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RESEARCH ARTICLE

Comparison Of Efficacy And Safety Profile Of Pregabalin And Gabapentin In Painful Diabetic Neuropathy

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Abstract:
Major objective of the study was comparison of efficacy and safety profile of Pregabalin and Gabapentin in painful diabetic neuropathy. It was an open label 12 weeks randomized controlled trial which was conducted in Department of Pharmacology & Therapeutics Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Center (JPMC) in collaboration of Diabetic Clinic of Medical Unit III of JPMC Karachi. Study was conducted from December 2010 to May 2011. 60 diagnosed patients of painful diabetic neuropathy were selected for 12 weeks' trial after taking written consent. The patients were randomly placed into two groups, 30 patients each. One group received Pregabalin (n=30) while the other group received Gabapentin (n=30). The primary outcome was reduction in pain scale. It was compared on 11-point numerical visual analog scale (VAS). In Pregabalin group the reduction in pain VAS was 6.20±0.14 on day 0 to 2.37±0.09 on day 90. The percentage of change was 61.8% (p-value 0.001). In Gabapentin group the reduction in pain VAS was 6.17±0.15 on day 0 to 3.5±0.15 on day 90. The percentage of change was 43.3% from baseline (p-value 0.001). The secondary outcome was improvement in sleep interference that is measured on 11-point numerical VAS of sleep interference. It also improved in both groups which is highly significant. In patients of diabetic painful neuropathy Pregabalin and Gabapentin both are effective but Pregabalin is superior in relieving symptoms than Gabapentin.

Keywords: D.M: Diabetes Mellitus, PDPN: Painful Diabetic Peripheral Neuropathy, DPN: Diabetic Peripheral Neuropathy,VAS: Visual Analog Scale

Introduction

Diabetic neuropathy is defined as clinically diagnosed signs or symptoms of nerve dysfunction in diabetic patients after exclusion of other causes of neuropathy [1]. Diabetic peripheral neuropathy is defined as bilaterally decreased or absent ankle reflexes or decreased vibration, pinprick, fine touch or temperature perception in distal lower extremities at screening [2]. The peripheral neuropathy is one of the most common long standing complications of both type1 and type2 diabetes [3]. The incidence of diabetes mellitus is increasing all over the world. The projected incidence will be 3 million till 2025[4]. The studies claim that one-third of diabetic patients develop peripheral diabetic neuropathy [5] [6].

In cross sectional study in U.K. the overall prevalence of chronic pain for diabetic peripheral neuropathy of more than a year was estimated to be 16.2% among the patients with diabetes compared with 4.9% in people free from diabetes [7]. Diabetes mellitus is one of the major causes of neuropathic pain, as long term it damages the micro vessels supplying the nerves so it causes the damage in nervous system which remains unnoticed initially. There are different factors which are considered by diabetes control and complications trial it has shown that tight glycaemic control in insulin dependent diabetes can decrease the risk of diabetic neuropathy 62% [8]. Baron(2000) claimed that diabetes

causes damage to peripheral nerves which results hyper excitation by causing increased sensitivity of nociceptors which leads to hyper excitation in central neurons dorsal route ganglia[9]. All Diabetic neuropathy does not cause pain only 60%-20% experiences chronic pain [10].
According to Boulton's classification of diabetic peripheral neuropathy (table1,2) it may be focal or diffused, most common among the neuropathies are the chronic sensory motor, distal symmetrical poly neuropathy and autonomic neuropathies although patients may have more than one type of painful diabetic neuropathy [1].

Table 1. Classification of diabetic neuropathy. Adapted from Boulton et al.[10]

Poly neuropathy	Mononeuropathy
Sensory	Isolated peripheral
• Acute sensory	Mononeuritis multiplex
• Chronic sensorimotor	Truncal
Motor	
Autonomic	
• Cardiovascular	
• Gastrointestinal	
• Genitourinary	
• Other	
Proximal	
Truncal	

PATIENTS AND METHODS:

This was an open label randomized controlled trial conducted in the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Centre (JPMC), Karachi in collaboration with Diabetic Clinic of Medical Unit III, JPMC, after approval from ethical committee of JPMC. The study participants included were selected from the diabetic clinic, irrespective of gender, age and duration of diabetes. Patients having diabetic peripheral neuropathic pain in extremities were type 2 diabetes and the pain were at least ≥4 on 11-point numerical visual analog scale were selected and enrolled from medical OPD of JPMC.

Table 2. Classification of painful diabetic neuropathy. Adapted from Boulton.[1]

Focal and multifocal painful neuropathy
• Cranial (e.g. N.III mononeuropathuc pain)
• Focal limb (e.g. entrapment neuropathic pain)
• Amyotrophy (proximal motor)
• Truncalradiculo neuropathic pain
Generalised symmetrical painful neuropathy
• Acute sensory (always painful)
• Chronic sensorimotor (DPNP)
• Chronic predominantly sensory

Key: DPNP = diabetic peripheral neuropathic pain

PAIN DIARY:

Pain diary was provided to the enrolled patients to note the daily pain intensity on an 11 point numerical scale, the scale starts from 0 no pain to 10 was the worst possible pain.

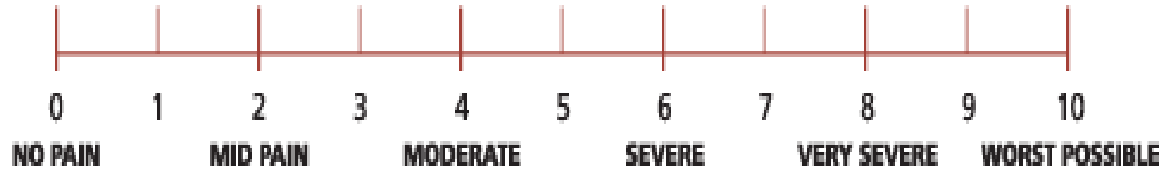
SLEEP DIARY:

The sleep diary was provided to the enrolled patients to note the sleep interference. The scale started from 0 which means pain does not interfere with sleep where as 10 was considered as completely intereference with sleep. Patient was directed to note the sleep intereference after awakening on every day.

GROUPING OF PATIENTS:

60 diagnosed patients of painful diabetic neuropathy were included in 12 weeks trial after taking written consent. The patients were randomly placed into two groups. 30 patients were in each group. One group received Pregabalin and the other group received Gabapentin. The drugs were started with low dose and gradually increased with monitoring of response and adverse effects. In Pregabalin group, it was given 50mg B.D to 150mg B.D and in Gabapentin group the dose was started from100 mg BD to 300 mg TDS. The detailed history was taken and clinical examination including general physical examination, respiratory system, GIT, CVS and CNS of patients were examined.

PAIN DIARY:



SLEEP DIARY:

No interference | Mild interference | Moderate interference | Severe interference | Complete intereference

Group	No. of patients	Therapy
Pregabalin	30	Cap.Pregabalin (100-300mg/day)
Gabapentin	30	Cap. Gabapentin (200-900 mg/day)

SAFETY PROFILE:

The drug compliance and any adverse effects such as nausea, vomiting, diarrhea, constipation, pedal oedema, palpitations, dizziness, somnolence and other systemic side effects were observed during study and for this purpose the following labs investigations were done at day 0 and repeated at the end of the study.

Complete blood count, liver function test, serum urea/creatinine, fasting blood sugar/Random blood sugar, lipid profile, ECG.

RESULT:

60 enrolled patients of diabetic neuropathy were treated with Pregabalin and Gabapentin. All 60 patients were placed in two groups. All groups contained 30 patients. All groups were enrolled for 3 months duration after taking written consent.

Pregabalin Group

In Pregabalin group there were 23.34% male and 76.66% females, the mean age was 56.40±7.39. The mean duration of diabetes was 14.46±4.20 years. The mean duration of diabetic peripheral neuropathic pain was 1.95±0.93 years (mean) as depicted in table 3. The intensity of pain was compared on visual analog scale (VAS). The primary out come of the study was reduction in mean VAS of pain. In Pregabalin group, the changes in pain score from initial VAS mean i.e. 6.20±0.14 on day 0 falling to 5.23±0.14 on day 30; 3.43±0.14 on day 60 to 2.37±0.09 on day 90. The percentage of change was 61.78% which is highly significant as depicted in table 4 and 5.

The secondary outcome was reduction in sleep interference recorded on 11 point numerical VAS. On day 0 the VAS mean was 2.77±0.14 remains same on day 30 then falls to 1.28±0.14 on day 60 and falls to 0.18± 0.24 on day 90 which is highly significant.(table 6)

The adverse effects which were noticed were nausea, vomiting, diarrhea, constipation, pedal oedema, palpitations, dizziness and somnolence. The vitals remain within normal range during the study period, the adverse effects started after 2 weeks of the treatment and the noticeable side effects were somnolence 1(3.3%), palpitation off and on 6.6%dizziness 1 (3.3%) and pedal oedema 1(33%) of mild in nature ECG shows no changes. All patients completed the study period. The complience were good and drug was well tolerated as depicted in table 8.

Gabapentin group

In Gabapentin group 16.66% male and 83.34% females, the mean age was 54±1.35 years, the duration of diabetes was 13.36years mean, the mean duration of diabetic peripheral neuropathic pain was2.01years (table 3) The primary out come of the study of reduction in pain of VAS in this group, the initial mean of VAS was 6.17±0.15 on day 0, falling to 5.4±0.13 on day 30, 4.6±0.15 on day 60 and 3.5±0.15 on day 90. The percentage of change was 43.3% which is highly significant (P value 0.001) as depicted in table 4and 5.

The secondary outcome was reduction in sleep interference recorded on 11 point numerical VAS. In Gabapentin group on day 0 2.10±0.14 Mean ±SEM and fall to 0.35±0.06 Mean ±SEM on day 90 which is highly significant (p value 0.0001)(Table 6).

The adverse effects which were noticed were nausea, vomiting, diarrhea, constipation, pedal oedema, palpitations, dizziness and somnolence. The vitals remain within normal range during the study period i.e. pulse, blood pressure,observed adverse effects started after 2 weeks of treatment. The most common side effects were somnolence 6.6% and palpitation on and off mild to moderate in nature ECG shows no changes. The drug was well tolerated and the compliance were good (Table 8).

Pregabalin group VS Gabapentin group

In both groups the mean baseline characteristics of patients are similar and there is insignificant difference in mean age, BMI, duration of diabetes mellitus, duration of diabetic peripheral neuropathy and baseline mean VAS of pain (table 3). In Pregabalin group the mean reduction in VAS of pain from day0 to day90 was 3.83±0.14 (61.8%)and in Gabapentin group the mean reduction in pain VAS from day0 to day90 was2.67±0.12 (43.3%) as depicted in table 4.The reduction in mean sleep interference is similar in both groups i.e. 1.90±0.14 in Pregabalin group and 1.77±0.14 in Gabapentin group (table 6).

DISCUSSION:

Diabetic peripheral neuropathy affects approximately half of patients with diabetes mellitus approximately 11% experience chronic painful symptoms that diminishes quality of life, disturb sleep and may lead to depression[11]. In the absence of curative therapy, the main aim of management is to provide symptomatic pain control using pharmacological and non-pharmacological agents, and to preserve good glyceamic control. Pharmacological therapy includes tricyclic anti-depressant, narcotic analgesics and anticonvulsants, but adverse effects have limited the effectiveness of these agents. Although a goal of 100% pain relief is ideal but the patient must understand that complete pain relief may not be achieved despite the best effort of the physician. In reality many patients with diabetic peripheral neuropathic pain achieve no more than 30% to 50% pain reduction[12].

Pregabalin is currently the only anticonvulsant approved by the FDA for the treatment of diabetic peripheral neuropathy. It has been studied in 3 randomized, double blind, placebo controlled trials for the treatment of diabetic peripheral neuropathic pain. Lesser et al. (2004), Richteo et al. (2005) and Rosenstock (2004) concluded good efficacy of pregbalin in pain reduction and improvement in function measures.

Lesser et al. (2004) assessed the efficacy of Pregabalin Pregabalin was administered in doses 300 mg/day and on 338 patients of diabetic peripheral neuropathic pain. 600 mg/day which reduced statistically highly significant mean pain score. Pregabalin or placebo was administered, treatment with 300 mg/day or 600 mg/day resulted statistically significant (P<0.001) lower mean pain score on VAS than those of placebo. These doses of Pregabalin also improve sleep. A limitation of Pregabalin is the potential for abuse and dependence, necessitating the monitoring of patients for signs of Pregabalin abuse[13].

Rosenstock (2004) concluded in 146 patients of diabetic peripheral neuropathic pain with fixed dose of Pregabalin 300 mg/day and placebo were given for 8 weeks. The mean VAS was 6.50 Pregabalin and mean VAS was 6.10 in placebo group and the reduction in pain was 38.61% in Pregabalin group and 10.4% in placebo group. The Pregabalin was well tolerated in the study. The most common adverse events were dizziness, somnolence and peripheral oedema.[14]
Richter et al. (2005) did the 6 week study of 246 patints with DPNP and randomly assigned to placebo or treatment of 150 mg/day or 600 mg/day of Pregabalin. The primary efficacy end point was change in pain score >50%. The most common adverse effect was dizziness. In presant study the Pregabalin showed reduction in VAS of pain was (6.20-2.37) i.e 61.78% reduction in pain scale from baseline and sleep interference also improved significantly, these results are very much similar with Richter et al 2005.[15]

In a clinical trial conducted by Serpell (2002) enrolled 305 patients of mixed neuropathic pain syndromes including painful diabetic neuropathy and post-herpetic neuralgia, given Gabapentin and placebo for 8 weeks and observed the mean daily pain score reduction was 7.1-5.6 (21.13%) after 8 weeks treatment.[16]

In one randomized trial by Backonja et al. (1998) has proved affectivity of Gabapentin for treatment of diabetic peripheral neuropathy with history of 1-5 years painful diabetic neuropathy (n=84) and (n=81) for Gabapentin and placebo respectively. Gabapentin was given at a dosage of 900mg-3600mg/day the daily pain diary measured on VAS and secondary end point was sleep interference, at the end of the study patients who were on Gabapentin showed significant improvement in all end points compared with those who received placebo, mean pain score were reduced from 6.4 to 3.9 (39.1%) in Gabapentin and 6.5-5.1 in placebo.[17] In present study the Gabapentin group the mean baseline severity was 6.17 and it decreased to 3.5 on VAS of pain at day 90. The percentage change was 43.3% that is very much similar with Backonja's study.

TABLE 3
BASELINE CHARACTERISTICS OF THE TREATED GROUPS

Variable	Pregabalin	Gabapentin
Mean Age (Years) Median	56.40±7.39 55.00	54.00±7.39 51.00±1.35
Sex Male % Female %	23.34% 76.66%	16.66% 83.34%
Mean Height (m)	158.4±8.08	157.5±7.17
Mean Weight (Kg)	66.19±7.72	67.00±6.64
Mean Duration of diabetes (Years)	14.46±4.20	13.30±4.07
Median Duration of diabetes (Years)	15	13.5
Mean DPNP (Years)	1.95±0.93	2.01±0.95
BMI	26.38±05.09	26.83±0.93
Baseline severity (24 hours pain score) (Mean) (Median)	6.20±0.76 6.00±0.14	6.16±0.76 6.00±0.14

TABLE 4
VISUAL ANALOG SCALE OF PAIN AT DIFFERENT DURATIONS IN TREATED GROUPS

Drug	VAS (Day 0) Mean	VAS (Day 30) Mean	VAS (Day 60) Mean	VAS (Day 90) Mean	Percentage of change
Pregabalin	6.20±0.14	5.23±0.14	3.43±0.14	2.37±0.09	61.8%**
Gabapentin	6.17±0.14	5.40±0.13	4.63±0.15	3.50±0.15	43.3%**

**Highly significant as compared to day 0.

TABLE 5
MEAN REDUCTION IN VISUAL ANALOG SCALE OF PAIN IN TREATED GROUPS

Visual analog scale	Pregabalin Mean±SEM	Gabapentin Mean±SEM
Day-0-day-30	0.97±0.11	0.77± 0.08
Day-30-day-60	1.80± 0.12	0.77± 0.10
Day-60-day-90	1.07± 0.12	1.13± 0.09
Day-0-day-90	3.83± 0.14**	2.67± 0.12**

TABLE 6
VISUAL ANALOG SCALE OF SLEEP INTERFERENCE IN TREATED GROUPS

Drug	VAS (Day 0) Mean±SEM	VAS (Day 30) Mean±SEM	VAS (Day 60) Mean±SEM	VAS (Day 90) Mean±SEM
Pregabalin	2.27±0.14	2.27±0.14	1.28±0.14	0.18±0.03**
Gabapentin	2.10±0.14	2.10±0.14	1.08±0.14	0.35±0.06**

** Highly significant

TABLE 7
MEAN REDUCTION IN VISUAL ANALOG SCALE OF SLEEP INTERFERENCE IN TREATED GROUPS

	Pregabalin Mean±SEM	Gabapentine Mean±SEM
Day 0 – Day 30	0	0
Day 30 – Day 60	0.99±0.13	0.92±0.10
Day 60 – Day 90	0.91±0.12	0.75±0.09
Day 0 – Day 90	1.90±0.14**	1.77±0.14**

**Highly significant as compared to day 0.

TABLE 8
ADVERSE EFFECTS

Adverse effects	**Pregabalin** (n=30)	**Gabapentin** (n=30)
Nausea # (%)	1 (3.3)	0
Vomiting #(%)	0	0
Diarrhea #(%)	0	0
Dizziness #(%)	1(3.3)	2(6.6%)
Somnolence #(%)	1(3.3)	1(3.3%)
Pedal oedema# (%)	1(3.3)	1(3.3%)
Palpitation # (%)	2(6.6%)	2(6.6%)
Total adverse effects #(%)	6 (28%)	6 (20%)

CONCLUSION:

In present study both two drugs were effective in reduction of diabetic peripheral neuropathic pain but the Pregabalin was more effective as compared to Gabapentin, whereas the adverse effects noted were same in both treated groups. Pregablin was observed more effective than Gabapentin and a good tool for the treatment of diabetic peripheral neuropathic pain.

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