To Compare the Efficacy of Pregabalin and Amitriptyline for Pain Relief in Patients with Diabetic Peripheral Neuropathy

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ABSTRACT

BACKGROUND: Diabetic neuropathy affects more than 50% patients with diabetes mellitus of more than 25 years' duration. Up to 16.2% of diabetic patients have painful neuropathy which can profoundly undermine the quality of life. Both Pregabalin and Amitriptyline are commonly used to relieve symptoms of painful diabetic peripheral neuropathy (DPN).The objectives were to compare efficacy of Pregabalin and Amitriptyline in relieving pain associated with DPN and to compare their adverse effect profiles.

METHODS: We conducted a non-blinded, randomized controlled trial at the Diabetic Clinic, Department of Medicine at Benazir Bhutto Hospital, Rawalpindi, Pakistan from January 2015 to August 2015 on a total of 320 patients who met the inclusion and exclusion criteria. 160 patients each were randomly allocated to either Pregabalin group or Amitriptyline group for up to 6 weeks. Likert Numeric Rating Scale (NRS) was used to assess the severity of pain at the start and six weeks later. Patient-reported adverse outcomes were recorded. Chi-square test was applied to compare the pain relief amongst the two groups.

RESULTS: Of the 320 patients, 180 (56.3%) had pain relief (Likert NRS improvement > 50% from the baseline). Of the 160 patients assigned to Pregabalin group, 104 (65%) achieved good pain relief as compared to just 76 (47.5%) of the 160 patients assigned to Amitriptyline group (p-value= 0.002).

CONCLUSION: Pregabalin is more effective and safer than Amitriptyline for control of symptoms of painful DPN

Keywords: Diabetic Peripheral Neuropathy; Likert Numeric Rating Scale; Pregabalin; Amitriptyline

INTRODUCTION

World Health Organization (WHO) ranks Pakistan 7th on diabetes mellitus prevalence list with an estimated overall prevalence of diabetes at 11.45%. Diabetic neuropathy affects more than 50% of patients with diabetes of more than 25 years' duration [1]. Painful neuropathy is present in up to 16.2% of diabetic patients and can profoundly undermine their quality of life [2]. Symptoms include paresthesia in feet (and rarely in hands), pain in lower limbs (dull, aching and/or lancinating, worse at night, and mainly felt on the anterior aspect of legs), burning sensations in soles of feet, cutaneous hyperesthesia and an abnormal gait (commonly wide-based), often associated with a sense of numbness in feet [3].

More importantly, however, is the pathogenic mechanism behind painful neuropathy, which is multifactorial and includes metabolic disturbances such as hyperglycemia, impaired glucose tolerance, dyslipidemia, oxidative and nitrosative stress, growth factor deficiencies, micro-vascular insufficiency and autoimmune damage to nerve fibers [4]. Current first-line therapies for painful diabetic peripheral neuropathy (DPN) are tricyclic antidepressants (TCA) such as Amitriptyline, SNRI such as Duloxetine or anticonvulsants such as Pregabalin or Gabapentin [5].

One limitation of evidence in the treatment of DPN is relative lack of comparative studies. Often, the treatment of DPN is not entirely

satisfactory and the aim is to achieve 50% reduction in pain intensity [6]. NICE Guidelines recommend Duloxetine as first-line treatment for painful DPN, with Amitriptyline as alternative and Pregabalin as second-line agent [7]; whereas the American Academy of Neurology (AAN) considers Pregabalin as the first line and all other treatment options as second line [8]. Amitriptyline (25-75 mg) is effective in painful DPN and the dramatic response is seen within 48-72 hours. Drowsiness is its major concern which usually improves with time [9]. There are limited head-to-head studies comparing Pregabalin with Amitriptyline. In one study, good pain relief was seen in 48% of patients in Pregabalin group as compared to 34% in Amitriptyline group [10].

Both American Diabetic Association (ADA) and AAN guidelines recommend that Pregabalin should be used as a first-line drug (Level A evidence) for DPN, however, they also agree on the role of Amitriptyline in reducing pain associated with DPN (Level B evidence). Because of major cost difference between the two drugs and lack of evidence from local studies, we conducted this trial to examine the difference in DPN pain control between the two drugs.

METHODS

This randomized non-blinded controlled trial was conducted at the Diabetic Clinic of Department of Medicine at Benazir Bhutto Hospital, Rawalpindi, Pakistan between January and August 2015. We enrolled patients between the ages of 18 and 60 with at least 5 years history of diabetes and symptoms of pain, numbness, paresthesia, tingling sensation, burning or hyperesthesia, symptoms consistent with diabetic neuropathy for at least 6 months. Patients had an average pain score of at least 4 or higher during a 7-day pre-enrollment period on a 10-point Likert scale. We excluded patients with peripheral neuropathy due to other causes, patients who were pregnant or were lactating, critically ill patients or those who were taking Amitriptyline or Pregabalin during the 3 months prior to the screening for study enrollment.

Study Protocol: Patients were randomly assigned to Pregabalin or Amitriptyline groups using the RandList 1.2 software. The study duration was 6 weeks. The starting dose was 75 mg twice daily for Pregabalin and 10 mg at bedtime for Amitriptyline. Doses were titrated upwards if needed at week 1 and week 3 follow-up visit to a maximum dose of 300 mg twice daily for Pregabalin and 75 mg at bedtime for Amitriptyline. We used a Likert Numeric Rating Scale (NRS) to assess the severity of pain at the time of enrollment in the study and six weeks later. The primary outcome was good pain relief which was defined as a decrease in NRS pain score of more than 50% at 6 weeks from baseline. Patient-reported adverse outcomes were recorded. Chi-square test was applied to compare pain relief amongst the two groups. SPSS 19 was used for the statistical analysis.

RESULTS

Out of the 320 patients, 46.6% (149) were male with a mean of 45.2±9.7 years of age. As expected secondary to randomization, both study groups were homogenous based on demographic characteristics and mean duration of diabetes. Fifty percent or greater improvement in NRS scores from baseline was noted in 180 (56.3%). Significantly higher number of patients in the Pregabalin group had pain relief than patients in the Amitriptyline group (104 vs 76; p= 0.002). Amitriptyline was associated with dry mouth, daytime somnolence and postural hypotension, whereas, the main side effects seen with Pregabalin were confusion and headache. Overall more patients in the Amitriptyline group reported adverse events than the Pregabalin group (256 vs 128; p= <0.001; Table 1).

DISCUSSION

In this randomized controlled trial of patients with DPN, we found Pregabalin to be significantly more effective than Amitriptyline in pain relief during the 6-week study period. Furthermore, we found a significantly higher risk of adverse events with Amitriptyline. DPN is a common complication of long-standing, poorly controlled diabetes and is associated with significant morbidity. The prevalence of DPN is about 30% in hospitalized patients and 20% in the community-dwelling with an annual incidence rate of 2% [11]. Painful DPN is marked by pain, paresthesia and sensory loss. The pathology of DPN involves oxidative stress, advanced glycation end products, polyol pathway flux and protein kinase C activation, all contributing to micro-vascular disease and nerve dysfunction [12]. For symptom management, current evidence from clinical trials support the use of Desipramine, Amitriptyline, Capsaicin,

Table 1: Patient Reported Adverse Outcomes

n = 320	Amitriptyline (%)	Pregabalin (%)	P value
Increase in sleep duration	102 (39.8)	40 (31.3)	0.10
Tiredness	15(6)	8 (6.3)	0.91
Dizziness	15 (6)	16 (12.5)	0.03
Peripheral edema	0 (0)	0(0)	1
Daytime somnolence	5 (2.0)	16 (12.5)	0.26
Difficulty in urination	5 (2.0)	0 (0)	0.49
Dry mouth	31 (12)	0 (0)	<0.001
Constipation	51 (19.9)	16 (12.5)	0.07
Postural hypotension	30 (11.7)	0 (0)	<0.0001
Flu-like Symptoms	2 (0.8)	14 (10.9)	<0.001
Headache	0 (0)	14 (10.9)	<0.001
Confusion	0 (0)	14 (10.9)	<0.001
Total	256 (80)	128 (40)	<0.0001

Gabapentin, Pregabalin, Bupropion and Venlafaxine as the preferred medications. Escitalopram, Non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics may be used as adjuvant agents. Glycemic control remains the foundation and the prerequisite of prevention and adequate control.

A recent trial [13] did not find a significant difference between Pregabalin and Amitriptyline in the main study outcome of pain relief. The overall response rates in this study were 77% for Pregabalin and 73% for Amitriptyline. The discrepancy between results of our study and this study may stem from the difference in definition of outcomes. While we defined a 50% or greater reduction in pain as pain relief, this study defined pain relief as any reduction in pain from baseline.

Another study from a population similar to ours by Shabbir *et al* [14] showed that only 12.8% of the patients demonstrated better response with Pregabalin compared to Amitriptyline. The discrepancy might stem from the fact that our trial was non-blinded and the patients knew which drug they were taking which could have affected compliance and hence the results of our trial.

Pregabalin is approved by the Food and Drug Administration in the United States for management of DPN. The drug acts peripherally at GABA receptors to block the perception of pain. Pregabalin is relatively well tolerated and causes less sedation than Gabapentin, another drug that acts on GABA receptors. However, Pregabalin is associated with other adverse events including rhabdomyolysis, acute renal failure, central nervous system dysfunction, hyperthermia and secondary acute glaucoma. Patients on Pregabalin therapy must be monitored closely for myopathy and ocular complaints. Pregabalin is also associated with peripheral edema and weight gain; this adverse event is intensified when given with thiazolidinediones. Pregabalin should be avoided in patients with hypertension and congestive heart failure.

Our study has some limitations. First, it was a non-blinded, non-placebo, active-control, randomized trial so the elements of bias due to non-blinding cannot be eliminated. An alternative could have been the use of a crossover study design with a placebo washout period. The outcome was measured using an NRS which is a crude assessment of pain.

CONCLUSION

In conclusion, we found that Pregabalin is a more effective drug than Amitriptyline for improving symptoms of painful DPN over a 6-week period. Longer duration studies are needed to examine if

Figure 1: Graph of Age Distribution

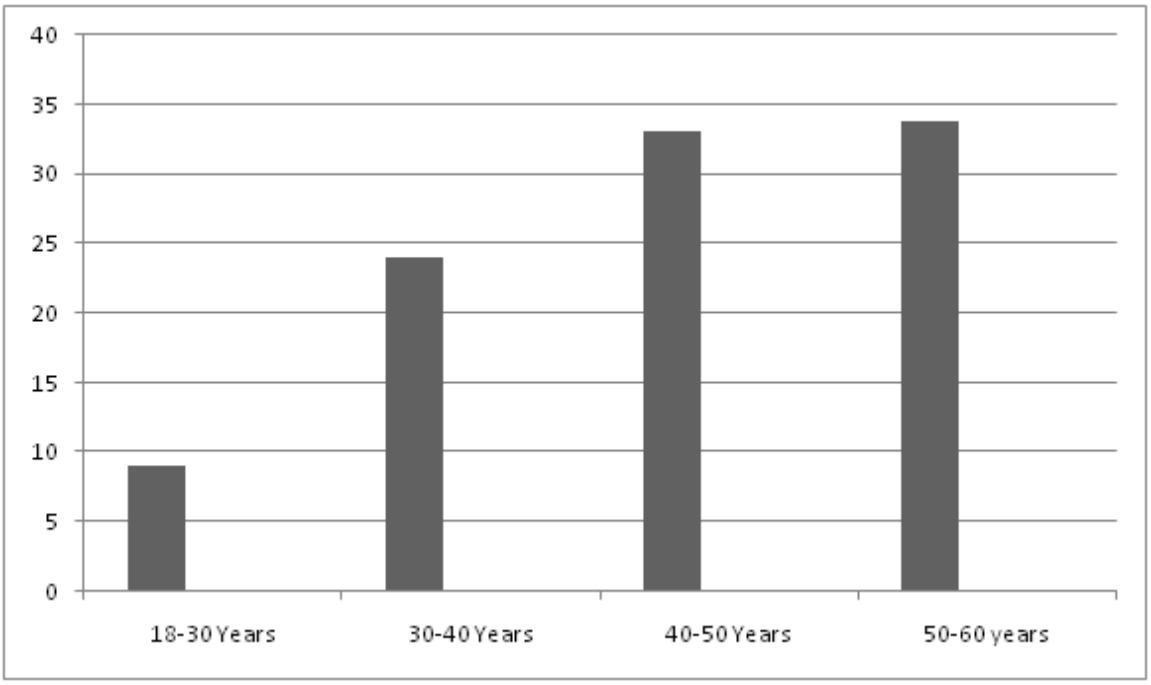
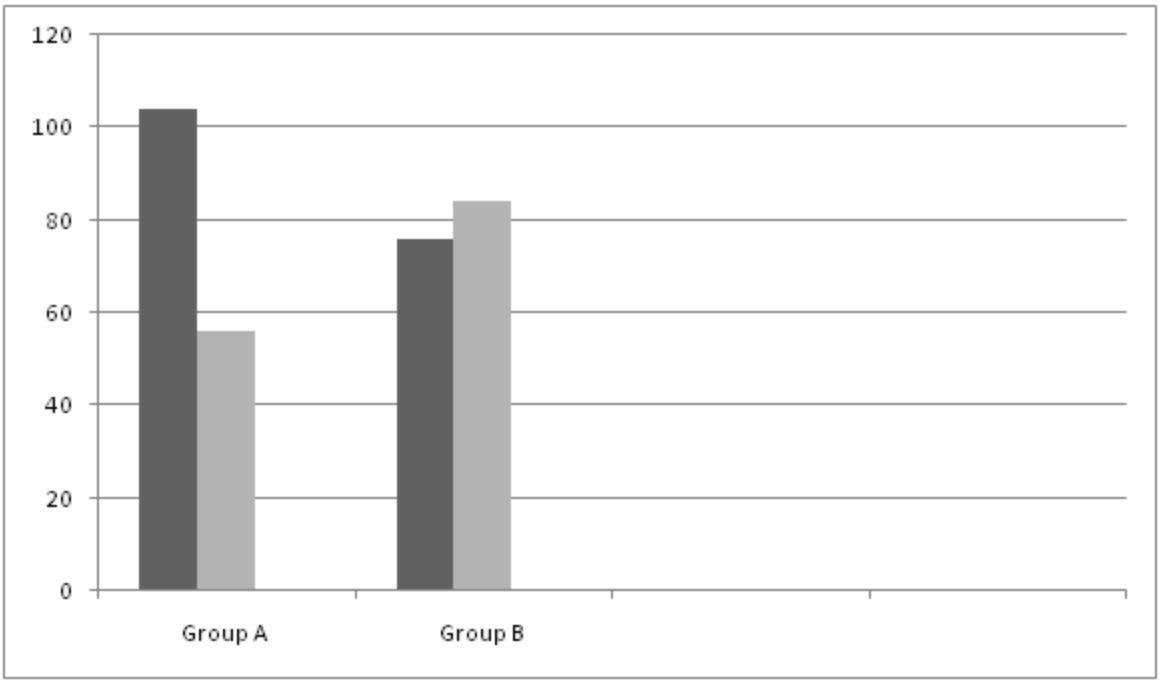


Figure 2: Graph of Pain Relief among Groups



the difference between the two drugs is sustained after 6 weeks of therapy. Furthermore, cost-effectiveness studies are needed to examine the cost of additional benefit obtained from Pregabalin.

REFERENCES

1. Masharani U. Diabetes mellitus. Diabetes mellitus and hypoglycemia. In: Tierney LM, Mcphee SJ, Papadkis MA, eds. *Current Medical Diagnosis and Treatment, 43rd edn. New York: McGraw Hill.* 2004;1146–1179.
2. Daousi C, MacFarlane IA, Woodward A, Nurmikkot TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med.* 2004;21(9):976–982
3. Frier BM, Fisher M. Diabetes mellitus. In: Colledge NR, Walker BR, Ralston SH (Editors). Davidson principles and practice ofMedicine.21st ed. New Delhi: *Elsevier Limited* 2010;796-834
4. Vinik A. The Approach to the Management of the Patient with Neuropathic Pain: *J Clin Endocrinol Metab.* 2010;95(11):4802-11
5. Tesfaye S. Advances in the management of diabetic peripheral neuropathy. *Curr Opin Support Palliat Care*. 2009;3(2):136-43
6. Tesfaye S, Boulton AJ, Dickenson AH. Mechanisms and management of diabetic painful distal symmetrical polyneuropathy. *Diabetes Care.* 2013;36(9):2456-65
7. NICE Clinical Guideline 96: Neuropathic Pain. The pharmacological management of neuropathic pain in adults in non-specialist settings. March 2010
8. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, *et al*. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;3(4):345-52
9. Masharani U. Diabetes mellitus & hypoglycemia. In McPhee SJ. Papadakis MA. Rabow MW.(editors) Current Medical Diagnosis & Treatment. Mcgraw Hill LANGE. 2012;1193-4
10. Bansal D, Bhansali A, Hota D, Chakrabarti A, Dutta P.Amitriptyline vs. Pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial. *Diabet Med.* 2009;26(10):1019-26
11. Duby JJ, Campbell RK, Setter SM, White JR, Rasmussen KA. Diabetic neuropathy: an intensive review. *Am J Health Syst Pharm.* 2004;61(2):160-73
12. Hosseini A, Abdollahi M. Diabetic neuropathy and oxidative stress: therapeutic perspectives. *Oxidative medicine and cellular longevity*. 2013.
13. Vega, C. (2017). *Amitriptyline vs Pregabalin for Painful Diabetic Neuropathy*. [online] Medscape. Available at: http://www.medscape.com/viewarticle/718278 [Accessed 23 Mar 2017]
14. Shabbir BI, Shafi FA, Mahboob FA. Amitriptyline vs Pregabalin in painful diabetic neuropathy: a randomised placebo-based study. *Pakistan J Med Heal Sci.* 2011;5(4):745-7