Opinion paper

A study protocol on nerve mobilization induced diffusion tensor imaging values in posterior tibial nerve in healthy controls and in patients with diabetic neuropathy-multigroup pretest posttest design

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ABSTRACT

Background: Diabetic neuropathy is the commonest chronic disabling complication of diabetes which may lead to amputation and compromising patient's quality of life. It is characterized by pain, sensation loss associated with neural edema. Diffusion tensor imaging parameter i.e. fraction anisotropy determines the free water proton diffusion in the healthy nerve. Since the diabetes leads to altered mechanosensitivity of the posterior tibial nerve thereby, might interferes with the water molecules movement. Therefore the present clinical trial will provide the evidence of improving the diffusion tensor imaging in the diabetic neuropathy directly by targeting the nerve through nerve mobilization treatment.
Methods: Participants with Type II Diabetes Mellitus induced peripheral neuropathy will be selected randomly on the basis of eligibility criteria and informed consent will be taken. Participants will be recruited into three groups. Group A (experimental group A) will receive neural mobilization technique, Group B (experimental group B) will receive conventional therapy and Group C (control group) will receive sham treatment for 3 weeks. MRI technique, Visual analogue scale and neuropathy specific quality of life questionnaire will be used as assessment tools. Assessment will be taken at baseline and post intervention.
Conclusion: this clinical trial will provide the evidence of efficacy of nerve mobilization in determining the diffusion tensor imaging (DTI) changes in the posterior tibial nerve in patients with diabetic neuropathy. This trial will also be the first one in itself to look at the treatment induced DTI changes in the peripheral nerve.
Trial Registration: Clinical Trial Registry of India (CTRI/2019/06/019552).

1. Introduction

Diabetic Peripheral Neuropathy (DPN) affects 50% of Type II diabetes patients [1–3]. DPN is commonest symmetrical type of chronic complication with higher prevalence in individuals with higher percentage of glycosylated haemoglobin (HbA1C) [4,5]. DPN individuals presents with neuropathic pain and altered neural mechanosensitivity, balance and gait problems [6,7] due to impaired proprioception [8], limited ankle joint movement and reduced muscle flexibility [9,10].

The late detection, progression and treatment of DPN yields in the deterioration of the quality of life of the sufferers [11]. Peripheral neuropathy can be detected through NCS, ultrasonography, and MRI [12–14]. Diffusion Tensor Imaging (DTI) may be used as the assessment tool in the peripheral nerve related disease and also monitor re-innervation through fractional anisotropy (FA), apparent diffusion coefficient (ADC) [15].

Hyperglycemia leads to the altered nerve biomechanics due to fluid accumulation in the nerve [16] which can be targeted through nerve mobilization (NM) in the form of the neurodynamics and the nerve massage [17–19]. The NM techniques are useful in restoring the normal
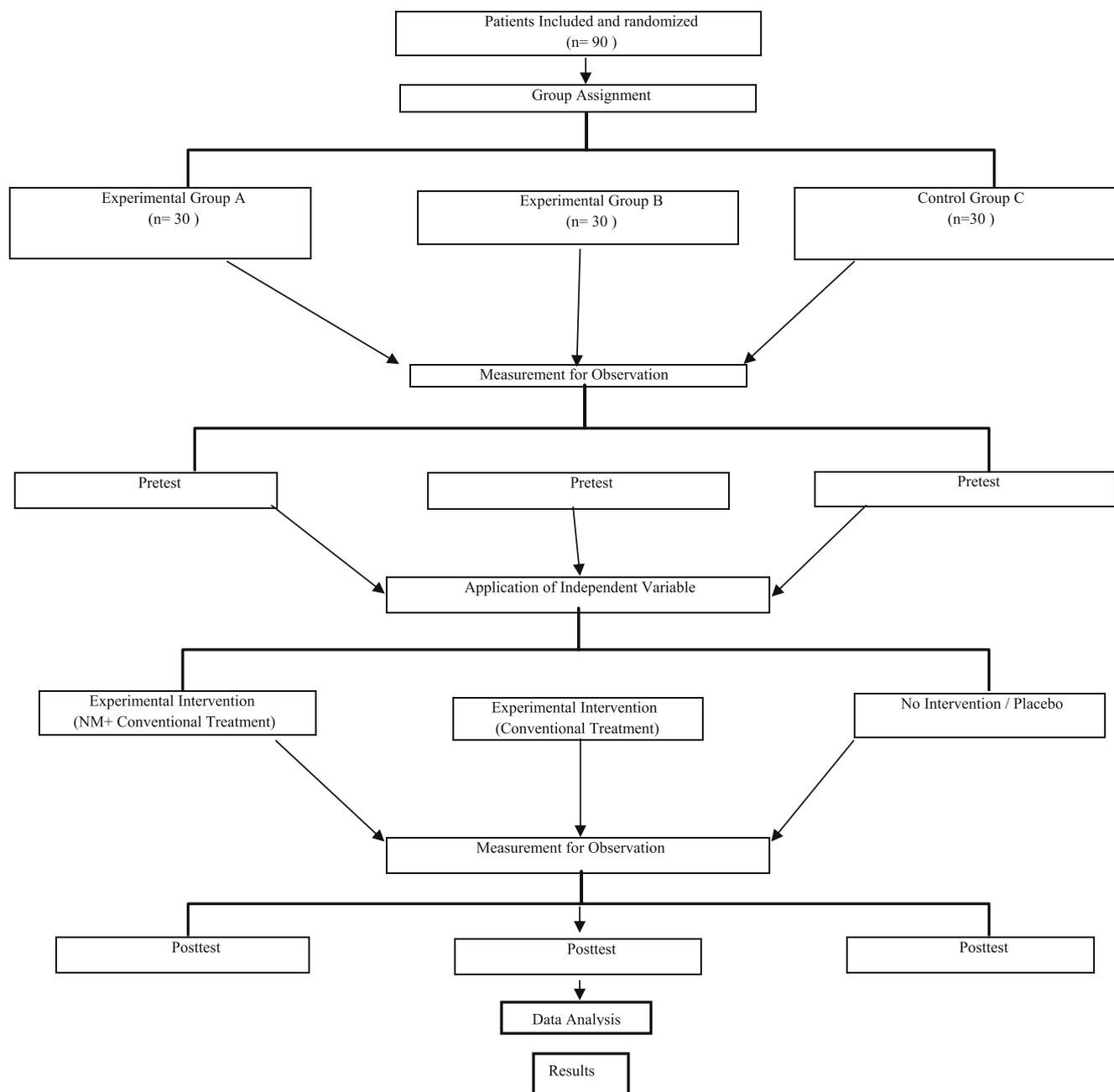
Fig. 1. Flow chart to show the protocol.

physiological function through both the intraneural and extra neural effect [20,21]. The purpose of current research is to explore the effect of NM on the DTI parameters in healthy individuals and in DPN patients.

2. Materials and methods

2.1. Research design

The study is a multigroup pretest-posttest design. Fig. 1 shows an overview of this trial plan. The selection of the participants will be done randomly and informed consent will be obtained from the selected participants. The baseline and post treatment data for FA and ADC, pain and disability will be recorded using the MRI 1.5- Tesla MR System Multiva- Philips; VAS and universal goniometer respectively. During the treatment period participants will follow their medical treatment protocol without any alteration in their medical management; if there is any alteration then the patient will be excluded from further analysis

and there data will be considered for analysis using intention to treat analysis method.

The study has been approved by Institutional Research Ethics Committee of Maharishi Markandeshwar (Deemed to be University), Mullana- Ambala, and Haryana, India. The trial is registered at Indian Clinical Trials Registry (CTRI/2019/06/019552) on 6/6/2019 and Universal Trial Number is U1111-1238-5094. The data will be collected from Outpatient Department of the Musculoskeletal Physiotherapy, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation. The patients will be recruited from Maharishi Markandeshwar Institute of Medical Sciences and Research- Radiology Outpatient department.

2.2. Participants

Patients with Type II Diabetes Mellitus induced peripheral neuropathy will be taken for the participation in the study. The selection of

Table 1
Selection criteria for the study participation.

Inclusion Criteria	Exclusion Criteria
Aged between 36 and 70 years. Individuals with unilateral or bilateral CSMDPN. Individuals with confirmed chronic sensory motor diabetic peripheral neuropathy (CSMDPN) diagnosed by physician as per diagnostic criteria [22]. Individuals with Type II DM, with HbA1C < 10%. Individuals who will give the informed consent.	Diabetic foot ulcer and Neuropathic joints History of cardiac pacemakers and MRI contraindications. Central nervous system and autonomic nervous system pathology. Diabetic foot ulcer and Neuropathic joints. Any other co morbidities.

Matrix / Rows	1	2	3	4	5	6
1	$2E_1$	1C	$1E_2$	$2E_2$	2C	$1E_1$
2	●	●	●	●	●	●
3	●	●	●	●	●	●
4	●	●	●	●	●	●
5	●	●	●	●	●	●
6	●	●	●	●	●	●
7	●	●	●	●	●	●
8	●	●	●	●	●	●
9	●	●	●	●	●	●
10	●	●	●	●	●	●
11	●	●	●	●	●	●
12	●	●	●	●	●	●
13	●	●	●	●	●	●
14	●	●	●	●	●	●
15	●	●	●	●	●	●

Fig. 2. Block Randomization (6 × 15 matrix design).

90 patients will be done using the criteria – based purposive sampling. Selection criteria are given in Table 1.

2.3. Randomization

Block randomization will be done. Random allocation of the eligible subjects for treatment will be done by the sealed opaque envelope method. We will make 6 blocks, with the matrix design of 6 × 15 (as shown in Fig. 2) here 15 being rows. Each block will contain 6 chits (3 chits for each group). The subjects will be allotted to the group based on the chits what they will pick. Once the box get empty, next box will be opened. Subjects will be randomized using the computer generated randomization method into three groups: Group A (NM + Conventional treatment) and Group B (Conventional treatment alone) and Group C (Sham intervention). Participants will be blinded before allocation into groups.

2.4. Intervention

Nerve Mobilization Technique [23] –

• Slider technique (Fig. 3):

Proximal Sliding of the tibial nerve:

Patient Position – will be supine lying.
Therapist Position – will be standing by the side of the patient couch.

Fig. 3. Slider technique.

The therapist will hold the patient lower extremity in the horizontal position with the hip at 45° of flexion. The movement components to mobilize the nerve will be in a sequence of dorsiflexion (DF) and eversion (Ev) at the ankle and foot with DF of toes; knee extension and proper stabilization will be provided to the remaining lower extremity joints. At the end of the nerve bias, DF of the foot and toes will be released in the plantarflexion movement to allow the tibial nerve to slide proximally further.
Distal Sliding of the tibial nerve:

Patient Position – will be supine lying.
Therapist Position – will be standing by the side of the patient

Fig. 4. Tensinor technique.

couch.

The therapist will hold the patient lower extremity in the horizontal position with the hip at 45° of flexion. The nerve will be moved into its mechanical interface distally by adding DF and Ev of the foot and also adding the DF of toes for releasing the proximal tension and allow the nerve to slide distally.

- Tensioner technique of the tibial nerve (Fig. 4):
  Patient Position – will be supine lying.
  Therapist Position – will be standing by the side of the patient couch.

Movement Components – Hip flexion 45° with ankle DF and foot Eversion with extension at knee joint.
The NM will be done by the experienced physiotherapist for 2 times/week for 3 weeks and the patients will receive 5 sets of 10 cycles with a rest period of 1 min in each set [24].
Conventional Therapy:

Nerve Massage [25] (Fig. 5)–

Both the longitudinal and transverse nerve massage will be done by the experienced physiotherapist for 2 times/week for 3 weeks along the course of the tibial nerve (popliteal fossa to foot) for 4 min in total and the patients will receive total of 6 times for 10 repetitions.
Transcutaneous Electrical Nerve Stimulation (TENS) (Fig. 6) [26] – Patients will receive 10 sessions of TENS (80 Hz, 50 Amp, 0.2 ms square pulses, 2 to 3 times sensory threshold) every alternate day for 3 weeks for 20 min, with one electrode placement over the proximal tibia and other electrode over the ankle.

2.5. Outcome measures

Demographic and anthropometric characteristics will be taken before the outcome measurements.

Fig. 6. Transcutaneous electrical nerve stimulation (TENS).

2.5.1. Primary outcomes

MRI technique will be performed by the experienced radiologist having more 10 years or more of experience using the 1.5- Tesla MR System Multiva- Philips magnet, Baltimore, Netherland, Holland with a typical spine/knee range loop with the magnetic field centered on the ankle joint. MRI scans of the conventional leg will also be done. The conventional MRI sequences will include axial and sagittal T2WSE and STIR for path anatomic relationship [27]. Free – breathing single – shot echo – planar Diffusion weighted images (DWI) neurography will be done by means of couple of b – values of 0 and 800 s/mm^2 respectively [28]. ADC and FA data will be procured by adding the axial DWI and axial DTI sequences respectively.

2.5.2. Secondary outcomes

The Visual Analog Scale (VAS) is the pain measurement scale which is most commonly used with high reliability (ICC = 0.98). It is a 100 mm horizontal or vertical straight line with description of no pain at one end and worst pain on the other end of the line respectively. The patients will be instructed to report the intensity of pain experienced at that moment with a mark on the line. Pain measurement scoring is done in the millimeters from the no pain end of the scale to the mark by the patient on line [29].

Neuropathy specific quality of life questionnaire (Neuro QoL) is used in the diabetic peripheral neuropathy patient's assessment and follows up after treatment intervention. It assesses the physical and emotional aspects related to quality of life and daily living of the diabetic neuropathy patients. Neuro QoL questionnaire is divided into six sub scales with total 27 questions having 5 – point Likert scale for each question, where 1 represents "never" and 5 represents "all the time" frequency of symptoms. Six sub scale domains includes, pain and parasthesias; loss of temperature and object feeling in the feet; impaired standing and walking balance; restriction in activities of daily living; interpersonal physical and emotional dependence; emotional distress and two additional questions to assess the overall influence of neuropathy on life quality [30].

2.6. Data monitoring

Statistical analyses and datasets will be done by independent researcher to the group allocation examiner. Treatment sessions in each

Fig. 5. Nerve massage along the nerve course.

group will be monitored by the treating therapists.

2.7. Sample size

The sample size based on selection criteria will be 90 patients.

3. Data analysis

The Normality test, Kolmnogorov Smirnov will be used to check the normal distribution of the sample size. Appropriate statistical test will be used to achieve the aims of study like Mean, standard deviation (SD) and the level of significance (LOS) will be kept at 0.05 with 95% confidence interval (CI). Within the group analysis will be performed using repeated measures ANOVA if normal, otherwise Friedman test if not normal and between the group analysis will be done by independent t – test if normal, or Mann U Whitney if not normal.

4. Discussion

Diabetic neuropathy is a diagnosis of exclusion as suggested by the members of the International Consensus Meeting [3]. It is characterized by the altered neural mechanosensitivity leading to the disturbed sensation in the extremity and foot resulting in the poor quality of life and disability [6–8]. Peripheral neuropathies can be diagnosed with various investigative tools like ultrasonography, NCV and MRI [12].

The previous literature have shown the efficacy and effectiveness of nerve mobilization and conventional physiotherapy in the improvement of conduction parameters [20,21]. However, it remains unclear in the literature existed the effect of nerve mobilization and conventional physiotherapy in dissipating the neural edema in the patients with diabetic neuropathy; therefore, this experimental trial will help to provide the neural mobilization impact on the free water proton diffusion detected through the diffusion tensor imaging values in the posterior tibial nerve. The results obtained from the clinical trial will help to improve the nerve health in the diabetic population and hence will protect them to undergo foot and extremity amputations.

Diabetic neuropathy is a common significant complication in the diabetic population [1]. The primary goal of this clinical trial is to evaluate the efficacy of nerve mobilization in improving the nerve sensitivity measured through diffusion tensor imaging. Furthermore, upon completion of this trial the evidence of nerve mobilization in the pain management in diabetic neuropathy will be strengthened by the Diffusion tensor imaging values in the posterior tibial nerve.

Funding

Conflicts of interest

Nil.

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