

Comparison of Efficacy and Safety Profile of Gabapentin and Carbamazepine in Painful Diabetic Neuropathy

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ABSTRACT

Objective: Comparison of efficacy and safety profile of Gabapentin and Carbamazepine in painful diabetic neuropathy.

Study Design: open label 12 weeks randomized controlled trial.

Settings: The present study 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 Period: December 2010 to May 2011.

Subjects and Methods: 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 Gabapentin (n=30) while the other received Carbamazepine (n=30).

Result: The primary outcome was reduction in pain scale. It was compared on 11-point numerical visual analog scale (VAS). 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). In carbamazepine group the reduction in pain VAS was 6.07 ± 0.13 on day 0 to 4.23 ± 0.13 on day 90. The percentage of change was 30.4% (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.

Conclusion: In patients of diabetic painful neuropathy Gabapentin and Carbamazepine both are effective but Gabapentin is superior in relieving symptoms than Carbamazepine.

Key words: DM: 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 UK, 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 microvessels 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 glycemic 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 20%-60% experiences chronic pain.¹⁰

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According to Boulton’s classification of diabetic peripheral neuropathy (table 1,2) 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	

Table 2. Classification of painful diabetic neuropathy. Adapted from Boulton.

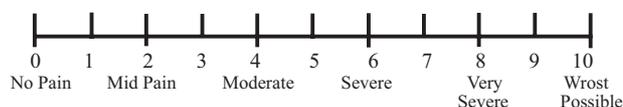
Focal and multifocal painful neuropathy
Cranial (e.g. N.III mononeuropathic pain)
Focal limb (e.g. entrapment neuropathic pain)
Amyotrophy (proximal motor)
Truncal radiculo neuropathic pain
Generalised symmetrical painful neuropathy
Acute sensory (always painful)
Chronic sensorimotor (DPNP)
Chronic predominantly sensory
Key: DPNP = diabetic peripheral neuropathic pain

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.

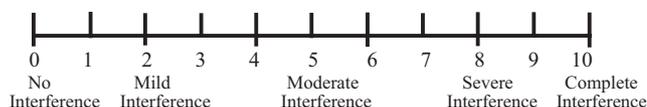
PAIN DIARY:

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 whereas 10 was considered as completely interference with sleep. Patient was directed to note the sleep interference after awakening on every day.



GROUPING OF PATIENTS:

Sixty 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 Gabapentin and the other group received Carbamazepine. The drugs were started with low dose and gradually increased with monitoring of response and adverse effects. In Gabapentin group, it was given 100 mg BD to 300 mg TDS and in Carbamazepine group the dose was started from 200 mg BD to 400 mg TDS. The detailed history was taken and clinical examination including general physical examination, respiratory system, GIT, CVS and CNS of patients were examined.

Group	No. of Patients	Therapy
Gabapentin	30	Cap. Gabapentin (200-900 mg/day)
Carbamazepine	30	Tab. Carbamazepine (400-1200 mg/day)

Safety Profile:

The drug compliance and any adverse effects such as nausea, vomiting, diarrhea, constipation, pedal edema, 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.

RESULTS

60 enrolled patients of diabetic neuropathy were treated with Gabapentin and Carbamazepine. 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.

Gabapentin group

In Gabapentin group 16.66% male and 83.34% females were inducted, the mean age was 54±1.35 years, the duration of diabetes was 13.36 years mean, the mean duration of diabetic peripheral neuropathic pain was 2.01 years (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) (table 4).

The secondary outcome was reduction in sleep interference recorded on 11 point numerical VAS (Table 6). 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).

The adverse effects which were noticed were nausea, vomiting, diarrhea, constipation, pedal oedema, palpitations, dizziness and somnolence. The vital remain win normal range during the study period i.e. pulse, blood pressure, 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 was good (Table 8).

Carbamazepine group

In Carbamazepine group 23.34% were male and female were 76.66%, the mean age in years was 50.63±1.58, the duration of diabetes in 13.3 years (mean), the duration of diabetic peripheral neuropathic pain was 1.95 years (mean). In Carbamazepine group the changes in pain score on VAS from initial mean of 6.07±0.13 on day 0, falling to 5.6±0.14 on day 30, 4.90±0.13 on day 60 and 4.23±0.13 on day 90. The percentage of change was 30.4% which is highly significant (p value 0.001) (Table 3 and Table 4).

The secondary outcome was reduction in sleep interference, recorded on 11 point numerical VAS. In Carbamazepine group sleep interference was 1.93±0.14 (Mean ±SEM) on day 0 falls to 0.95 ±0.10 (Mean ±SEM) on day 90 which is highly significant (p value 0.0005) (Table 6).

The adverse effects noticed were nausea, vomiting, diarrhea, constipation, pedal oedema, palpitations, dizziness and somnolence. The vitals remain in normal range during the study period i.e. pulse, blood pressure, adverse effects started after 4 weeks of treatment, The most common side effects were dizziness 4(13.3%), palpitation 2(6.6%), pedal edema 3.3% of mild to moderate in intensity no ECG changes were noticed (Table 8). The compliance and tolerance were good.

Gabapentin group VS Carbamazepine 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 that is 6.17±0.14 in Gabapentin and 1.83±0.11 in Carbamazepine group. In mean sleep interference reduction is similar in both groups i.e. 1.77±0.14 and 1.10 in Carbamazepine.

Table 3: Baseline Characteristics of All Three Treated Groups

Variable	Gabapentin	Carabamazepine
Mean Age (Years)	54.00±7.39	50.63±8.65
Median	51.00±1.35	48.00±1.58
Sex Male %	16.66%	23.34%
Female %	83.34%	76.66%
Mean height (m)	157.5±7.17	158.1±8.20
Mean weight (Kg)	67.00±6.64	66.36±7.45
Mean duration of diabetes (Years)	13.30±4.07	13.36±4.22
Median duration of diabetes (Years)	13.5	12.5
Mean DPNP (Years)	2.01	1.95
BMI	26.83±0.93	26.90±0.93
Baseline severity (24 hours pain score) (Mean)	6.16±0.76	6.06±1.17
(Median)	6.00±0.14	6.00±0.76

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
Gabapentin	6.17±0.14	5.40±0.13	4.63±0.15	3.50±0.15	43.3%
Carbamazepine	6.07±0.14	5.60±0.14	4.96±0.13	4.23±0.13	30.4%

Table 5: Mean Reduction in Visual Analog Scale of Pain in Treated Groups

Visual analog scale	Gabapentin Mean	Carbamazepine Mean
Day-0-day-30	0.77± 0.08	0.47± 0.09
Day - 30 - day - 60	0.77± 0.10	0.70± 0.11
Day - 60 - day - 90	1.13± 0.09	0.67± 0.10
Day-0-day-90	2.67± 0.12	1.83± 0.11

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
Gabapentin	2.10±0.14	2.10±0.14	1.08±0.14	0.35±0.06**
Carbamazepine	1.93±0.13	1.93±0.13	1.10±0.10	0.95±0.10**

** Highly significant

Figure 1: Visual Analog Scale of Pain at Different Durations in Two Treated Groups

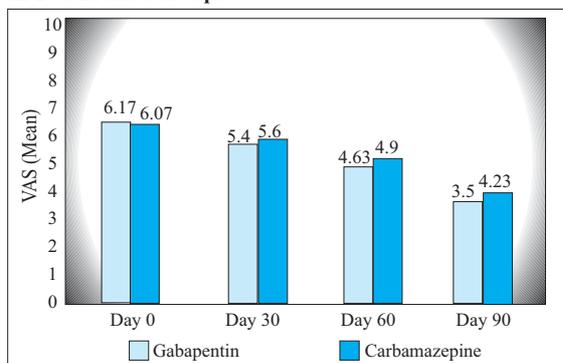


Table 7: Comparison of Visual Analog Score of Pain Among Drugs

Drugs	VAS (Day 0)	VAS (Day 30)	VAS (Day 60)	VAS (Day 90)
Gabapentin	0.77±0.08	0.77±0.10	1.13±0.09	2.67±0.12
vs Carbamazepine	0.47±0.09	0.70±0.11	0.67±0.10	1.83±0.11

Table 8: Adverse Effects

Adverse effects	Gabapentin (n=30)	Carbamazepine (n=30)
Nausea no (%)	0	2(6.6%)
Vomiting no(%)	0	0
Diarrhea no(%)	0	0
Dizziness no(%)	2(6.6%)	4(13.3%)
Somnolence no(%)	1(3.3%)	0
Pedal oedema no. (%)	1(3.3%)	2(6.6%)
Palpitation no (%)	2(6.6%)	1(3.3%)
Total adverse effects (%)	6 (20%)	9 (30%)

DISCUSSION

Diabetic peripheral neuropathy affects approximately half of patients with diabetes mellitus approximately 11% experience chronic painful symptoms that diminishes quality of life, disturbed sleep and may lead to depression (Barbano et al., 2003). 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 glycemic control. Pharmacological therapy includes tricyclic anti-depressants, 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 (Max et al 1991). Carbamazepine was one of the first anticonvulsants studied for treatment of painful diabetic neuropathy. Rull et al. (1989) in a cross over study, 28 out of 30 patients reported pain relief when treated with Carbamazepine 600 mg/day, adverse effects were mild. However, Beydoun et al. (2006) in larger trial of 347 patients of Oxcarbamazepine and placebo insignificant change in mean visual analog scale score was observed from baseline to the last week of the study. In a multicentral placebo controlled 16 week trial of 146 patients with diabetic peripheral neuropathy randomized to Oxcarbamazepine with placebo Dogra (2005) observed significant decrease in VAS symptoms and significant improvement in the global impression of change in pain and sleep disturbance.

In present study Carbamazepine has showed effectivity in reducing VAS of pain (30.4%) from day 0 and sleep interference statistically significant the adverse effects were mild to moderate in nature, the drug was well-tolerated.

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.

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. In the 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.

CONCLUSION

In the present study both two drugs were effective in reduction of diabetic peripheral neuropathic pain but Gabapentin was more effective as compared to Carbamazepine, whereas the adverse effect was more noted in Carbamazepine-treated group as compared to the Gabapentin group. Gabapentin was observed more effective and safety wise may be a good tool for the treatment of diabetic peripheral neuropathic pain.

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