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Original Research Paper

Diabetology

ASSESSMENT OF THERAPEUTIC EFFICACY AND SAFETY OF DELPHINIUM DENUDATUM WALL (JADWAR) AND LOCAL APPLICATION OF IRIS FLORENTINA (ROGHAN SOSAN) IN PAINFUL DIABETIC NEUROPATHY: A RANDOMISED SINGLE BLIND STANDARD CONTROLLED STUDY.

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ABSTRACT

The current study was conducted to assess the efficacy and safety of Delphinium denudatum (Jadwar)and roghan sosan in patients with painful diabetic neuropathy. A randomised single-blind standard controlled trial was carried out on 30 diagnosed patients of painful diabetic neuropathy at National Institute of Unani Medicine Bangalore-India. After obtaining ethical clearance, 30 eligible patients were randomly allocated into test and control groups, comprising 15 patients in each group. Patients of test group were given Delphinium denudatum wall (Jadwar) 500mg in tablet form twice daily and local application of; Iris florentina (roghan sosan) on both feet twice daily. The patients of control group were given Strychnos nuxvomica (Azaraqi) 500 mg in tablet form twice daily for a period of 45 days. The subjective parameter- Visual analogue scale (VAS) was statistically analysed by applying Student's 't' test, two tailed dependent for intragroup comparison, two tailed independent for intergroup comparison and Levene's test for the homogeneity of variance. VAS showed strongly significant difference ($p<0.001$) in intragroup comparison in both groups. The study revealed that test drugs appeared to be efficacious in the management of painful diabetic neuropathy and exhibited significant effects in improvement of neuronal function. No adverse effects or toxicity has been reported during or after the trial.

KEYWORDS : Painful Diabetic neuropathy; Visual analogue scale; Delphinium denudatum; Iris florentina Strychnos nuxvomica

INTRODUCTION

The painful symptomatology of diabetic neuropathy has been documented for many years and one of the first descriptions of neuropathic pain is attributed to Rollo (1), who described pain and paraesthesia in the legs of a diabetic patient in the 18th century. Painful symptoms are common in many of the neuropathic syndromes of diabetes: these include both focal and multifocal neuropathies, proximal motor neuropathy or amytrophy, and the symmetrical sensory polyneuropathies. A simple definition of diabetic neuropathy, approved by an international consensus group, is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes" (2). This definition refers to the chronic sensorimotor diabetic neuropathy, which is really a paradoxical condition as up to 50% of patients might experience painful or uncomfortable symptomatology, whereas the remaining 50% might experience no pain whatsoever putting them at risk of foot ulceration and other late sequalae of neuropathy including Charcot neuroarthropathy (3). Thus, one patient with sensorimotor neuropathy might experience severe pain clearly described by Pavy (4) in 1887 as being "of a burning and unremitting character," whereas another patient with the same deficit might be completely asymptomatic: patients such as the latter one lack what Dr. Paul Brand described as "the gift of pain"(5).

MATERIALS AND METHODS

A randomised single blind, standard controlled study was carried out at National institute of Unani medicine, hospital over a period of 8 months from March 2013-October 2013.The study was permitted by the institutional ethical committee on 18th April 2012 with IEC No. NIUM/IEC/2011-12/001/Moal/01. After ethical clearance patients were questioned and screened for inclusion and exclusion criteria. Comprehensive information about the study was explained to the participants and written informed consent was taken from all the eligible participants before starting the treatment plan.

Inclusion Criteria

- Clinically diagnosed patients of diabetic neuropathy with type-2 diabetes mellitus.
- Patients having type-2 diabetes mellitus for more than 3 years.
- Patients between 20-60 years of age of either gender.
- Patients on standard antihyperglycemic drugs.
- Patients having kidney and liver function tests within normal limits

Exclusion Criteria

- Physiological status: Pregnancy and lactation.
- Pathological states: cardiovascular, renal and hepatic disorders.
- Patients below 20 and above 60 years of age.
- Complications of diabetes other than diabetic neuropathy.
- Causes of neuropathy other than diabetes

In this study, a total of 120 patients having type-2 diabetes mellitus were assessed for diabetic neuropathy by clinical examination and confirmed by vibration perception threshold. During assessment 43 cases of diabetic neuropathy were diagnosed, 7 patients out of 43 did not fulfil the inclusion criteria and therefore were excluded from the study; remaining 36 patients of diabetic neuropathy were randomly allocated by lottery method into the test (Group A) and control (Group B) respectively, 4 patients from Control group and 2 patients from test group withdrew from the study.15 patients in control group and 15 patients in test group have completed the full course of treatment for a period of 45 days and assessed fortnightly for amelioration or even the progression if any in the signs and symptoms of the disease in both groups. Patients of test group were given Delphinium denudatum (Jadwar) 500mg in tablet form twice daily and local application of Roghan-e-sosan over feet twice daily. The patients of control group were given Strychnos nuxvomica (Azaraqi) 500 mg in tablet form twice daily for a period of 45 days. Before starting the treatment, detailed information about the patient including signs and symptoms were recorded in the case record form. For the assessment of painful diabetic neuropathy, Visual analogue scale (VAS) was the subjective parameter by which pain was assessed. Visual Analogue Scale is one of the most common measures of neuropathic pain in clinical trials is the visual analogue scale (VAS), originally described by Scott and Huskison (6) The VAS is a straight line the ends of which are the extreme limits of the sensation being assessed The VAS has been shown to be a satisfactory method for assessing pain or the relief of pain. The line is normally 10 cm in length and is frequently referred to as the 10 cm VAS. A VAS with descriptive terms placed along the length of the line is known as a verbal descriptor scale. Thus a 10 cm VAS with the terms "mild, moderate, and severe" along the base of the line is known as a 10 cm verbal descriptor scale.

Statistical Methods

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements were presented by Mean SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5 % level of significance. Student's 't' test, two tailed dependent for intragroup comparison, two tailed independent for intergroup comparison was applied and Levene's test was used for the homogeneity of variance. Chi-square and Fisher Exact test was

used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures: + Suggestive significance (P value: 0.05 < P< 0.10);* moderately significant (P value: 0.01< P < 0.05); ** strongly significant (P value: P <.001) were used for the connotation of the significant differences.

RESULTS AND DISCUSSION

Diabetic neuropathy is currently the most common neuropathy in the world, and it is associated with a wide range of clinical manifestations and occurs approximately in 50% of individuals with long standing diabetes mellitus and is characterised by loss of sensation in the extremities, typically in a stocking and glove pattern.(7,8) In our study the prevalence of diabetic neuropathy was 35.83% which is in conformity with the findings reported by Fayaz.A and associates who found diabetic neuropathy in 30- 40% of patients with diabetes mellitus.(9 In our study the incidence of diabetic neuropathy increases with the age and duration of diabetes, which is in consonance with the findings described by Tesfaye S et al reported that increasing age appears to favour the progression of neuropathy in diabetics.(10) When the gender in diabetic neuropathic patients was studied, we found almost equal percentage in both sexes, which is in consonance with the study conducted by Morkrid and associates.(11)(Table 1)

Table 1: Demographic characteristics of participants included in the study

Demographic data	No. of Patients (n=30)	Percentage (%)	
Age group			
	30-40	2	6.67
	41-50	3	10
	51-60	25	83.33
Gender			
	Male	16	53.33
	Female	14	46.67
Marital status	Married	30	100
	Unmarried	0	0

Risk factors like Duration of diabetes, age above 40 years, poor glycaemic control and obesity have also been studied. Out of 30 patients 16 diabetics were found obese and is in accordance with the statement reported by Tesfaye S(10) who reported obesity as a risk factor in the pathogenesis of diabetic neuropathy. Regarding duration of diabetes, The Mean ± SD was 8.40 ± 3.98 in control group and 11.13±5.34 in test group . In our study 28 out of 30 patients were above the age group of 40 years .In our study The Mean ± SD of FBS, PPBS and HbA1C in both groups were significantly higher. (Table2) The above mentioned data is in conformity with the findings described by Shaw JE,Tesfaya S, and Maser RE who reported that duration of diabetes, age above 40 years and poor glycemic control are the potential risk factors for the development of diabetic neuropathy.(12,13,14,15)(Table 2)

Table 2: Risk factors for diabetic neuropathy

Risk factors	Control group(n=15)	Test group(n=15)	P value
Obesity	6(40.0%)	10(66.7%)	0.272
Duration of Diabetes	8.40±3.98	11.13±5.34	0.123
Age above 40 years	14(93.3%)	14(93.3%)	-
FBS	141.33±45.61	176.67±50.17	0.053+
PPBS	223±62.07	270.87±69.88	0.057+
HbA1c	9.73±2.51	9.61±2.08	0.894

The results of our study revealed that both test and control drugs exhibited statistically significant difference in subjective parameter i.e. VAS which showed strongly significant difference (p< 0.001) in intra group comparison in both groups. The intergroup results are not significant (p> 0.05) i.e. efficacy of both groups was similar in improvement. (Table3)

Table 3: Effect of test and control drugs on VAS

VAS	BT	AT	P value
Control group	4.00±1.81	2.20±1.47	<0.001**
Test Group	4.40±1.35	2.53±1.13	<0.001**
P value	0.499	0.492	-

The improvement in VAS is due to Muqavvi aasab (nervine tonic), Musakkin auja (analgesic) and, Muhallil (resolvent) properties possessed by the test drugs (Habbe jadwar and Roghan sosan). These findings are in accordance with the description of Nadkarni KM, Prajapatj ND, Khare CP, Ghani N, Hakjm MA ,Ibne Baitar, Kabeerudin and Razi(16,17,18,19,20,21,22,23) who mentioned that the test drugs possess the above mentioned properties and is effective in relieving neuropathic pain ('wajaul aasab') and protects the nerve function. Besides analgesic and neuroprotective properties, ethanolic extract of Delphinium denudatum is reported for the antioxidative properties and reduces the oxidative stress in the nerves by the regulation of redox signalling and inhibiting the excess reactive oxygen species (ROS)(24)

After completion of duration of treatment all safety markers were found within the normal limits suggesting that it can be safely used at described therapeutic dose. Thus it can be stated that the test drugs are safe and effective in the management of diabetic neuropathy without producing any obnoxious effects, and may delay the complications of diabetic neuropathy like diabetic foot.

Conclusion

Appropriate diagnosis of diabetes mellitus with proper treatment and strict glycaemic control can prevent the onset of diabetic neuropathy and contributes to its effective management. The study revealed that the test drugs appeared to be efficacious in the management of diabetic neuropathy and exhibited significant effects in improvement of neuronal function.

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