) were enrolled into the study over a period of 4 months and followed up from August 2015–December 2015.

The demographic characteristics of the study population are presented in Table 1. Out of the 34 patients, 18 (52.94%) were females and 16 (47.06%) were males. The distribution of individuals affected with diabetes shows that a majority (52.94%, n=18/34) of the cases did not have diabetes in their first degree relatives, whereas the father, mother and sibling were affected with diabetes in 20.58% (n=7), 17.64% (n=6), and 8.82% (n=3) cases, respectively.

The dose and pain wise distribution of study subjects for Pregabalin and Duloxetine is given in Table 2. The McGill Pain Questionnaire revealed that a significant relief from pain was seen with the use of Pregabalin from Day 0 through 90 at 50 mg, 75 mg, and 150 mg doses. However, the Numerical Pain Rating Scale showed a significant reduction in neuropathic pain from Day 14 onwards to Day 90. Similarly, for Duloxetine, the McGill Pain Questionnaire showed a significant reduction in pain from Day 14 onwards, whereas based on the Numerical Pain Rating Scale, a significant reduction in neuropathic pain was observed from...
Table 1: Demographic characteristics of the study population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.8 ± 8.59</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.73 ± 5.3</td>
</tr>
<tr>
<td>Duration of diagnosis (years)</td>
<td>10.56 ± 8.39</td>
</tr>
</tbody>
</table>

Biochemical values:

- Sodium (mmol/L) 13.8 ± 3.74
- Potassium (mmol/L) 4.50 ± 1.79
- Urea (mg/dl) 28.54 ± 8.90
- Creatinine (mg/dl) 1.42 ± 1.39
- Fasting blood sugar (mg/dl) 165.5 ± 48.11
- Post prandial blood sugar (mg/dl) 247.38 ± 68.6

Hemoglobin (Hb) (g/dl) 13.40 ± 0.83

Triglycerides (mg/dl) 145.40 ± 52.84

Cholesterol (mg/dl) 179.94 ± 40.6

Albumin (g/dl) 3.88 ± 0.53

Bilirubin (mg/dl) 0.47 ± 0.16

Body mass index (kg/m²) 28.73 ± 5.3

Table 2: Dose and Pain wise distribution of the study subjects taking Pregabalin and Duloxetine

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>0</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numeric Rating Scale (NRS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>50 mg</td>
<td>6.2 ± 1.47</td>
<td>6.26 ± 1.5</td>
<td>5.76 ± 1.45</td>
<td>4.9 ± 1.3</td>
<td>4.5 ± 1.3</td>
<td>3.67 ± 1.2</td>
<td>3.61 ± 0.78</td>
</tr>
<tr>
<td>75 mg</td>
<td>6.27 ± 1.52</td>
<td>6.26 ± 1.5</td>
<td>5.76 ± 1.57</td>
<td>4.9 ± 1.5</td>
<td>4.5 ± 1.5</td>
<td>3.9 ± 1.3</td>
<td>3.61 ± 0.88</td>
</tr>
<tr>
<td>150 mg</td>
<td>6.27 ± 1.60</td>
<td>6.26 ± 1.74</td>
<td>5.76 ± 1.71</td>
<td>4.97 ± 1.74</td>
<td>4.5 ± 1.71</td>
<td>3.97 ± 1.62</td>
<td>3.61 ± 0.91</td>
</tr>
<tr>
<td>P-value</td>
<td>0.88</td>
<td>0.38</td>
<td>0.001*</td>
<td>0.000*</td>
<td>0.000*</td>
<td>0.000*</td>
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</tr>
</tbody>
</table>

McGill pain questionnaire:

- 50 mg 12.25 ± 4.74, 12.35 ± 4.7, 11.52 ± 4.58, 9.94 ± 4.45, 9.94 ± 4.29, 7.97 ± 4.13, 6.85 ± 3.15
- 75 mg 12.25 ± 4.59, 12.35 ± 4.58, 11.52 ± 4.43, 9.94 ± 4.45, 9.94 ± 4.29, 7.97 ± 4.13, 6.85 ± 3.06
- 150 mg 12.25 ± 5.78, 12.35 ± 5.64, 11.52 ± 5.80, 9.94 ± 5.43, 9.94 ± 5.29, 7.97 ± 4.86, 6.85 ± 3.87

Duloxetine:

- 20 mg 6.27 ± 1.41, 6.26 ± 1.43, 5.76 ± 2.01, 4.97 ± 2.24, 4.5 ± 2.08, 3.97 ± 1.63, 3.61 ± 1.46
- 30 mg 6.27 ± 1.45, 6.26 ± 1.48, 5.76 ± 1.49, 4.97 ± 2.07, 4.5 ± 1.88, 3.97 ± 1.83, 3.61 ± 1.29

P-value | 0.007 | 0.32 | 0.088 | 0.000* | 0.000* | 0.000* | 0.000* |

McGill pain questionnaire:

- 20 mg 12.25 ± 5.3, 2.35 ± 5.34, 11.52 ± 6.06, 9.94 ± 5.48, 9.0 ± 5.10, 7.97 ± 4.77, 6.85 ± 3.94
- 30 mg 12.25 ± 5.84, 12.35 ± 5.85, 11.59 ± 6.00, 9.94 ± 5.70, 9.0 ± 5.32, 7.97 ± 5.06, 6.85 ± 4.10

P-value | 0.031 | 0.109 | 0.000* | 0.000* | 0.000* | 0.000* | 0.000* |

HbA1c (%): 8.96 ± 1.8

Discussion

Pregabalin and Duloxetine are the two main drugs approved by the U.S Food and Drug Administration (FDA) for the treatment of diabetic neuropathic pain. We compared the effectiveness of these two drugs in our small population subset of a tertiary care hospital. In our study, the responses obtained for determining the effectiveness of Duloxetine and Pregabalin in treating Diabetic Neuropathy pain among the study population revealed that Duloxetine was more effective compared to Pregabalin. Quilici S et al. and Tanenberg RJ et al. reported Duloxetine to be non-inferior to Pregabalin.4,18 On the contrary, in a study by Devi P et al., better results for pain reduction were observed for Pregabalin compared to Duloxetine or Gabapentin.19

In a study by Tanenberg RJ et al., more discontinuations were observed with Duloxetine therapy (n=27, 19.6%, P = 0.04) compared to Pregabalin (n=14;10.4%).18 Similar findings were reported by Sultan A et al.3 In our
study 57.1% cases discontinued Duloxetine in the same line, whereas no discontinuation was observed with Pregabalin. One of the reasons for a smaller sample size in our study could also be attributed to the increase in side-effects associated with Duloxetine, due to which the drug had to be discontinued in some of the patients.

Adverse events such as drowsiness or somnolecence, vomiting, dizziness, and headache were more frequently associated with Duloxetine compared to Pregabalin in our study. This is in accordance with studies by Raskin J et al., Sultan A et al., and Tanenberg RJ et al., where more side effects were observed with Duloxetine compared to the placebo or Pregabalin.5,14,15

Our study had a few advantages. The questionnaires and pain rating scales used for assessing patient responses were effective and easy tools for data collection and interpretation. The limitations in this study were a small sample size and the short duration of the study, due to which the effectiveness and side effects of the two drugs could not be assessed for a longer duration.

In conclusion, findings from the study indicate that Pregabalin has a better safety profile and tolerability compared to Duloxetine but the latter is more effective in treating Diabetic Peripheral Neuropathic Pain. However, further studies with a larger sample size and longer duration are warranted to validate the findings of our study.

Contributors

Dr. Sujeeet Jha was involved in the designing and conceptualization of this study. Mr. Om.Prakash Sahani did literature review, collected and compiled the data. Mr. Manoj Kumar Verma heled in Data collection. Ms. Samreen Siddiqui performed the data analysis and interpretation. Dr. Avijit Mazumder reviewed the manuscript. Dr. Swati Waghdhare was responsible for writing and editing the manuscript.

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References

Introduction

Sweta Pandey 1*, Sanjay Kumar Pandey 2, Vineet Shah 3

Polymorphism on Pathophysiology of Iron Deficiency Anemia

Role of TfR2-Y250X and TfR1-rs3817672 Single Nucleotide

Introduction

Iron deficiency anemia and screening for mutations of

TfR2 -Y250X and TfR1-rs3817672 SNP showed clinical association with

Conclusion:

rs3817672 SNP heterozygosity respectively.

one with homozygous condition. Controls were presenting 3% and 0.6% of TFR1

homozygous condition while four controls were presenting heterozygous and

6 patients with heterozygous conditions. None of the patients were presenting

five were homozygous for rs3817672 SNP . TFR2 (Y250X) mutation was detected in

Result:

Amongst the iron deficiency anemia patients, 13 were heterozygous and

SNP and TFR2 (Y250X) mutation was analyzed by using PCR RFLP method.

Wintrobes's method. CBC analysis was done by auto–analyzer. TFR1-rs3817672

analysis was done by ELISA method while ESR analysis was done according to

500 age and sex-matched healthy controls. Transferrin receptor, ferritin and CRP

Study subjects were 460 iron deficiency anemia patients and

Study Design:

of iron deficiency anemia.

However the clinical significance of the interaction of transferring mutations

excess iron absorption and abnormal iron distribution in iron related disorders.

cause change in iron homeostatis and provides a tool for investigating the

background of iron deficiency anemia. Alteration in genes encoding transferring receptor

Mutations in transferrin receptors (TfR2 and TfR1) may alter the pathophysiology

protein with a large extracellular domain, which is able to bind transferrin.

homology to transferrin receptor 1 (TFR1) gene and encodes a transmembrane

import of iron into the cell. The transferring receptor 2 (TFR2) gene showed

regulated in response to intracellular iron concentration and plays a role for

expression is regulated by cellular iron

transferrin bound iron uptake by

1 Senior Research Fellow, APS University, Rewa, Madhya Pradesh; 2 Scientist –II, 3 Scientist –I, Multidisciplinary Research Unit,


16. Wong DL, Baker CM. Pain in Children: Comparison of


