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Evaluation of therapeutic efficacy and safety of *Delphinium denudatum wall* (*Jadwar*) in patients with Diabetic Neuropathy: A Randomised single-blind standard controlled study

Zaffar Hussain[1*], Tanzeel Ahmad[1], Ghulamuddin Sofi[2]
1 Dept. of Medicine, National Institute of Unani Medicine, Bangalore 91, India
2 Dept. of Pharmacology, National Institute of Unani Medicine, Bangalore 91, India

ABSTRACT

The present study was conducted to evaluate the efficacy and safety of *Delphinium denudatum* (*Jadwar*) in patients with diabetic neuropathy. A randomised single-blind standard controlled trial was carried out on 30 diagnosed patients of diabetic neuropathy at National Institute of Unani Medicine Bangalore-India. After obtaining ethical clearance, 30 eligible patients were randomly assigned 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 the patients of control group were given *Strychnos nuxvomica (Azaraqi*) 500 mg in tablet form twice daily for a period of 45 days. The objective parameters-Vibration perception threshold (VPT), Toronto clinical neuropathy score (TCNS) and Visual analogue scale (VAS) were 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. Both test and control drugs exhibited statistically significant difference in objective parameters.VPT showed statistically significant difference ($p<0.05$) in intragroup comparison in both groups while as TCNS and VAS showed strongly significant difference ($p<0.001$) in intragroup comparison in both groups. The study revealed that test drug appeared to be efficacious in the management of 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: Diabetic neuropathy; Vibration perception threshold; Toronto clinical neuropathy score; Visual analogue scale; Delphinium denudatum; Strychnos nuxvomica.

*Corresponding Author Email hussainzaffar6@gmail.com
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INTRODUCTION

Diabetes mellitus is an emerging global health problem that involves the general population in an overwhelming manner, and is a physical, psychological, and economic cataclysm to a number of those patients who are afflicted by it. Diabetic neuropathy is the most common and devastating complication of diabetes mellitus, leading to huge morbidity and mortality and resulting in a massive economic burden for diabetes care[1].The prevalence of diabetic neuropathy varies from 10% within 1 year of diagnosis of diabetes to 50% of patients with diabetes for more than 25 years [2]. Duration of diabetes, age, long-term poor glycaemic control (raised HbA_1c), high blood pressure, high triglyceride levels are the various risk factors studied and proved that raises the likelihood of neuropathy[3]. The exact pathogenesis of diabetic neuropathy in spite of current advances remains unclear; however, unanimity is in the fact that neuropathy in diabetes mellitus is a complex disease. Chronic hyperglycaemia is an important factor in the development of diabetic peripheral neuropathy, the diabetic condition produces impaired neurotropism, axonal transport and gene expression through four main pathways viz. Polyol pathway (Sorbitol pathway), Advanced glycation end products (AGE'S), Protein Kinase C Pathway (PKC pathway) and Hexosamine pathway[4,5,6,7,8]. The most common presentation of diabetic peripheral neuropathy is diabetic peripheral neuropathic pain (DPNP), which typically manifests as burning, shooting pain in the feet or lower limbs. Symptoms related with large fibre damage include weakness, numbness, burning or tingling, and loss of balance, while those related with small fibre damage include pain, anaesthesia to pin and temperature sensation, and autonomic dysfunction[9,10,11]. Clinical diagnosis of diabetic neuropathy is established on the basis of good clinical history, complete physical and neurological examination, includes certain diagnostic tests like Vibration perception threshold, Monofilament test, Electromyography (EMG) and Nerve conduction studies, (NCS) [12, 13, 14]. Foot wounds are now the most common diabetes related cause of hospitalisation and are a frequent precursor to amputation[15,16]. Strict glycaemic control is perhaps the single greatest preventive measure of diabetic neuropathy[17]. Contemporary treatment options are not specific for the primary cause of nerve damage and are intended often only at partially palliate the symptoms due to major adverse effects. *Delphinium denudatum (Jadwar)* is a potent drug of central nervous system in Unani system of medicine which has been reported to be useful in neuralgia, paralysis, Bell's palsy, epilepsy etc. It is endued with properties like *Muqavvi aasab* (nervine tonic), *Musakkin auja* (analgesic) and *Muhallil* (resolvent) [18,19,20,21]. Besides analgesic and neuroprotective properties, ethanolic extract of

Delphinium denudatum, possess the antioxidative properties, reduces the oxidative stress in the nerves by the regulation of redox signalling and inhibiting the excess reactive oxygen species (ROS) [22]. In view of the endorsed effects of *Delphinium denudatum* and relevant reports of neuroprotective activity, present study was carried out to evaluate the efficacy of *Delphinium denudatum* in the management of diabetic neuropathy.

MATERIALS AND METHODS

A randomised single blind, standard controlled study was carried out at NIUM hospital over a period of 8 months from March 2013-October 2013.The study was approved 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. Detailed information about the study was explained to the participants and written informed consent was taken from all the eligible participants before starting the treatment schedule.

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 antidiabetic treatment.
- Patients having kidney function test, liver function test within normal limits.

Exclusion Criteria

- Physiological status: Pregnancy and lactation.
- Pathological states: cardiovascular, renal and hepatic diseases.
- 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 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 diabetic neuropathy, Vibration perception threshold (VPT), Toronto clinical neuropathy scores (TCNS) and Visual analogue scale (VAS) were the three objective parameters that were assessed. VPT was evaluated with the biothesiometer (Vibrosense). The biothesiometer is essentially a glorified tuning fork and can be used for assessment of vibration in a graded manner using the dial upto a maximum of 50mV.When the neuropathy is mild, the reading is more than 15mV, more than 25mV when it is moderate and more than 40mV when the neuropathy is severe. Measurements were recorded at the plantar aspect of both right and left foot at 6 points i.e. Great toe, 1st metatarsal, 3rd metatarsal, 5th metatarsal, Instep and heel. In Toronto clinical neuropathy scoring system the grading of neuropathy was determined on the basis of symptoms (Pain, numbness, burning or tingling, weakness, ataxia and upper limb symptoms) reflexes (Ankle and Knee) and sensory scores (Pin prick, Temperature, Light touch, Vibration sense and position sense) The responses were graded as: 0-5 (No Neuropathy), 6-9 (Mild Neuropathy), 10-14 (Moderate Neuropathy), and 15-19 (Severe Neuropathy). Pain was assessed by VAS and is a subjective measure of pain (0, no pain; 10, worst possible pain). For safety evaluation Hb, TLC, DLC, ESR, LFT, KFT, FBS, PPBS, HbA_1c and ECG were carried out at baseline and at the end of the treatment.

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: $0.01 < P \leq 0.05$); ** strongly significant (P value: $P \leq 0.001$) were used for the connotation of the significant differences.

Statistical software

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate tables**.**

RESULTS AND DISCUSSION

Diabetic neuropathy is the most common neuropathic syndrome seen in patients with diabetes 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[23,24] The patient with the insensate foot is blissfully unaware of the trauma of the bare foot walking and hence wounds occur in the sole. More than half of all foot ulcers (wounds) will become infected requiring hospitalisation and are a frequent precursor to amputation. Individuals with diabetes have 30-fold higher life time risk of undergoing lower extremity amputation compared with those without diabetes.[25] In our study the prevalence of diabetic neuropathy was 35.83% which is in conformity with the findings reported by F. Liu and associates who found diabetic neuropathy in 32% of patients with diabetes mellitus.[26] (Table 1)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 Arumugam Sarasa Bharathi and Martin who reported that increasing age appears to favour progression of neuropathy and estimated neuropathy in 85% of diabetics over the age of 40 years.[27] When the gender in diabetic neuropathic patients was studied, we found almost equal proportion in both sexes, which is in consonance with the study conducted by Morkrid and associates.[28]

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
SES	**I**	2	6.67
	II	3	10
	III	19	63.33
	IV	4	13.33
	V	2	6.67
Diet	**Vegetarian**	12	40
	Mixed	18	60
Marital status	**Married**	30	100
	Unmarried	0	0

Risk factors like obesity, duration of diabetes, age above 40 years and poor glycaemic control

have also been studied. Out of 30 patients 16 diabetics were found obese and is in accordance with the statement reported by Zeigler D and Vincent AM[29, 30] 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 (Table 2). The data obtained is in conformity with the findings described by Boulton AJ[31] who reported that duration of illness is an important risk factor for the development of diabetic neuropathy. In our study 28 out of 30 patients were above the age group of 40 years which is in conformity with the findings described by Arumugam Sarasa Bharathi and Martin[27] who reported that increasing age appears to favour development of neuropathy. In our study The Mean ± SD of FBS, PPBS and HbA_1C in both groups were significantly higher as shown in Table 2 which corresponds to the study of Booya *et al*[32] who reported that poor glycaemic control is a potential risk factor for the development of diabetic neuropathy.

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+
HbA_1c	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 objective parameters.VPT showed statistically significant difference ($p< 0.05$) in intra group comparison in both groups while as TCNS and VAS 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. VPT was measured in both groups and assessed before and after treatment. It was evident from statistical analysis that in test group there were 6 moderately significant points ($p < 0.05$), 5 suggestive significant points ($p\ 0.05< p < 0.10$), and 1 strongly significant point ($p < 0.001$) in right and left foot respectively in intragroup comparison. (Table 3). In control group, there were 6 suggestive significant points ($p\ 0.05< p< 0.10$), and 3 moderately significant points ($p< 0.05$) in right and left foot respectively in intragroup comparison.

Table 3: Effect of test and control drugs on VPT

Site	Right Side			Left Side		
	BT	AT	P value	BT	AT	P value
Great TOE						

Control	27.53±14.97	22.8±11.8	0.052+	29.87±14.02	24.47±11.03	0.082+
Test	30.07±13.92	22.07±12.66	0.016*	32.93±11.23	27.07±11.7	0.032*
P value	0.635	0.871	-	0.514	0.536	-
1st MT						
Control	29.2±14.3	25.53±13.28	0.132	30.4±14.0	24.6±11.12	0.079+
Test	29.07±12.4	23.73±12.6	0.097+	31.4±9.63	26.47±11.47	0.041*
P value	0.978	0.706	-	0.821	0.654	
3rd MT						
Control	30±13.86	25.6±12.16	0.075+	31.8±14.24	24.8±11.1	0.036*
Test	31.47±14.23	25.4±13.45	0.011*	32.33±11.56	24.47±8.79	0.001**
P value	0.777	0.966	-	0.911	0.928	-
5th MT						
Control	30.07±13.89	25.8±12.17	0.080+	32.2±14.54	25.13±11.05	0.048*
Test	31.47±14.64	26.73±15.41	0.060+	33.33±12.67	27±11.28	0.011*
P value	0.790	0.855	-	0.822	0.651	-
Instep						
Control	30.80±13.95	26.67±12.5	0.075+	33.13±14.07	28.87±13.45	0.181
Test	30.87±12.83	24.80±11.12	0.017*	32.4±11.74	27.93±12.56	0.086+
P value	0.989	0.669	-	0.878	0.846	-
Heel						
Control	36.20±14.87	28.40±12.48	0.013*	35.13±13.99	29.87±13.47	0.127
Test	33.93±14.59	28.13±12.77	0.059+	33.27±11.51	28.73±13.17	0.055+
P value	0.677	0.954	-	0.693	0.817	-

Toranto clinical neuropathy score (TCNS) was used to assess the degree of neuropathy and is based on symptoms, reflexes and sensory scores. When before and after treatment values of TCNS in control and test group were statistically analysed, the p value was strongly significant ($p< 0.001$) in intragroup comparison in both groups.(Table4)

Table 4: Effect of test and control drugs on TCNS

TCNS Score	0 day	15th day	30th day	45th day	P value at 45th day
Control group	13.33±3.06	12.2±3.32	10.67±2.66	9.13±2.67	<0.001**
Test group	13.33±2.85	12.53±2.85	10.87±2.64	9.33±2.19	<0.001**
P value	1.000	0.770	0.838	0.824	-

Pain was assessed by Visual analogue scale (VAS). When before and after treatment values of VAS in control and test group were statistically analysed, the p value was strongly significant ($p< 0.001$) in intragroup comparison in both groups. (Table5).

Table 5: 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 objective parameters is due to *Muqavvi aasab* (nervine tonic), *Musakkin auja* (analgesic) and, *Muhallil* (resolvent) properties possessed by the test drug. These findings are in accordance with the description of Nadkarni KM, Prajapatj ND, Khare CP, Ghani N, Hakjm MA Ibne Baitar and Kabeerudin[18,19,20,21,33,34,35] who mentioned that the test drug 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)[22] Thus we can state that the scientific studies and reported properties of test drug are in confirmation to a large extent with our hypothesis that we drew out for present study. To determine the adverse effects of test drug, safety parameters like Hb, TLC, DLC, ESR, LFT, KFT, FBS, PPBS, HbA_1c and ECG were carried out at baseline and at the end of the treatment. (Table 6).

Table 6: Safety profile

Safety parameters	Group	BT(n=15)	AT(n=15)	P value
Hb%	Control	12.35±1.31	12.91±1.23	0.110
	Test	13.05±1.47	12.89±1.49	0.651
	P value	0.179	0.968	-
TLC	Control	6253.93±1452.59	6340±1628.23	0.895
	Test	7080±2269.58	7210.71±1250.57	0.918
	P value	0.245	0.120	-
Polymorphs	Control	61.6±6.19	61.67±7.27	0.979
	Test	65.07±7.29	60.8±4.66	0.102
	P value	0.171	0.700	-
Lymphocytes	Control	35.2±5.85	34.8±7.08	0.886
	Test	30.93±6.49	35.27±4.76	0.072
	P value	0.069	0.834	-
Eosinophills	Control	2.2±1.08	2.53±1.55	0.527
	Test	2.6±1.59	2.73±1.49	0.830
	P value	0.428	0.721	-
Monocytes	Control	1±1	1.2±1.32	0.607
	Test	1.13±1.25	1.2±1.26	0.896
	P value	0.749	1.000	-
Basophills	Control	0.33±0.72	0.2±0.41	0.546
	Test	0.27±0.59	0±0	0.104
	P value	0.785	0.072+	-
ESR	Control	15.13±6.38	17.93±6.33	<0.001

	Test	22.67±10	20.2±9.82	0.203
	P value	0.020*	0.459	-
FBS	Control	141.33±45.61	152.4±46.21	0.167
	Test	176.67±50.17	177.87±49.18	0.807
	P value	0.053+	0.155	-
PPBS	Control	223±62.07	239.13±52.45	0.192
	Test	270.87±69.88	270.8±65.47	0.996
	P value	0.057+	0.155	-
HbA_1c	Control	9.73±2.51	9.43±2.38	0.532
	Test	9.61±2.08	10.31±1.83	0.018
	P value	0.894	0.262	-
SGOT	Control	23.93±11.66	21.27±7.81	0.260
	Test	23.2±13.5	25.47±15.28	0.108
	P value	0.875	0.351	-
SGPT	Control	23.47±9.49	19.93±7.59	0.151
	Test	20.4±8.89	21.2±9.58	0.696
	P value	0.369	0.691	-
ALP	Control	128.07±19.48	120.4±19.04	0.144
	Test	136.2±34.31	121.53±16.67	0.099
	P value	0.431	0.864	-
Total Bilirubin	Control	0.7±0.2	0.67±0.19	0.327
	Test	0.67±0.14	0.71±0.15	0.463
	P value	0.589	0.535	-
Serum Urea	Control	30.93±4.67	30.2±6.64	0.638
	Test	29.27±8	29.47±6.22	0.929
	P value	0.492	0.757	-
Serum Creatinine	Control	0.94±0.08	0.94±0.08	1.000
	Test	0.91±0.22	0.89±0.19	0.546
	P value	0.580	0.400	-
ECG	Control	0	0	-
	Test	0	0	-
	P value	-	-	-

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 drug is 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. The limitations inherent in this study includes, small sample size, short duration of study, single-blind trial, and non inclusion of objective parameters like Monofilament test, Nerve conduction velocity (NCV), and Electromyography (EMG). Hence further studies are imperative with modified methodology to overcome these limitations for wider reliability and acceptability.

CONCLUSION

Timely diagnosis of diabetes mellitus with appropriate treatment and strict glycaemic control can avert the onset of diabetic neuropathy and contributes to its successful management. The study revealed that the test drug appeared to be efficacious in the management of diabetic neuropathy and exhibited significant effects in improvement of neuronal function. No adverse effects or toxicity has been reported during or after the trial. Thus, it can be concluded that the test drug is safe and effective in the management of diabetic neuropathy. Furthermore, the medical community should intensify the research into the dynamic and multifaceted disease in order to provide a basis for the development of biologically active therapies.

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