COMPARATIVE STUDY OF EFFECTIVENESS OF VENLAFAXINE, DULOXETINE AND SERTRALINE IN MANAGEMENT OF DIABETIC SENSORY NEUROPATHY

Nabila Shaukat, Shazia Nisar*, Usman Sajid*, Osman Ali Jan*, Amjad Mahmood, Huma Zahid

DHQ Teaching Hospital, Mirpur, Azad Kashmir Pakistan, *Combined Military Hospital Jhelum/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To compare efficacy of 3 commonly prescribed anti-depressants from classes' selective serotonin reuptake inhibitor and serotonin-nor epinephrine reuptake inhibitors i.e. Venlafaxine, Duloxetine and Sertraline in the management of diabetic sensory neuropathy in subjects with type 2 diabetes mellitus.

Study Design: Comparative, prospective study.

Place and Duration of Study: Combined Military Hospital Jhelum, Mar 2018 to Jul 2018.

Methodology: This study included 94 patients with metabolically stable type 2 Diabetes Mellitus with diabetic sensory neuropathy. Patients were randomly assigned into 3 treatment group, treatment group 1 (n1=29) receiving Venlafaxine 37.5mg × BD, treatment group 2 (n2=33) receiving duloxetine 30mg × BD and treatment group 3 (n3=25) receiving Sertraline 50mg × OD, each group being treated for 6 weeks, with optional dose titration fortnightly. The efficacy measure was done by revised Neuropathy Disability Score (NDS), measured at baseline and at the end of treatment period i.e. 6 weeks. The primary outcome of this study was "functional outcome" assessed by Disability Neuropathy scale (DNS) and overall improvement and adverse events were measured as secondary outcome measures.

Results: There was significant improvement in Neuropathy Disability scale (DNS) at the end of treatment period in all treatment groups from their baseline score, with comparable efficacy among all drug groups i.e. *p*-value between venlafaxine and duloxetine, venlafaxine and sertraline were non-significant i.e. $p>0.05$ except between Duloxetine and Sertraline group where there was significant difference in efficacy ($p<0.05$). Good, moderate and mild improvement in symptoms was noticed in all study groups.

Conclusion: Non-tricyclic Anti-depressants i.e. Venlafaxine, Duloxetine and Sertraline demonstrate comparable efficacy, safety and tolerability in managing Diabetic sensory neuropathy.

Keywords: Diabetes mellitus, Diabetic sensory Neuropathy, Duloxetine, Sertraline, Venlafaxine.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder due to defect in insulin secretion, insulin action or both. In 2000, >175 million people all over the world suffered from diabetes mellitus and estimated burden of the disease is expected to be 360 million by 2030[1]. Diabetes can induce multiple complications, including nephropathy, retinopathy, neuropathy and many other macrovascular complications. Most common micro vascular complication in both type-I and type-II DM is peripheral neuropathy. Diabetic peripheral neuropathy (DPN) is defined as "presence of symptoms and/or signs of peripheral nerve destruction in people with DM, after exclusion of other causes of neuropathy"[2]. The International Diabetes Federation gives figure of 7 million people with DM in year 2015 and anticipated rise to be 14 million by 2040. Number of deaths due to diabetes and its complication are estimated to be 48,800 per year bet-ween ages of 30-69 years and 47,700 in the age group of 70 years and above[3].

Diabetic neuropathy is most frequently encountered microvascular complication of DM. It is estimated that diabetic neuropathy is present in approximately 60% of subjects with long duration of diabetes, both type-I and type-II. However, there are no country wide cross-sectional studies on the prevalence figure of Diabetic peripheral neuropathy in Pakistan.

Correspondence: Dr Nabila Shaukat, House No G-19 Staff Colony, Mirpur Azad Kashmir Pakistan

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Diabetic sensory neuropathy is the most common component in the causal sequence of foot ulceration, which may lead to amputation in 10-30 times higher amongst this group of individuals. Diabetic peripheral neuropathy has extremely negative effect on the quality of life, social function and psychological health of patients[4]. Therefore, it is necessary to inform, educate and treat patients with Diabetic peripheral neuropathy aptly. When diabetic peripheral neuropathy is diagnosed late, treatment becomes more difficult with mild or no benefit at all.

METHODOLOGY

The study was conducted during March to July 2018 in Combined Military Hospital Jhelum. This study was a comparative prospective trial to compare efficacy of venlafaxine, duloxetine and sertraline in management of diabetic sensory neuropathy in patients with type-II DM. A sample size of one hundred and ten patients was calculated to compare the effect of SSRIs (Sertraline) and SNRIs (Duloxetine, Venlafaxine) with a 90% confidence level and with ± 4.72% margin of error of population proportion value *p*=0.90 using the formulan = Z21-@/s 1-P/E2 P with the help of WHO calculator. Of these 110 patients, 94 patients of either sex, male or female with type-II DM, aged >40 years with body mass index <35 kg /m^2, who were in stable glucose-lowering medications with stable glycemic control i.e. fasting blood glucose level <7 mmol/L or random blood glucose level <11 mmol/L during preceding month and who had diabetic sensory neuropathy for at least one month were considered eligible for the trial. However, patients with existing overt neuropathy with ulcers, or patients on insulin therapy, pregnant/lactating women, patients testing positive for HIV, HbsAg or Anti-HCV serology, those taking anticonvulsants, anti-depressants, local anesthetics or opioids, and those having clinically significant cardiovascular, hepatic, renal, gastrointestinal or neurological diseases, which are capable of altering the absorption, metabolism or elimination of the study drugs were excluded from our study. Permission from Institutional Ethics Review Board (IERB) was taken before starting study and written informed consent was taken from the study participants prior to enrolment for study. Diabetic neuropathy was confirmed by past medical history, Diabetic sensory neuropathy symptom score >1 (table-I)[5] and Visual analog scale for pain scoring>50%[6].

Patients were randomized using heads or tails method and divided into three treatment groups: Treatment group-1 (n1=29) received Venlafaxine 37.5mg × BD (effective dose = 75-375 mg), treatment group-2 (n2=33) received Duloxetine in dose of 30mg × BD (effective dose 40-120 mg), and treatment group-3 (n3=25) received Sertraline 50mg per day (effective dose = 50-200 mg), for 6 weeks, with optional dose up-titration fortnightly. Patients were assessed using revised Neuropathy Disability Score (NDS) system at "0" week, 3rd week and at the end of study i.e. on 6th week[7]. The primary outcome of this study was "Functional outcome" determined by reduction in Neuropathy Disability Score (NDS) as compared to that on the start of the treatment (table-II). The secondary outcome was improvement in HbA1C level along with improvement in sleep pattern. The primary and secondary efficacy analysis were performed on the Intention-To-Treat (ITT) population, defined as patients who received at least one dose of randomized study medication and had at least one post baseline efficacy assessment[8].

The follow up of the patients was done by study personnel at baseline, on 3rd week and on 6th week of treatment, at which time Neuropathy Disability Score (table-II) was measured along with side effect profile of the study drugs. Statistical analysis was performed by using Statistics Package for Social Science (SPSS) version 20.0. Participants were categorically marked as showing good, moderate and mild response to drugs in terms of reduction in Neuropathy Disability Score (NDS) score at the end of study i.e. on 6th week.

RESULTS

Of 94 screened patients 87 completed study (92.5%) with >88% compliance. The reasons for

non-compliance included frequent follow-up visits and long distance of their living places from hospital. The total 94 patients selected for the trial, were allocated into three study drug groups (group-I, II & III) randomly. Patient demography and clinical characteristics were summarized in table-III.

Table-I: Diabetic neuropathy symptoms score[5].

Diabetic Neuropathy Symptoms Score	
Paresthesia / prickling sensation	1
Unsteadiness in walking	1
Numbness	1
Burning, aching pain / tenderness	1

Table-II: Neuropathy Disability Score (NDS).

Neuropathy Disability Score (NDS)	
Vibration perception threshold 128 HZ tuning fork; apex of big toe; Normal=can distinguish vibrating / not vibrating	Normal=0 Abnormal=1
Temperature perception on dorsum of the foot Use tuning fork with beaker of ice / warm water	Present = 0 Present with reinforcement = 1 Absent = 2
Pin-prick Any pin proximal to big toe nail just enough to deform the skin; Trial pair = sharp, blunt Normal=can distinguish sharp/ blunt	
Achilles reflex	
NDS Total score=10	

At the end of study duration following results was obtained:

With Venlafaxine 13 (44.8%) showed good response, 15 (51.7%) showed moderate response and 1 (3.5%) showed mild improvement.

With Duloxetine 18 (56.2%) showed good response, 12 (37.5%) showed moderate response and 2 (6.4%) showed mild improvement. Similarly, with Sertraline 7 (28%) showed good response, 16 (64%) showed moderate response and 2 (8.0%) showed mild improvement.

All the drugs relieved symptoms and signs of Diabetic sensory neuropathy, measured by Neuropathy Disability Scale (NDS) by a significant amount at 6 weeks of treatment with comparable efficacy, except for Duloxetine and Sertraline group which showed significant difference in efficacy between these two drugs i.e. *p*-value was <0.05 (table-IV).

Table-III: Demographic data of study population.

Characteristics	Values
Age (years, mean)	59.21 ± 9.30
Sex (%)	
Male	38 (44)
Female	49 (56)
Weight (kg)	72 (68-82)
Height (cm)	166.1 (155.9-166)
Body Mass Index (Kg/m²) %	28 (26-30.1)
Duration of diabetes (years)	7 (2-12)
Duration of pain (months)	16 (6-35)
Site of Pain	
Foot	67 (77.01)
Foot and hand	20 (22.98)
Hypertension	56 (65)
Diabetic Neuropathy symptom score (DNS)	
>1 point abnormal	87 (100)
>2 points abnormal	87 (100)
Neuropathy Disability Score (NDS) scale	
1-3	2.87 ± 0.35
4-7	5.6 ± 1.1
>7	8.2 ± 0.42

Data are mean ± SD, n (%) or median (IQR)

Table-IV: Results of the trial.

Variable	Drug	Drug (for comparison)	Mean difference
Neuropathy Disability score (NDS)	Venlafaxine	Duloxetine	0.173
		Sertraline	0.923
	Duloxetine	Venlafaxine	-0.173
		Sertraline	-1.096
	Sertraline	Duloxetine	1.096
		Venlafaxine	0.923

The more common adverse events noted with these drugs were nausea, constipation and somnolence. No anticholinergic side effects were noticed with any of these drugs. The mean HbA1C level was improved from 8.2% to 7.8%. Fasting and post-prandial glucose level, lipid profile, renal function tests, liver function tests did not change at start an at end of study duration.

No patient suffered from depression as per Hamilton Depression Rating Scale[9].

DISCUSSION

Diabetic polyneuropathy affects approximately 30-50% of all diabetic patients and is the most common neuropathy worldwide[10].

DPN encompasses several neuropathic syndromes, by far the most common of which is distal symmetrical sensory polyneuropathy. The proposed mechanism of neuropathy is damage to large A-type alpha and beta fibers, which cause abnormal sensation of vibration and proprioception. Pain and abnormal sensation of hot and cold temperature results from damage to small, thinly myelinated A-type delta fibers and small, unmyelinated C-type fibers[11].

Two main clinical consequences of Diabetic sensory polyneuropathy foot ulceration, sometimes leading to amputation and painful neuropathy are associated with high rates of patient morbidity and mortality, therefore early diagnosis and treatment of diabetic polyneuropathy is imperative to prevent irreversible damage[12].

Assessment and management of neuropathic pain continues to pose a considerable challenge to clinician. Diagnosis is clinical and involves a through history and physical examination, focusing on vascular and neurological examination and assessment of feet. Reduced sensation of vibration (an early indicator of neuropathy) is measured by 128HZ Tuning fork. A 1g semmesweinstein monofilament can be used to detect change in sensation of touch (indicator of increased foot ulceration). Other tests to detect neuropathy are close examination of feet and deep tendon reflexes.

Objective tests are required to make a definitive diagnosis of diabetic polyneuropathy, although it is not essential for establishing the diagnosis or for clinical care and it includes Quantitative sensory testing, Nerve Conduction Velocity (NCV) and tests for autonomic function.

Laboratory studies are essential to rule out other causes mimicking DPN or causing polyneuropathy and these include; complete blood count, Thyroid profile, Vitamin B.12, Folic acid level and serum Immunoelectrophoresis (chronic demyelinating polyneuropathy).

Control of Diabetes Mellitus without risk for hyperglycemia is essential and the most crucial step in preventing disease progression as delay in diagnosis and poorly controlled DM has an extremely negative effect on the quality of life, social function and psychological health of patients, that is why it is important to educate patient about diabetic sensory polyneuropathy and promptly treat it because when it is diagnosed late, treatment becomes more difficult.

Two main treatment modalities for Diabetic polyneuropathy include (a) Non-pharmacologic methods and (b) Pharmacologic methods. Non-pharmacologic methods include life style interventions (diet and exercise) and good glycemic control and pharmacologic agents include various groups of drugs including; Anticonvulsants, Anti-arrythmics, Local anesthetics, Opioid analgesics, Topical agents, Tricyclic antidepressants and Non-tricyclic antidepressants. One of the main difficulties in management of this problem is, having no consensus for first line treatment agent for patient with diabetic polyneuropathy as approved by literature. Hence selecting an appropriate pharmacologic agent is more difficult as various alternative drugs are readily available for management of diabetic polyneuropathy[13].

Among these groups non-tricyclic antidepressants which include serotonin nor-epinephrine reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) are most investigated group of drugs. Anti-depressants are one of the most effective class of drugs in treatment of various kinds of pain, its adverse effect profile is better than tricyclic antidepressants. Venlafaxine, Duloxetine and Sertraline are the most studied drugs amongst their groups, these drugs not only inhibit reuptake of serotonin and nor epinephrine but also inhibit muscarinic, histaminergic and adrenergic receptors, hence lowering the adverse side effects. Duloxetine was the first anti-

depressant to receive FDA approval in year 2004 as afirst line agent to treat diabetic polyneuropathy[14]. There are many studies done at international level which reviewed the chemistry, pharmacology, metabolism, safety and adverse effects, clinical use and therapeutic indications of each anti-depressants. A 2014 Cochrane review of 8 studies showed that Duloxetine at dose of 60 mg daily led to at least 50% pain reduction in patients with neuropathic pain, although this study could not show superiority of SNRIs over commonly used anti-epileptics (gabapentin) in terms of pain reduction, however, SNRIs were better tolerated and have fewer side effects and drug interactions when compared to first line agents[15]. Another study done by Selvy *et al* also showed that SNRIs have better effects and safety profile for treatment of neuropathic pain as compared to other anti-depressants and anti-epileptics[16]. There are studies at international level which compared SSRIs with SNRIs. One study which was conducted by Mawla *et al* compared SNRIs (Duloxetine) with SSRIs (Sertraline) and showed that they both have comparable effect and *p*-value was 0.463 which is statistically not significant[17], however this result differs when compared to our study, the reason being loss to follow-up in sertraline treatment group and delayed improvement in symptoms as compared to Duloxetine and Venlafaxine in our trial. Another study with similar objectives showed that SNRIs were better option than SSRIs when Drug-Drug interactions were suspected with same side effect profile with both drug groups[18]. There was one study conducted by Docu Axelerad Anya, Docu Axelerad Daniel[19] which showed superiority of Duloxetine as compared to sertraline, hence proving the difference in our study was not accidental. Moreover, there was improvement in Visual Analog Scale (VAS) scores of pain.

CONCLUSION

The current study compared the efficacy and safety of venlafaxine, Duloxetine and Sertraline in patients suffering from Diabetic sensory neuropathy. Improvement in diabetic neuropathy symptoms score (table-I) and Neuropathy Disability Scale score was significant in all of the three groups, and the efficacy was comparable in each drug group except in Duloxetine and Sertraline where there was significant difference in efficacy of both these drugs, Duloxetine being more efficacious in management of diabetic polyneuropathy than sertraline i.e. *p*-value <0.05 (table-IV). There was significant improvement in HbA1C level over the trial period which can be a contributing factor to reduce sensory neuropathy improvement or may have a confounding effect on the efficacy assessment.

There was no significant alteration in laboratory parameters before and after the studies, implying safety of these three drugs. In conclusion, Non-cyclic Anti-depressants i.e. Venlafaxine, Duloxetine and Sertraline demonstrate comparable efficacy, safety and tolerability in managing Diabetic sensory neuropathy.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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