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PROTOCOL STUDY

A Study Protocol on the Evaluation of Comparative Efficacy of Waj (Acorus calamus Linn.) versus Pregabalin in Diabetic Peripheral Neuropathy

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ABSTRACT

Background: Diabetes is a major global health concern in the twenty-first century. The International Diabetes Federation (IDF) estimates that by the end of 2021, complications from diabetes would have killed 747,000 peoples in India. Diabetic peripheral neuropathy (DPN) is a disorder that develops in patients with diabetes (type 1 and type 2) and is not attributable to any other peripheral neuropathy causes. Clinically, it may manifest as burning, tingling, numbness, or neuropathic pain in the foot that tends to get worse at night. DPN frequently results in ulceration, infection, deterioration of the skin, and ultimately amputation. **Methods:** This study will be conducted as randomized standard-controlled, single-blind trial on 150 DPN subjects with type 2 diabetes by randomly assigned them to two groups (test or standard), where test group will receive two capsules twice (containing 500 mg powder of test drug in each capsule) with water and control group will receive one capsule of pregabalin 75 mg twice. Both groups will be treated for 60 days with 30 days post treatment follow-up addition to their regular anti-diabetic treatment. The subjective parameters of burning, tingling, and pain in the feet will be evaluated every two weeks using the visual analog scale (VAS) and arbitrary scale. Objective parameters, Toronto Clinical Scoring System (TCSS) will be assessed fortnightly along with vibratory perception threshold (VPT), assessed pre and post-treatment. Data will be assessed statistically with appropriate tests.

1. INTRODUCTION

1.1 Background and rationale (6a)

Diabetes is one of the serious worldwide health issues of the twenty-first century, and its incidence is rising day by day.[1] Diabetic peripheral neuropathy (DPN) is one of the most common microvascular consequences of diabetes. [2] Clinically, it may manifest as burning, tingling, numbness, or neuropathic pain in the foot that tends to get worse at night. About 80% of people with diabetes have the typical polyneuropathy and distal sensory peripheral neuropathy. [3,4] The prevalence of DPN is ranging from 18.8 to 61.9% in India. [5,6] Although, DPN is not directly mentioned in Unani literature, but such conditions are treated as Waja-ul-Asab (neuropathic pain) [1]. DPN is managed by strictly controlling hyperglycemia and using of drugs such as analgesics, antidepressants, and anticonvulsants properties, etc. [6] Presently, many therapeutic options are available for the treatment and control of DPN progression, like alpha

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lipoic acid, aldose reductase inhibitors, and benfotiamine, etc.[1,7] Symptomatic relief can be achieved with the use of anti-depressants (duloxetine) and calcium channel ligands (pregabalin). [8] Drugs used to manage DPN as analgesics may have adverse effects such as drowsiness, headache, nausea, tremor, erectile dysfunction, disorientation, increased suicidal propensity, peripheral edema and dry mouth. [9,10] In Unani medicine, numerous medications have been used as Muqawiye asab (nervine tonic, neuroprotective) such as Azaraqi, Balchad, Beesh, Darchini, Waj, etc and other polyherbal formulations like Habb-e-Asab, and Habb-e-Azaraqi, etc. [11-15] Acorus calamus Linn. (Family: Acoraceae) is known as Waj in Unani medicine being used as neuroprotective (Muqawi-e-Dimagh wa Asab). [13-15] In preclinical study, Waj has shown anti-oxidative, anti-inflammatory, neuroprotective, and calcium inhibitory actions. [16,17] Clinical studies on Waj stated that it affects obesity, depression, neuroprotection, and cardiovascular disorders. [18-20]

1.2 Objective of the study (7)

This clinical trial will evaluate the effect on subjective parameters like pain, burning, and tingling in the foot, as well as the objective measures TCSS and VPT.

1.3 Explanation for the choice of comparator (6b)

Pregabalin is well acknowledged as an effective treatment for neuropathic pain, including diabetic peripheral neuropathy and fibromyalgia. Pregabalin's FDA approval lends legitimacy to its use as a valid comparison in clinical trials. Its safety profile is well documented, with recognized side effects and contraindications, allowing for a more accurate interpretation of trial results when comparing the safety and efficacy of novel treatments. Furthermore, pregabalin is a commonly prescribed medication for neuropathic pain; its use as a comparator in clinical trials ensures that study results are directly relevant to current clinical practice, and if a new drug proves superior or comparable, it may represent a significant advance in patient care.

2. METHODOLOGY

2.1 Subjective parameters

- Pain in feet (VAS).
- Burning sensation in feet.
- Tingling sensation in feet.

2.2 Objective parameters

- Toronto Clinical Scoring System (TCSS).
- Vibration Perception Threshold (VPT).

Results will be assessed after 60 days, and participants will be monitored for an additional 30 days to look into the long-term effects of the intervention.

2.3 Trial design (8)

A randomized single blind controlled comparative clinical trial. This is a superiority trial with a 1:1 allocation ratio between two parallel groups.

3. METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

3.1 Study setting (9)

This clinical trial will be conducted on subjects recruiting from the OPD and IPD of National Institute of Unani medicine (NIUM), Bengaluru, India.

3.2 Eligibility criteria (10)

3.2.1 Inclusion Criteria

- Diagnosed cases of DPN with Type 2 DM.
- History of DPN with /without medication within the period of 6 months to 60 months.
- Subjects of DPN with TCSS score >5 up to 11.
- HbA1c < 7.
- All gender.
- Age between 30-60 years.
- Normotensive (without taking any anti-hypertensive medicines).

3.2.2 Exclusion Criteria

- Known cases of peripheral nerve dysfunction; vitamin deficiency (B12 and E), peripheral vascular disease.
- History of positive alcoholism.
- Patient on Insulin.
- Known history of thiazolidinedione antidiabetic agents.
- Patients with a history of cancer, autoimmune diseases (multiple scelerosis, GB syndrome, myasthenia gravis), and vasculitis (polyarteritis nodusa).

- Pregnant & lactating mothers.

4. INTERVENTIONS

4.1 Intervention description (11a)

Eligible participants will be randomly assigned to one of two groups (test or standard) and monitored for a period of ninety days. For the duration of 60 days, the control group will receive pregabalin 75 mg twice a day, 12 hours apart, in addition to their regular anti-diabetic treatment. The test group will receive two capsules, each containing 500 milligrams of the test drug powder. We will purchase test drug rhizomes of high quality, properly identified and verified, from the nearby market. The Plant Anatomy Research Institute, Tambaram, Chennai, India, will identify and validate the herb botanically. After that, the rhizomes will be pulverized into a powder and sieved (no. 80). It will be allowed to cool at room temperature and filled in capsule shells, stored in tightly closed containers to protect them from light and moisture. The National Institute of Unani Medicine's pharmacy will carry out the complete capsule-making process while adhering to Good Manufacturing Practices (GMP).

4.2 Guidelines for ending or modifying allotted interventions (11b)

Participants may withdraw from the study at any time and for any reason without consequence. If a person is uncooperative or misses research appointments, the investigator may also decide to terminate their participation. If a person declines to take the study medication two or more times, they will be deemed withdrawn from the study. The analysis will still contain the data that was gathered up until the withdrawal point. If study participants have an adverse reaction (AR), the medication will be stopped. The assessment will be carried out by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 at each follow-up. A complete hemogram, liver function tests (ALT, AST, total bilirubin), and kidney function tests (blood urea, serum creatinine) will be performed on all study participants at baseline and on the 60th day.

4.3 Approaches to improve compliance of interventions (11c)

The investigator will supervise treatment to ensure adherence, keeping track of tablet counts and a treatment record. The record will be retained until the conclusion of the 60-day therapy session and examined at each follow-up. Throughout the trial, the treatment record will be an essential tool for monitoring drug adherence. Researchers hope to increase the reliability of study outcomes by counting the remaining tablets regularly and establishing data.

4.4 Permission or prohibition for essential concurrent treatment during the trial (11d)

Drug history will be noted upon enrollment and at all subsequent follow-up visits. Any new drugs introduced during the trial will be evaluated by the study physician for potential drug interactions. Participants will continue to receive normal anti-diabetic therapy at their chosen clinics.

5. OUTCOMES (12)

The primary outcome is improvement in subjective parameters such as pain, burning sensation and tingling sensation in feet using VAS and arbitrary scale and objective parameters like VPT measured by using NEURO TOUCH device and TCSS.

The secondary outcome are improvement in diabetic neuropathy symptom score (DNS), and in EuroQol 5-Dimension 5-Level (EQ-5D-5L) score.

6. PARTICIPANT TIMELINE (13)

The participant timeline during clinical trial is presented in table

7. Sample size (14)

The sample size calculation was based on a study conducted by Fathima Nafha Nizamdeen and Yuwei Feng et al. [1,21] The primary outcome measure was used for the sample size estimation. A previous study demonstrated a 40% reduction in moderate to severe pain in the test group, in comparison to 10% in the control group. In this study, a sample size of total of 126 subjects (63 subjects each group) was estimated to achieve a power of 90%, considering an alpha error of 0.05. With an anticipated 20% dropout rate, the final sample size was estimated to be 150 (75 each group). *The sample size was calculated using G power software version 3.1.9.6.*

8.RECRUITMENT (15)

To increase participant enrollment in a clinical study on diabetic peripheral neuropathy, we will work with healthcare providers such as endocrinologists, neurologists, and primary care physicians to hold educational sessions to boost patient referrals. To reach a larger audience, we plan to use a combination of online and offline channels, including social media, websites, diabetes forums, clinics, hospitals, and community centres. We will make the enrollment process simple by offering clear instructions and support to encourage participation. To improve engagement and retention, we will communicate with participants frequently, provide study progress updates, and show our gratitude for their participation.

9. ASSIGNMENT OF INTERVENTIONS (FOR CONTROLLED TRIALS)

9.1 Allocation: sequence generation (16a)

Eligible participants will be randomly allocated to receive either a test drug or a standard drug in a 1:1 ratio.

9.2 Concealment mechanism (16b)

Each group will receive a unique code, which will be carefully printed, folded several times, and securely placed inside sealed, opaque envelopes, each labelled with its own distinct identifier. These envelopes will then be shuffled and opened in sequence as participants are enrolled in the study.

9.3 Implementation (16c)

The randomization schedule and allocation list will be generated via an internet platform or a computer. Participants will be recruited and randomly assigned to two groups using simple randomization. This method was chosen because for large sample sizes, simpler randomization methods may be more practical and sufficient. The randomization sequence will be created using MS Excel with a 1:1 allocation. An independent researcher will generate the random numbers and assign participants randomly to either the test or control treatment groups.

10. BLINDING (MASKING) (17A)

Single blinding will be used. Participants won't know their group (treatment or control) to prevent their expectations from influencing the study's outcomes. Researchers will not be blinded.

10.1Emergency unblinding (17b)

Emergency unblinding is not required as it is single blinded clinical trial.

11. DATA COLLECTION AND MANAGMENT

11.1 Plans for assessment and collection of outcomes (18a)

Data will be collected from OPD/IPD of Moalajat, NIUM Hospital, Bangalore. All the type 2 diabetes mellitus patient will be screened and recruited based on inclusion and exclusion criteria. The eligible participants will be randomly allocated to Group A (n=75) and Group B (n=75) after obtaining written informed consent. In group A test drug will be given orally in the form of capsules for 60 days. In Group B Pregabalin will be given as described in intervention. The follow up of patients for assessment will be done on every 15th day from baseline. Assessment of subjective parameters will be done on each follow-up except VPT (pre and post intervention), assessment of quality of life (EQ-5D-5L) will be done at baseline and on last follow-up. Safety assessment will be done by CBC, LFT and RFT before and after the treatment. The VAS scoring interpretation is 0- to 4-mm range on a 100-mm VAS can be said to represent no pain, 5 to 44 mm to represent mild pain, 45 to 74 mm to represent moderate pain, and 75 to 100 mm to represent severe pain. A VPT value of ≥15 V is suggested as the diagnostic threshold for DPN. The interpretation of burning and tingling sensation in feet will be assessed by an arbitrary grading scale (0-No symptom, 1-Mild, 2-Moderate, and 3-Severe). The DNS score is a simplified technique for determining the existence of neurological symptoms in diabetes patients, including pain, numbness, tingling, and ataxia. The score goes from 0 to 4, with a value of 1 or higher indicating the existence of diabetic neuropathies. A questionnaire will be used to assess the quality of life of patients with DPN.

11.2Plans to promote participant retention and complete follow-up (18b)

To increase enrolment in a clinical study on diabetic peripheral neuropathy, we plan to collaborate with healthcare providers and use both online and offline channels for outreach. Subjects will get a phone call reminder prior to follow-up visits. Those who fail to show up for a hospital visit will be contacted by phone before being declared lost to follow-up. Primary outcome data cannot be collected from participants who leave the trial.

12. DATA MANAGMENT (19)

Clinical record forms (CRF) and written informed consent form will be used for recording and safety of data. All documents will be stored safely in confidential conditions and held for 3 years after the end of the trial in accordance with good clinical practice (GCP) principles in the department of Moalajat of NIUM. To enable more efficient data management, the data from the laboratory forms will also be entered into CRF. Data will be updated at each follow-up and signed by the supervisor of the trial on daily basis. Furthermore, quality control checks will be performed weekly, including consistency cross-checks between forms.

13. STATISTICAL METHODS

13.1Statistical analysis for primary and secondary outcomes (20a)

Analysis of the data will be done by appropriate statistical test. Data will be analysed on the intention to treat (IIT) principle. Descriptive and inferential statistical analysis will be carried out in the present study. Results on continuous measurements will be presented on Mean ± SD or Median and Inter Quartile Range. Categorical measurements like gender, family history etc will be presented in number (%).

Repeated measures ANOVA and one-way ANOVA with Tukey post hoc multiple comparison test on a continuous scale. Kruskal-Wallis and Friedman's test is applied to analyze the data that do not follow normality.

The Chi-square/ Fisher Exact test will be used to find the significance of study parameters on a categorical scale between the groups. McNemar's test will be used for

comparing paired proportions. P <0.05 will be considered as statistically significant.

13.1.1 Statistical software

The Statistical software namely IBM SPSS version 29.0, will be used for the analysis of the data, and Microsoft Word and Excel have been used to generate graphs, tables, etc.

13.2 Methods for any additional analyses (20b)

ANCOVA analysis will be used to analyse the confounding effects. The effect size for the treatment will be calculated and 95% confidence intervals will be reported. Subgroup analysis if required will be carried out.

13.3 Methods in of analysis population relating to protocol non-adherence and any statistical methods to handle missing data (20c)

Data Imputation Techniques such as Mean Imputation or Last Observation Carried Forward (LOCF) will be used for handling missing data. Outliers will be handled during the analysis by examination and verification and by using appropriate statistical measures. During the informed consent process, participants will be clearly explained about the importance of adherence to the study protocol. Regular communication will be maintained and reminders through phone calls to minimize non-adherence.

14.DATA MONITORING: FORMAL COMMITTEE (21A)

Not applicable in this trial.14.1Interim analyses (21b)

No interim analysis is scheduled for this trial, as it is not necessary for the study's objectives, and avoiding it helps reduce costs and streamline trial logistics.

15. PLANS FOR REPORTING HARM AND ADVERSE EVENT (22)

Any adverse reaction of the interventions will be assessed and documented and the same will be submitted to Pharmacovigilance centre for Unani Drugs.

16. FREQUENCY AND PROCEDURES FOR AUDITING TRIAL CONDUCT (23)

The trial will be implemented following the Declaration of Helsinki principles, as well as all relevant regulations and the ICH guidelines for good clinical practice. Periodic monitoring at every six month will be carried out by institutional ethical and technical review committee.

17. ETHICAL APPROVAL AND CONSENT FOR PARTICIPATION (24)

All participants will be asked for written informed consent in local vernacular language for the trial. The NIUM Institutional Ethics Committee for Biomedical Research approved the trial on May 15, 2024 (reference NIUM/IEC/2023-24/040/PhD/01).

18.PLANS FOR COMMUNICATING IMPORTANT PROTOCOL MODIFICATIONS (25)

In this study no amendment has been planned.

19.WHO WILL TAKE THE CONSENT? (26a)

The investigator will take the participant's written informed consent after checking the inclusion and exclusion criteria. All the patients with type 2 diabetes will be screened for eligibility to participate in this study at NIUM hospital's OPD/IPD based on the criteria listed above. Participants who match the inclusion criteria will be invited and provided complete information about the study by the investigator

19.1Consent or assent: ancillary studies (26b)

Not applicable as it not an ancillary study.

20. CONFIDENTIALITY (27)

A unique case record number will be assigned to each participant's data and specimens. Before analyzing the data, the patient's name and any other identifiable information will be removed. The primary investigator will sign a confidentiality agreement that prohibits any dissemination of the patient's personal information.

21. DECLARATION OF INTEREST (28)

None.

22. AVAILABILITY OF DATA AND MATERIALS (29)

Data will be kept confidential, only the investigator and biostatician will have data access. The results will be available after the study is published in a scholarly journal.

23. PROVISION FOR ANCILLARY CARE (30)

In the event of unbearable pain during trial, participants will be treated as per local norms, with a referral to the

hospital's medical team on duty. The study will not include management costs. At each follow-up visit, participants will be asked about any severe pain events, their treatment, and the outcomes. Participants will also be advised to call the investigator or attend an unplanned appointment if they want during follow-ups.

24. DISSEMINATION POLICY; TRIAL RESULTS (31a)

The trial's findings will be shared via posters and leaflets intended to inform participants about the study, policy briefs, press releases, national dissemination meetings, presentations at national and international conferences, and open-access publications in peer-reviewed journals.

24.1 Dissemination plans (31b)

Not applicable

24.2 Plans to give access to the full protocol, participant-level data and statistical code (31c)

Not planne d.

25. INFORMED CONSENT MATERIALS (32)

Informed consent material has been attached in appendices.

26.PLAN FOR COLLECTION, LABORATORY EVALUATION AND STORAGE OF BIOLOGICAL SPECIMENS FOR GENETIC OR MOLECULAR ANALYSIS IN THIS TRIAL/ FUTURE USE (33)

The sample will be collected by drawing venous blood from each subject using standard procedure. Approximately 5 ml of blood will be obtained in Ethylenediaminetetraacetic acid (EDTA) tubes for hematological analysis, with an additional 5 ml collected in plain tubes for biochemical evaluation. The samples in EDTA tubes will be promptly delivered to the laboratory for a complete blood count (CBC), which will be done on a fully automated hematological analyzer. This analyzer will provide precise readings of hemoglobin levels, red blood cell count, white blood cell count, and platelet count, among other parameters. The plain tubes will be allowed to clot before the serum is separated using centrifugation. The serum samples will next be tested for liver function tests (LFTs) and renal function tests (RFTs) on an automated biochemistry analyzer. The LFT panel will measure ALT, AST, and total bilirubin levels. The RFT panel will measure serum creatinine and blood urea nitrogen (BUN), providing information about kidney function. Quality control methods will be meticulously followed to ensure that the results are accurate and reliable. Storage of biological specimens for genetic or molecular analysis in future use has not been planned.

26.1 Oversight And Monitoring

This study is a part of PhD dissertation work, supported by the National Institute of Unani Medicine, Bengaluru.

27.DECLARATIONS

27.1.1Author contribution

The protocol was created and designed by Mohd Aleemuddin Quamri. Mohd Shahid wrote the first and final drafts of this manuscript. The final text was critically examined and approved by all authors, who are also responsible for the manuscript's content and similarity index.

27.1.2 Trial registration (2a)

Trial registration will be done in CTRI before enrolment of participants.

27.1.3 Protocol version (3)

Version 1.0, 21 September 2023

27.1.3 Funding (4)

Post Doctoral Academic research supported by National Institute of Unani Medicine, Bengaluru, India

27.1.4 Name and contact information for the trial sponsor (5a)

Not applicable, there is no sponsor for this study as it is the part of PhD thesis.

27.1.5 Role of sponsor (5b)

Not applicable, there is no sponsor for this study as it is the part of PhD thesis.

27.1.6 Composition of the coordinating centre and trial steering committee (5c)

Not applicable in this trial as it is not a sponsored clinical trial and it's a phase 2 clinical trial.

28. ACKNOWLEDGEMENT

Nil.

32. CONFLICTS OF INTEREST

Nil.

33. DATA AVAILABILITY

This is an original manuscript and all data are available for only review purposes from principal investigators.

34. PUBLISHERS NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation

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	Study period (90 days)					
	Enrolment	Post allocation (days)				
	0	15	30	45	60	90
Enrolment						
• Screening for eligibility	●					
• Informed consent	●					
• Clinical and diabetic history	●	●	●	●	●	●
• Clinical symptoms of DPN	●	●	●	●	●	●
• Allocation with randomisation	●					
Intervention						
• Supply of test and control drug	●	●	●	●		
• Assessment of compliance		●	●	●	●	●
Measurement						
• Pain in feet (VAS)	●	●	●	●	●	●
• Burning sensation in feet	●	●	●	●	●	●
• Tingling sensation in feet	●	●	●	●	●	●
• VPT	●				●	
• TCSS	●	●	●	●	●	●
• DNS	●	●	●	●	●	●
• EQ-5D-5L (QoL)	●				●	
Laboratory assessment						
• HbA1c	●					
• CBC	●				●	
• ALT levels	●				●	
• AST levels	●				●	
• Total bilirubin levels	●				●	
• Serum Urea levels	●				●	
• Serum creatinine levels	●				●	