Original Article

A Randomized, Double-Blind, Placebo-Controlled Study On Evaluation Of Safety And Efficacy Of Niruryadi Gulika Ayurvadic Therapy In Type Ii Diabetic Neuropathy Patients

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Abstract

Objective: To assess the safety and efficacy of Niruryadi Gulika ayurvadic therapy in Type II diabetic neuropathy patients

Methods: The study was a randomized, double-blind, placebo-controlled study that enrolled 40 patients were enrolled with diabetic neuropathy. The 40 patients were randomly assigned into two groups after obtaining written informed consent. The medication and placebo was provided with a sip of water orally to the patient. Patients participating in the Niruryadi Gulika group receiving 500 mg of Niruryadi Gulika twice daily and similar capsules were given to those in the placebo group.

Results: In total 102 patients were enrolled and randomized to receive Niruryadi Gulika ayurvadic therapy (n=80), Placebo (n=80) where treatment group showed significant reduction in $HbA_{1c,}$ FBS and PPBS. There was a significant reduction in FBS (p=0.001) and HbA1c levels (p0.001) in the treatment group compared to the placebo group. In addition, after the administration of Niruryadi gulika (poly-herbal formulation), changes in FBS and HbA1c levels remained significant. Furthermore, PPBS levels had more reduction in the Niruryadi gulika (poly-herbal formulation), group compared to the placebo group; however, its changes were not significant.

Conclusions: In this study Niruryadi Gulika ayurvadic therapy was showed more safe and effectiveness in the management of diabetic neuropathy.

Keywords: Diabetic neuropathy, Niruryadi Gulika, HBA1C, Type II diabetes, blood sugar levels.

INTRODUCTION:

Diabetic neuropathy is the chronic complication of diabetes mellitus and affects the various parts of the nervous system that represents several clinical manifestations in diabetic patients. Diabetic neuropathy is a common clinical disorder and affects the function of peripheral nerve dysfunction. In India, the diabetes mellitus prevalence is high (4.3%) as compared to other western countries (1%–2%). The Asian Indian population has a risk of insulin resistance which causes the advancement of future diabetic complications[1-5]. Diabetic neuropathy has been associated with multifactorial pathogenesis with different biochemical mechanisms include an increase in oxidative stress, neuro-inflammation, and hypoxia advance the risk of diabetic neuropathy.

The south Indian diabetic population incidence was 19.1%. Diabetes mellitus is one of the causative factors for developing peripheral neuropathy. Previous research studies demonstrated that two-thirds of diabetic patients have neuropathy. The diagnosis of diabetic neuropathy obligates electro diagnostic testing, quantitative sensory and autonomic testing[6-11].

The diabetes mellitus duration amplifies the development of diabetic neuropathy. Distal symmetrical polyneuropathy is a clinical symptom and impaired sensory, motor fibers increase the risk of neuropathy pain in diabetic patients.

Diabetic neuropathy is classified into large fiber and small fiber neuropathy. Large fibers neuropathy is painless paresthesia with impairment of vibration, and loss of ankle reflex. Large fiber neuropathy reduces the nerve conduction, poor quality of life and daily activities of the individual patients. Small fiber neuropathy is associated with burning, pain; altered temperature sensations at the damaged nerve area are associated with autonomic neuropathy. The diabetic neuropathy pain sometimes severe and intolerable and typically it worsens the individual patients at night time with burning pain, shooting, aching, sharp, cramping, and tingling. Few patients often develop small fiber neuropathy represented with pain and paresthesia early in the course of diabetes mellitus is linked with insulin treatment which is called insulin neuritis.

Chronic painful diabetic neuropathy occurs more than six months. These patients may develop tolerance to drugs and even get addicted. Neuropathy develops before the diagnosis of diabetes mellitus which is known as "impaired glucose tolerance neuropathy". For patients who newly diagnosed with diabetes, intermittent pain in distal lower limbs increases the risk of hyperglycemic neuropathy. The uncontrolled neuropathy pain renders the risk of foot injuries, ulcers, and foot destruction. Diabetic autonomic neuropathy affects the function of vital organs present in the body and results in the development of gastrointestinal, cardiovascular, urinary, and metabolic diseases[12-16]. Autonomic nerve involvement occurs after the detection of diabetes mellitus. The weakening of pelvifemoral muscles occurs in people above 50 years of age.

The weakness of the pelvis femoral muscles occurs abruptly in a stepwise manner in people above 50 years of age. The clinical symptoms of asymmetrical proximal diabetic neuropathy include pain in the low back, hip, anterior thigh. Diabetic tracheal neuropathy is associated with pain in the T4–T12 distribution in the chest or abdominal distribution. The bulging of the abdominal wall occurs with muscle weakness. The clinical diagnosis of diabetic neuropathy can be done by assessment of sensations of a pinprick, joint position, and vibration test done by tuning fork. The sensory examination should be performed on hands and feet bilaterally to check the condition of neuropathy pain. The American Academy of Neurology recommended that diabetic neuropathy is diagnosed in the presence of autonomic neuropathy.

Diabetic neuropathy can be diagnosed with careful examination of clinical symptoms of patients, electrodiagnostic tests, sensory, and autonomic testing can necessary to identify the neuropathy severity among diabetic patients. Hyperglycaemia increases the endothelial vascular resistance and lowers the blood flow and depletes nerve myoinositol levels which activates the polyol pathway in the nerve through enzyme aldose reductase creates the deposition of sorbitol and fructose in the nerves leads to glycosylation of structural nerve proteins. The activation of protein kinase C causes the damage of nerve fibers and modifies axonal transport. The effective measurement of glucose, sorbitol, and fructose levels in the nerves shows the severity of neuropathy. The hypoxia is produced by more vascular resistance and low blood flow levels in the nerve damages the capillary and lowers Na-K ATPase activity impair the nerve conduction properties. The development of neuropathy has been linked with several risk factors such as raised serum triglyceride, body mass index, smoking, diabetes mellitus, and hypertension[17-18]. The tramadol, dextromethorphan, and antidepressants medications have been used for the treatment of neuropathy pain. Henceforth, the aim of the study includes evaluating the effectiveness of Niruryadi Gulika ayurvedic therapy in Type II diabetic patients.

METHODOLOGY:

Study Population:

This study was conducted in the Ayurveda outpatient department of SRM Medical College Hospital and Research Centre from August 2020 to February 2021. About 80 patients of both sexes were recruited for the study. The patient's age range of 40 to 65 years with a past medical history of Type II diabetics with complications of clinical or electrophysiological signs of peripheral neuropathy, and HbA1c < 10% patients were selected under inclusion criteria and Patients who are older than 65 years, and younger than 18 years of age patients, previous history of hypersensitivity reactions, patients with a history of impaired liver and kidney function, pregnant or lactating females, subjects receiving of ALA, vitamin E, vitamin C or use of vitamin C tablets within the last 3-months, chronic alcoholic and patients with neuropathy due to other any known cause were all excluded from the study. Patients likewise were barred on the off chance that they burned-through under 90% of their enhancements or in the event that they rolled out any improvement in their eating routine or way of life and type or portion of their hypoglycemic medications during the intervention.

Study design:

This is a placebo-controlled, double-blind, randomised, parallel clinical trial that used intervention and placebo groups. Participants were allocated randomly into two groups by permuted-block randomization method including Niruryadi gulika (poly-herbal formulation) and placebo groups. The institutional human ethics committee approval for the trial protocol was formally obtained from the SRM Medical College Hospital and Research Centre, SRMIST Board of Ethics (Grant No: 876/IEC/2015). This trial was conducted according to the tenets laid down in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to study entry. The participants were free to withdraw from the study at any time without compromising their relationship with their health care provider.

STUDY ASSESSMENT:

Intervention drug:

Niruryadi Gulika is an ancient ayurvedic medicine used in treating diabetes and its complications. From reviewing the literature, individual herbal extract present in the herbal medicine is showing the beneficial effect on diabetes and its complications A random allocation sequence was generated and the participants were allocated by permuted-block randomization to two intervention arms using the computer-generated allocation table to receive either Niruryadi Gulika (n = 40) or placebo (n = 40) for 90 days. Participants were allocated sequentially numbered and airtight identical containers consisting of identical capsules and were advised to take two capsules of either Niruryadi Gulika or placebo per day (500 mg × 1) after breakfast and (500 mg × 1) after dinner on visit 1 (day 0) and visit 2 (day 90) for three months after visit 1 (day 0). The socio-economic variables (age, marital status, residence, education and occupation) have been identified. The details of side effects or pain were investigated weekly by daily telephone and short message services. The study data was collected on a 1-12-week basis from subjects documented at each visit on the physician treatment note. The participants were asked to report to the principal investigator after an adverse event and were subsequently removed from the trial. The enrolled patients were subject to nerve conduction velocity neuropathy monitoring.

Participants underwent general and systemic evaluations at each follow-up visit and diabetic parameters were noted at baseline and after 180 days. The end of the research tested the tolerability of Niruryadi gulika and a placebo was noted. Blinding was opened after completion of the study period to know which group was placebo and which group was receiving Niruryadi Gulika. Niruryadi Gulika contains powders of:

NiruriMoola	:*Sterculiafoetida*	Sita	: Sugar
Vairi	: *Salaciareticulata*	Udumbara	: *Ficusracemosa*
Kataka	: *Strychnospotatorum*	Kapitha	: *Feroniaelephantum*
Chincha	:*Tamarindusindicus*	Kumuda	: *Nelumbonucifera*
Abhaya	: *Terminaliachebula*	Nisa	:*Curcuma longa*
Amalaki	: *Emblicaofficinalis*	Darvi	: *Berberisaristata*
Vibhitaki	: *Terminaliabellirica*	Usira	: *Vetiveriazizanioides*
Kantakari	:*Solanumxanthocarpum*	Gairika	: Purified Red ochre

Nerve conduction velocity:

Assurance of nerve conduction velocity (NCV) is not simply the most sensitive test for diabetes, but offers a few features, such as repeatability. It is also everything but a specific neurological exam. Standard surface invigoration and recording techniques have been used to assess nerve lead velocity. Electric-conductive gel was covered in cathodes and kept with sticky tape. In both top and bottom annexes reciprocally, the speed of nerve conduction (m/s) was assessed. The nerves Middle, Ulnar, Common Peroneal, Posterior Tibial and Median and Sural nerves were used for the motor nerve conduction research.

Blood sampling and biochemical assay:

Abstained venous blood tests were taken at the gauge and following two months of intercession. Blood testing was separated to get serum at −80°C and removed at 3000 rpm for 10 minutes at 4°C, until the biochemical assays were finished. The auto-analyzer (ERBA) instrument using the business packages was calculated at Faster Blood Sugar (FBS) and Blood Sugar after 2 hours (Bs2hp) (Pars Azmoon, Iran). High-performance Liquid Chromatography (HPLC) estimates of glycised haemoglobin (HbA1c) (Advance logical instrument, Germany).

STATISTICAL ANALYSIS:

All data were presented as the mean and standard deviation. For independent samples, the Mann-Whitney U test is conducted. A P-value less than 0.05 is considered to be statistically significant. Nonparametric method tests include spearman's rank correlation coefficient was used to evaluate the associations between the electrophysiological data and the clinical variables of the patients. SPSS version v27 was used for statistical analysis.

RESULTS:

Patient Disposition:

Patient disposition is shown in fig.1.of the 102 Screened patients, after Screening of the patients, 22 patients were excluded from the study and 14 patients were not meeting the inclusion criteria during the study and 8 patients declined to complete the study due to personal reasons. Due to personal reasons, two patients in the intervention group were unable to finish the research. Meanwhile, three individuals in the placebo group were removed from the trial because they had moved to another city and were unable to complete the study. The Niruryadi Gulika group had a mean capsule consumption of 99 percent, whereas the placebo group had a mean capsule intake of 99.1 percent. The ITT technique was used to examine 80 participants.

Patient demographics:
Table 1 illustrates the patient demographics and baseline evaluations by therapy group. The majority of patients were male, with a proportion ranging from 66.6 percent in the placebo group to 58.33 percent in the therapy group. All of the patients were type 2 diabetics with duration of at least of 12.5 years with diabetic neuropathy for 4.2 years.

Efficacy:
When compared to the placebo group, the therapy group had significantly lower FBS (p=0.001) and HbA1c levels (p0.001). Furthermore, changes in FBS and HbA1c levels remained substantial following administration of Niruryadi gulika (poly-herbal formulation). Furthermore, when comparing the Niruryadi gulika (poly-herbal formulation) group to the placebo group, PPBS levels were lower in the Niruryadi gulika (poly-herbal formulation) group, although the differences were statistically not significant Table.2.

Table 3 shows the degree of polyneuropathy in diabetic individuals at baseline and after 12 weeks. When compared to the placebo group, there was a significant drop in NCV (nerve conduction velocity) in the Median wrist elbow (MWE) (p=0.001), Ulnar wrist elbow (UWE) (p0.001), CPN ankle head of fibula (p0.001), and ptn (p0.001). Furthermore, alterations in MWE, UWE, CPN, and PTN remained significant following administration of Niruryadi gulika (poly-herbal formulation). Furthermore, as compared to the placebo group, UWE and PTN had higher reduction in the Niruryadi gulika (poly-herbal formulation) group; nevertheless, the differences were not significant.

Co-relation Analysis:
We performed multiple linear regression analyses to confirm the association of NCV parameters with FBS, PPBS and HBA1C.As shown in Fig. 2, FBS had a no significant correlation with NCV (Median wrist elbow, r = 0.2710, p = 0.2002) (Ulnar wrist elbow, r = 0.4551, p = 0.0255); (CPN ankel heald of fibula r = -0.2111, p = 0.3221); (Ankel pop fossa r = -0.3759, p = 00702),. PPBS had a tendency toward a positive correlation with NCV, but this effect was not significant (Median wrist elbow, r = 0.05789, p = 0.7882) (Ulnar wrist elbow, r = 0.241, p = 0.2560); (CPN ankel heald of fibula r = -0.2725, p = 0.1977); (Ankel pop fossa r = -0.09910, p = 0.6450),. HBA1c had a significantly negative correlation with NCV but this effect was not significant (Median wrist elbow, r = -0.0031, p = 0.9882) (Ulnar wrist elbow, r = -0.08388, p = 0.6968); (CPN ankel heald of fibula r = -0.3161, p = 0.1324); (Ankel pop fossa r = -0.1359, p = 0.5266).

Safety:
The reported side effects were 3-4 cases with hypoglycemia and diarrhoea in the first few days of study. Niruryadi gulika was safe and well-tolerated in this study.

DISCUSSION:
Our findings showed that treating T2DM patients with Niruryadi gulika (poly-herbal formulation) improved the patient health and decreased the severity of DSPN. Furthermore, we determined that Niruryadi gulika (poly-herbal formulation) had a significant effect on FBS, PPBS, and HbA1c levels.

Medical treatments for diabetic peripheral neuropathy typically seek to improve the patient's clinical state by lowering blood glucose levels, improving nerve conduction velocity, and improving the patient's quality of life. Niruryadi Gulika is useful in the treatment of type 2 diabetes and diabetic peripheral neuropathy. The traditional ayurvedic medication Niruryadi Gulika is used to treat diabetes and its complications.

The maximum drug in Niruryadi Gulika has a Kashaya, Tikta, and Madhur Ras; Laghu, Rukshya, and Guru guna; Sheeta Virya; Madhur, and Katu Vipaka. Dravyam gunen paken prabhaven cha kinchan || Ch.Su. 26/71 || Charak Kinchidrasena kurute karma viryane chaparam The medication operates in the body in a variety of ways, according to the statement above.

The Niruryadi gulika group showed a significant reduction in the severity of DSPN, HBA1C, and PPBS. According to S. Krishna Rao, the main components of Niruryadi gulika, Chincha and Amalaki, have been shown to be beneficial in the treatment of sensory and motor symptoms of DPN[19].

Another component of Niruryadi gulika Nisa (Curcuma longa) has antioxidant properties, including inhibiting free radical production or elimination, as well as activating antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Curcumin, according to Sara Asadi, suppresses the production of pro-inflammatory cytokines such as TNF- and Interleukin-1 (IL-1) as well as NO generation. Curcumin's antioxidant and anti-inflammatory properties may help treat diabetes and associated complications, such as neuropathy. Curcumin inhibits NF-KB, which enhances insulin action and lowers insulin resistance and blood glucose[20].

In another animal study, Kapittha is another (ingredient of Niruryadi gulika)fruit indicated in Diabetes. For 30 days, alloxan-induced hyperglycemic male Wistar rats were given the aqueous fruit extract of F.elephantum in 500 mg/kg p.o. The Kit technique was used to estimate blood glucose on the 31st day. In hyperglycemic rats, the aqueous fruit extract of F. elephantum Correa. had a significant hypoglycemic effect[21].

Salacia reticulate (family *Celastraceae*, known in Sanskrit as *Vairi or Pitika)* inhibited alpha-glucosidase enzymes in a similar way. Administration of 200 mg p.o. SRE 5 minutes before sucrose loading (50 g) substantially reduced postprandial hyperglycemia in human volunteers in a sucrose tolerance test. Human volunteers with moderate Type II diabetes participated in double-blind placebo-controlled studies, which yielded good outcomes[22].

There are several strengths to this study. First, to our knowledge, this is the first research to look into the effects of Niruryadi gulika (poly-herbal formulation) on DSPN patients. Second, we employed NCV, which has been used to classify the degree of neuropathy and depicts clinical changes as diabetic neuropathy progresses.

CONCLUSION:

The study concludes that the treatment group have is a substantial effect on neuropathic pain management as compared to the placebo group. Prompt identification of diabetic neuropathy causative factors and regular follow-up of diabetic patients could reduce the reoccurrence of diabetic complications. Proper understanding of therapeutic effectiveness of placebo and treatment group responses will direct the beneficial use of medications to avoid the further prescribing of unnecessary medications to the patients which will ultimately lower the neuropathy pain.

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Table: 1 Patient Baseline Demographic Characteristics.

PARAMETERS	PLACEBO Mean ±SD or (N %) (N=40)	Treatment Mean S.D or (N %) (N=40)
Age (yrs.)	59.62±8.9	61.6±7.5
Gender		
Male	26 (66.6%)	23.3(58.33%)
Female	13(33.33%)	16.6(41.6%)
Height (ft.)	166.2±8.4	167.91±6.17
Weight (kg)	65.04±7.5	69.83±8.88
BMI	23.5±3.49	24.49±2.45
Systolic blood pressure	123.04±11.07	125.41±9.82
Diastolic blood pressure	77.41±6.07	76.33±7.38
HBA1C	9.29±1.51	9.54±1.44
F.B.S (g/dl)	191.04±6.53	185.25±3.67
P.P.B.S (g/dl)	296.87±38.01	282.58±36.45
Anti-Diabetic medications	38(95%)	34(85%)
Duration of Diabetes(months)	120 (96)	144(84)
Duration of Diabetic Nephropathy(months)	12 (19)	24 (24)

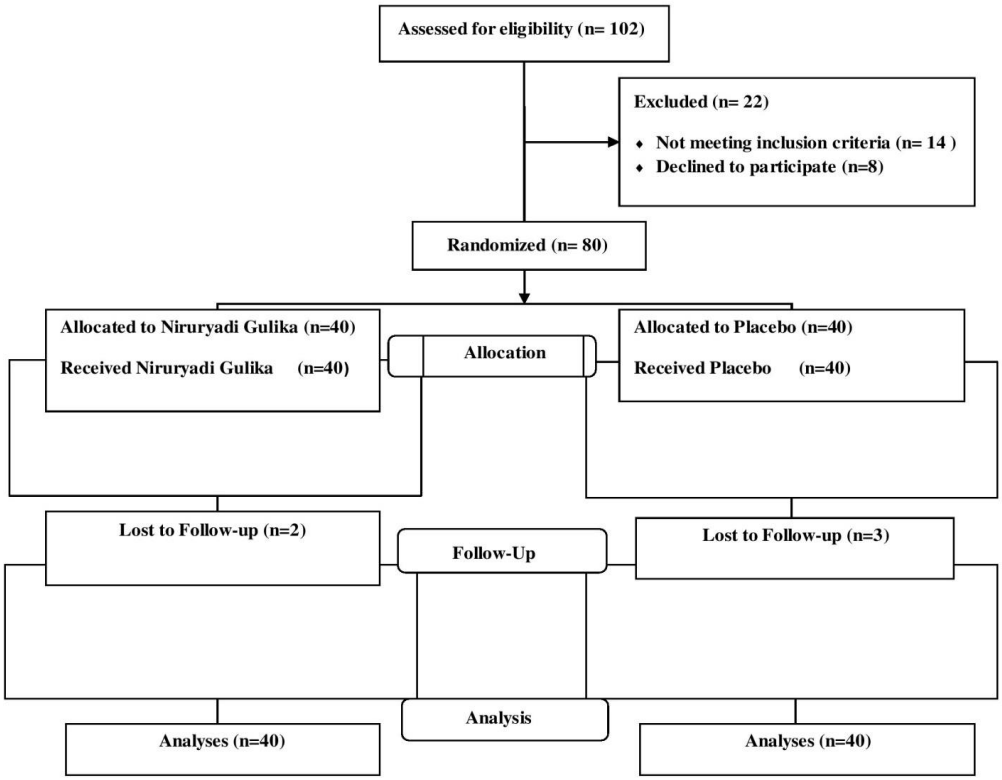
Table: 2 Glycemic indices of diabetic patients at baseline and after 12 weeks of Intervention

Variable	Group	Baseline	Follow up	Mean change S.D	p. value
F.B.S(mg/dl)	Placebo	191.04	188.75	-2.29	0.053
	Treatment	187.91	185.25	-2.66	0.001
P.P.B.S(mg/dl)	Placebo	296.87	279.12	-17.75	0.051
	Treatment	282.58	263.00	-19.58	0.001
HBA1C	Placebo	9.29	8.54	-0.75	0.056
	Treatment	9.54	7.83	-1.71	0.001

Table: 3 Baseline and 12 weeks changes in the Nerve conduction velocity of poly neuropathy Diabetic patients

Variable	Group	Baseline	Follow up	Mean change S.D	p. value
Median wrist-lbow(m/sec)	Placebo	54.79	52.79	-2.00	0.184
	Treatment	52.00	50.16	-1.84	0.001
Ulnar wrist-elbow (m/sec)	Placebo	52.54	54.20	1.66	0.264
	Treatment	50.16	47.83	-2.33	0.001
CPN ankle-head of fibula m/sec	Placebo	46.83	48.08	1.25	0.181
	Treatment	48.37	46.45	-1.92	0.001
Ankle (ptn) -pop fossa m/sec	Placebo	44.00	45.16	1.16	0.102
	Treatment	51.33	46.95	-4.38	0.001

Figure:1 Flow chart of the trail.


Assessed for eligibility (n= 102)
Excluded (n= 22)
Not meeting inclusion criteria (n= 14)
Declined to participate (n=8)
Randomized (n= 80)
Allocated to Niruryadi Gulika (n=40)
Received Niruryadi Gulika (n=40)
Allocation
Allocated to Placebo (n=40)
Received Placebo (n=40)
Lost to Follow-up (n=2)
Follow-Up
Lost to Follow-up (n=3)
Analysis
Analyses (n=40)
Analyses (n=40)

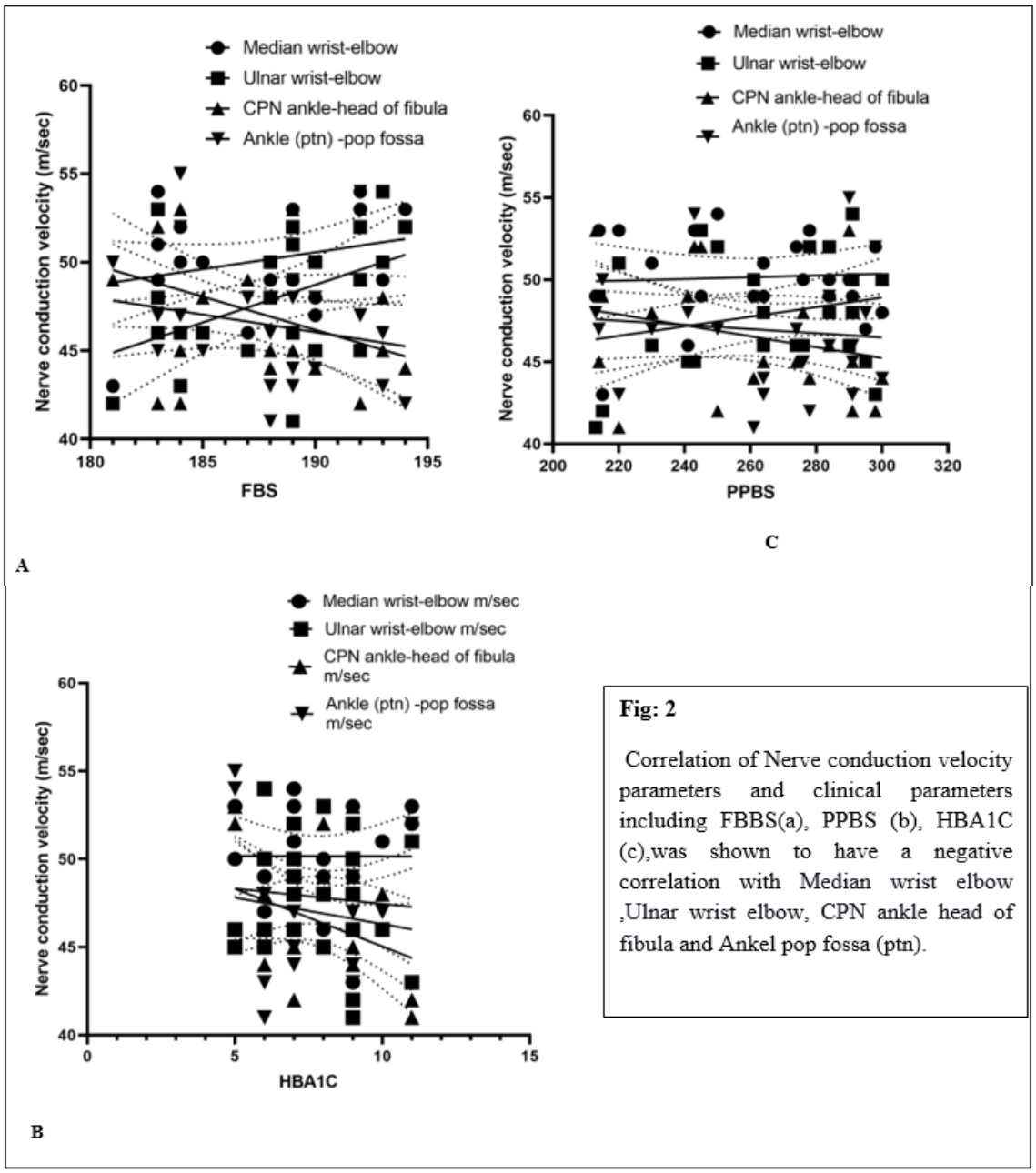


Fig: 2

Correlation of Nerve conduction velocity parameters and clinical parameters including FBBS(a), PPBS (b), HBA1C (c),was shown to have a negative correlation with Median wrist elbow ,Ulnar wrist elbow, CPN ankle head of fibula and Ankel pop fossa (ptn).