

Comparative role of pregabalin and carbamazepine regarding efficacy in painful diabetic neuropathy

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Abstract: Neuropathic pain is the most severe and resistant type of pain which has impact on quality of life and behaviour; it most commonly occurs at night causing disturbed sleep. Diabetes mellitus is a common cause of painful neuropathy. In this study, we are comparing the effectiveness of old treatment Carbamazepine with Pregabalin in painful diabetic neuropathy. The study was an open-label trial conducted in Diabetic Clinic of Medical Unit-III, Jinnah Post-graduate Medical Center, Karachi. The duration of the study was 90 days, from December 2010 to March 2011. The study has been approved from ethical committee of JPMC, Karachi with the reference NO.F.2-81/2010-GENL/195/JPMC. 60 established patients of painful diabetic peripheral neuropathy from Diabetic Clinic of Medical Unit-III OPD were included in the 90-day study, irrespective of gender, with duration of diabetes more than 10 years. All subjects are placed into two groups. In group A, comprising of 30 patients (n=30), Pregabalin was administered and in group B, also comprising of 30 patients (n=30), Carbamazepine. The intensity of pain was compared on visual analog scale of McGill pain questionnaire. In group A (Pregabalin), the mean pain score fell from 6.17±0.14 to 3.50±0.15 from day 0 to day 90 (p-value=0.001) and the percentage of change also in visual analog scale of McGill pain questionnaire was -43.31%. In group B (Carbamazepine), the changes in pain score from initially 6.07±0.14 falling to 4.23±0.13 from day 0 to day 90 (p-value=0.001) and the percentage of change was -30.31%. Pregabalin was observed to be more potent. Both drugs were well tolerated by all participants that also completed the entire duration of the trial.

Keywords: Painful neuropathy, diabetes mellitus, visual analog scale of pain, carbamazepine, pregabalin.

INTRODUCTION

Diabetes Mellitus is an increasing disease all over the world and it is expected that its incidence will rise to 4.4% by 2030 (Sarah *et al.*, 2004). Peripheral neuropathy is one of the major complications of long-term diabetes type I and II in a population-based study (Abbott *et al.*, 2002). The presentation of diabetic peripheral neuropathy could be creeping, tingling, burning sensation or shooting or severe aching pain in the feet. This is most severe at night (Barbano *et al.*, 2003). Painful diabetic neuropathy is a core cause of neuropathic pain; more than 14 million people in the United States are diabetic and nearly 25% of these develop painful diabetic neuropathy (Schmader *et al.*, 2002). In a recent community-based study in UK, the incidence of chronic painful peripheral neuropathy was 16.2% in patients having diabetes for more than 10 years (Daousi *et al.*, 2004). In Australia, population-based survey of 2436 patients with diagnosed diabetes showed that 13.1% of the patients had peripheral neuropathy (Tapp *et al.*, 2003). Sorensen and colleagues revealed neuropathic pain in 11.7% of diabetes mellitus (Sorensen *et al.*, 2002). Neuropathy is due to involvement of nerves and neuropathic pain is due to up regulation or down

regulation of neuropeptides and neurotransmitters which help in facilitation of pain transmission (Chen *et al.*, 2004). The drugs employed for the treatment of neuropathic pain, include a wide range of antiepileptic drugs, Carbamazepine, Phenytoin, oxa-carbamazepine, lomotrigine, valproic acid, Gabapentin and Pregabalin. These drugs reduce activity of neurons via blockade of voltage dependent sodium and calcium channels (Gidal and Bilington 2006). Older antiepileptic medications e.g. Carbamazepine and Phenytoin have been used for chronic pain but their use in neuropathic pain is limited by lack of efficacy and adverse effects (Backonja 2001). Various drugs are effective in painful diabetic neuropathy but none are ideal or absolute (Kocher *et al.*, 2004). Carbamazepine is in use to treat epilepsy, neuropathic pain and migraine prophylaxis. Adverse effects of Carbamazepine such as suicidal tendency, hypoventilation, arrhythmias, haemodynamic instability and coma on long term use limit its use (Schmidt and Schmitz 1995). Pregabalin is structural analog of Gabapentin and a selective high affinity ligand of α_2 -delta subunit of voltage gated calcium channel which has a major place in initiating neuropathic pain (Freyenhagen *et al.*, 2005). Gabapentin is a structural analog of γ -aminobutyric acid (GABA), which was first time recognized in 1994 as an antiepileptic drug (AED)

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particularly for partial seizures. Previously antiepileptic drugs were only used as adjunctive drugs for management of chronic pain syndromes. Gabapentin was found to be effective in treating neuropathic pain. Gabapentin readily crosses the blood brain barrier when given intravenously, although it alters the synthesis and release of Gamma amino butyric acid (GABA) (Mao and Chen, 2009).

MATERIALS AND METHODS

The 60 diagnosed patients of diabetic peripheral neuropathy were included in this 90-day study after written consent from Diabetic Clinic of Medical Unit-III, JPMC. The study has been approved from ethical committee of JPMC, Karachi with the reference NO.F.2-81/2010-GENL/195/JPMC. The criteria of the study included participants which were diagnosed patients of peripheral neuropathy due to diabetes, irrespective of gender and the intensity of pain should be at least 40 mm (moderate pain) to 100mm (worst imaginable pain) on Visual Analog scale (VAS) of McGill Questionnaire at base line (McCormack *et al.*, 1988, Hawker *et al.*, 2011). The patients were randomly placed into two groups. One group, group A, received Pregabalin and other, group B, received Carbamazepine. The drug was started at a low dose and increased gradually with monitoring of response and adverse effects. In group A, the dose of Pregabalin was 50mg BD to 150mg BD. In group B, Carbamazepine was given at a dosage of 200mg BD to 600 mg BD. All patients had detailed history and examination including General Physical examination, CVS, CNS, GIT and Respiratory System, baseline labs i.e. CBC, LFT, serum urea/creatinine, FBS, RBS, urine D/R, lipid profile done. FBS and RBS were monitored at a fortnightly visit to maintain the sugar profile and all investigations were repeated at the end of the study.

STATISTICAL ANALYSIS

All data collected were mentioned as the mean \pm standard error of mean (SEM) and analysed by using SPSS Version 19. Statistical significance was calculated by using One-way ANOVA, with $p < 0.05$ being significant, $p < 0.01$ being very significant and $p < 0.001$ being highly significant.

Pain diary

All the enrolled patients were provided with a pain diary to note down the intensity of pain which starts from 0 (no pain) to 10 (worst possible pain) (Hawker *et al.*, 2011).

0 1 2 3 4 5 6 7 8 9 10
No pain Mild pain Moderate pain Severe pain Very severe Worst possible

Sleep diary

The sleep diary was given to all enrolled participants to note sleep interference due to pain. It starts from 0 (no interference) to 10 (complete interference) (McCormack *et al.*, 1988, Hawker *et al.*, 2011).

0 1 2 3 4 5 6 7 8 9 10
No interference Mild interference Moderate interference Severe interference Complete interference

RESULTS

In group A (Pregabalin) the variations in the pain score from initial mean of VAS 6.17 ± 0.14 on day 0, decreasing to 5.40 ± 0.13 on day 30; 4.63 ± 0.15 on day 60 to 3.50 ± 0.15 on day 90. The percentage change is -43.31% (P-value 0.001). In group B (Carbamazepine) the changes in pain score from initial mean of VAS 6.07 ± 0.14 on day 0, decreasing to 5.6 ± 0.14 on day 30; 4.9 ± 0.13 on day 60, 4.23 ± 0.13 on day 90. The percentage change is -30.31% (P-value 0.001). The P-values in both drugs are highly significant. The adverse effects noted in Pregabalin were palpitation, dizziness which started after two weeks of study that was mild in nature, controlled and subsiding after 4-5 weeks of study. The reduction in sleep interference was more in the Pregabalin group i.e. 17.5% than the Carbamazepine group in which reduction is 9.8% on Visual analog scale. In Carbamazepine, long term increased risk of adverse effects remains there. As far as effectiveness was concerned, Pregabalin was more effective than Carbamazepine.

DISCUSSION

In this open-labeled trial, it was observed that newer generation anticonvulsant (Pregabalin) is more effective and more tolerant than old generation anticonvulsant (Carbamazepine) in painful diabetic neuropathy. Pregabalin has more efficacy in treating central pain as compared to peripheral neuropathic pain. Pregabalin also has an effect on disturbed sleep and anxiety (Finnerup and Jensen 2007). Pregabalin in addition to Duloxetine is approved by the FDA (Food and Drug Association) for the treatment of painful diabetic neuropathy (Boulton 2003). In recent multi centered placebo-controlled 16-wk study, of 146 subjects with DPN randomized to carbamazepine compared with placebo- observed significant decrease in visual analog scale of pain and with significant improvements in sleep disturbance (Dogra and Beydoun 2005). Pregabalin has been effective in treating neuropathic pain and sleep interference in diabetic peripheral neuropathy and post herpetic neuralgia (Dworkin *et al.*, 2003, Sharma *et al.*, 2002). The side effects with Pregabalin are mild to moderate orthostatic hypotension and palpitation. The risks of cardiac arrhythmias are not present in Pregabalin as associated with TCAs and gastrointestinal upset as in nonsteroidal anti-inflammatory drug (Singh 2000).

CONCLUSION

In patients of diabetic painful neuropathy Pregabalin and Carbamazepine both are effective and tolerated well. All participants of the study completed its entire duration. The drugs were started with low dose and progressively

Table 1: The mean \pm SEM of Visual Analog Scale (VAS) for pain by using the drugs Pregabalin and Carbamazepine on Day 0, 30, 60 and 90^a

Drug	VAS (Day 0) Mean \pm SEM	VAS (Day 30) Mean \pm SEM	VAS (Day 60) Mean \pm SEM	VAS (Day 90) Mean \pm SEM
Pregabalin	6.17 \pm 0.14	5.40 \pm 0.13	4.63 \pm 0.15*	3.50 \pm 0.15**
Carbamazepine	6.07 \pm 0.14	5.60 \pm 0.14	4.96 \pm 0.13*	4.23 \pm 0.13**

^an=30. All data were mentioned as the mean \pm SEM. *p<0.05 significant and **p<0.001 highly significant on comparison with day 0.

Table 2: The mean \pm SEM of Visual Analog Scale (VAS) for sleep interference by using the drugs Pregabalin and Carbamazepine on Day 0, 30, 60 and 90^a

Drug	VAS (Day 0) Mean \pm SEM	VAS (Day 30) Mean \pm SEM	VAS (Day 60) Mean \pm SEM	VAS (Day 90) Mean \pm SEM
Pregabalin	4.56 \pm 1.54	4.32 \pm 1.47	4.01 \pm 1.17	2.18 \pm 1.04*
Carbamazepine	4.76 \pm 1.73	4.56 \pm 1.33	3.78 \pm 2.10	3.41 \pm 1.14*

^an=30. All data were mentioned as the mean \pm SEM. *p<0.05 significant and **p<0.001 highly significant on comparison with day 0.

Table 3: The baseline characteristics of the groups treated using the drugs Pregabalin and Carbamazepine^a

Variable	Pregabalin	Carbamazepine
Mean Age (Years)	54.00 \pm 7.39	50.63 \pm 8.65
Male %	16.66%	23.34%
Female %	83.34%	76.66%
Mean Weight (Kg)	64.00 \pm 6.64	66.36 \pm 7.45
Mean duration of Diabetes (Years)	13.30 \pm 4.07	13.36 \pm 4.32
Mean DPNP (Years)	2.01 \pm 0.95	1.95 \pm 0.93
FBS (Mean \pm SD)	139.53 \pm 8.20	142.56 \pm 8.4
RBS (Mean \pm SD)	151.5 \pm 7.9	155.06 \pm 8.0
Baseline severity of pain score	6.17 \pm 0.14	6.07 \pm 0.14

^an=60. All data were mentioned as the mean \pm SEM, except the genders, which were mentioned as percentages.

increased with monitoring of side effects and response. The study showed reduction of pain and improvement in sleep disturbance with both drugs but Pregabalin proved to be the better option. Regarding the efficacy of drugs Pregabalin is superior to Carbamazepine and the long-term risk of toxicity is not present in Pregabalin as in Carbamazepine.

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