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Immediate effects of nerve sliders and nerve massage on vibration and thermal perception thresholds in patients with painful diabetic peripheral neuropathy- a pilot randomized clinical trial (UTRN 103229513-050820102510203)

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ABSTRACT

Background and purpose: Mechanosensitivity of peripheral nerves was earlier demonstrated in animal models and in experimental human models of diabetic neuropathy and also in asymptomatic human subjects. The purpose of this study was to assess the immediate effects of nerve sliders and nerve massage on vibration perception thresholds (VPT), heat perception thresholds (HPT) and cooling perception thresholds (CPT) in patients with painful diabetic peripheral neuropathy.,Materials and methods: The study was an observer-blinded pilot randomized sham-controlled clinical trial with concealed allocation on 34 patients (22 male, 12 female) of mean age 53.86 ± 9.85 years with type-2 diabetes mellitus, neuropathic pain for more than one-year, VPT > 25 volts in feet and positive lower extremity neurodynamic testing in bilateral lower limbs suggestive of distal symmetric type of diabetic neuropathy. The tester administered nerve sliders and nerve massage to one lower limb while sham intervention of passive joint movements was performed for the other limb. The choice of first limb was chosen randomly and block randomization was performed to minimize between-side confounding differences. The three outcomes of VPT, HPT and CPT were assessed pre, immediate post and 15 min-post intervention on both feet using a biothesiometer., Data analysis and results: The data was analyzed using repeated measures analysis of variance at 95% confidence interval using SPSS 12.0.1 for Windows. Secondary analysis was done using independent t-test for gender and choice of first side. The experimental side had a greater reduction of VPT (12.40 ± 4.90 volts), HPT (7.63 ± 5.18 degree Celsius) and CPT (8.02 ± 5.97 degree Celsius) from pre-treatment to 15-min post-treatment compared to the sham side ($p<.05$). The changes between immediate post-treatment and 15-min post-treatment was not significant ($p>.05$) for all three measurements., Conclusion: Neurodynamic mobilization comprising of nerve sliders and nerve massage was effective on short-term in reducing VPT, HPT and CPT in patients with painful diabetic peripheral neuropathy compared to a sham intervention. These immediate effects were maintained at 15 min post-treatment.

Key words: Neurodynamics, mechanosensitivity, diabetic neuropathy, manual therapy, quantitative sensory testing.

INTRODUCTION

Diabetic neuropathy is a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical that occurs in a setting of diabetes mellitus without other causes of neuropathy. The neuropathic disorder includes manifestations in both somatic and/or autonomic parts of the nervous system.[1] The first description of "diabetic neuropathy as a presence of pain and paresthesiae in lower limbs" was done by Rollo

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in 1798.[2] Diabetic peripheral neuropathic pain (DPNP) or painful diabetic peripheral neuropathy (PDPN) affects approximately 11% of patients with diabetic peripheral neuropathy (DPN). The most common type of neuropathy in DM is DPN, with up to 50% of patients experiencing some degree of painful symptoms and 10% to 20% having symptoms severe enough to warrant treatment. A classic population- based study found some degree of neuropathy in 66% of patients with DM. Among those with type 1 and type 2 DM, 54% and 45%, respectively, had DPN and 15% and 13%, respectively, were symptomatic.[3]

Neuropathic pain was defined by International Association for the Study of Pain as "pain caused or arising from the lesion or dysfunction of the nervous system.[4]" The term "dysfunction" here encompasses anatomical and/or physiological abnormality. Central neuropathic pain arises from central nervous system dysfunction and peripheral neuropathic pain arises from peripheral nervous system dysfunctions.[5] Peripheral nervous system dysfunction clinically manifest as peripheral neuropathies in a large proportion of diabetic patients, presenting either as painful or painless neuropathies.[6] Peripheral neuropathic pain often presents as a combination of nerve trunk pain and dysesthetic pain.[7] Nerve trunk pain is typically described as a deep and aching sensation that has been attributed to increased activity from mechanically or chemically sensitized nociceptors in the connective tissue sheaths of the nervous system (i.e. nervi nervorum and sinuvertebral nerves).[8] Dysesthetic pain is often characterized as an unfamiliar or abnormal sensation such as burning, tingling, electric, searing, drawing, or crawling,[7] and it is thought to be the result of volleys of impulses originating from damaged or regenerating afferent fibers that have become hyperexcitable (i.e. abnormal impulse generating sites).[9]

Nerve trunk pain typically presents as pain or abnormal sensations along the course of the peripheral nerve that can be clinically tested using the concept of neurodynamics. Neurodynamics is the concept based on a close interaction of mechanics and physiology of the nervous system which is to be considered while assessing and treating patients via nervous system mobilization and manual therapy.[10] The foundation of knowledge behind neural tissue mechanosensitivity arose from the fact that peripheral nerve trunks in diabetic neuropathy exhibited mechanical allodynia[11] and mechanical hyperalgesia in animal and human experimental models of neuropathic pain.[12-15]

Neurodynamic assessment involves neurodynamic testing[16] and nerve palpation.[17] Neural tissue mechanosensitivity was to be confirmed during neurodynamic testing by positive response to structural differentiation so as to identify neural from the non-neural sources of patient symptoms.[10] Presence of mechanical allodynia on nerve trunk palpation was another key diagnostic sign of neural tissue mechanosensitivity.[8,18]

Neurodynamic mobilization and its effects were studied in many disorders such as carpal tunnel syndrome,[19-29] cubital tunnel syndrome,[30,31] radial tunnel syndrome,[32] lateral epicondylitis,[33,34] thoracic outlet syndrome,[35,36] cervical cord compression,[37] cervical radiculopathy,[38] cervicobrachial pain syndrome,[39-42] non radicular low back pain,[43] lumbar nerve root irritation,[44] lower extremity symptoms[45,46] and lumbar spine surgery.[47]

Recent systematic review by Ellis and Hing[48] on neurodynamic mobilization as a treatment concluded overall in favor of the techniques. Another review by Nee and Butler[49] earlier emphasized the application of neurodynamic techniques for the management peripheral neuropathic pain since the techniques were shown to influence neurophysiological mechanisms. Neurophysiological effects of straight leg raise (SLR), a lower extremity neurodynamic test was studied by Ridehalgh et al[50] who examined the effects of superficial peroneal nerve tensioner technique- a modified straight leg raise with plantar flexion and inversion on vibration perception thresholds (VPT) and the findings showed that the tensioner technique increased the VPT compared to sham technique but the effects were reversible within ten minutes among both runners and non-runners. Earlier study by Humphreys et al[51] on ten healthy subjects, demonstrated longer tibial nerve F-wave latencies when measured in straight leg raise position, proposedly indicating the neurophysiological effect of the SLR position and the author

recommended neurophysiologic testing in nerve lengthened positions so as to elicit subtle neural involvement signs. These two studies[50,51] involved the use of SLR as a neurodynamic technique and the authors were able to demonstrate neurophysiological effects. Such an effect would be invaluable in PDPN patients who have abnormal vibration, touch and temperature perception in their lower leg and feet.

The aim of this study was to evaluate the immediate effects of nerve sliders and nerve massage on vibration perception thresholds (VPT), heat perception thresholds (HPT) and cooling perception thresholds (CPT) in patients with painful diabetic peripheral neuropathy.

MATERIALS AND METHODS

Study design

Observer-blinded randomized, sham-controlled, clinical trial.

Ethical clearance

The study conduct and protocol was approved by Institutional Ethics Committee, Kasturba Medical College, Mangalore and the trial was registered at Clinical Trials Registry- India under universal trial registration number UTRN 103229513-050820102510203.

Study location

Out-patient treatment unit of department of physiotherapy in a multi-specialty teaching hospital.

Patient selection

Patients enrolled in diabetes clinic of the hospital were screened initially for the following inclusion criteria;[52-55]

Known case of type-2 diabetes, with stable glycemic levels (on HbA_1c) for a minimum of six months.

Complaint of bilateral neuropathic pain in the legs and feet (screened using neuropathic pain scale) for a minimum of six months.

Vibration perception thresholds greater than 25 volts in both feet when assessed using a biothesiometer.

Tested positive on structural differentiation during lower extremity neurodynamic testing on both sides lower limbs. Sciatic neurodynamic test, tibial neurodynamic test and common peroneal neurodynamic test were used for this purpose.

Mechanical allodynia to manual palpation of nerve trunks in bilateral legs and feet. Manual palpation of sciatic, tibial and common peroneal nerve trunks were done for this assessment.

Patients with comorbid musculoskeletal disorders, history of fractures, trauma and surgery to lower limbs, and inability to understand therapist's instructions were excluded.

PATIENT RECRUITMENT

All patients were required to provide a written informed consent prior to their participation in the study. The consecutive patients were randomly assigned to either of two groups- based on side of lower limb treated first by block randomization. The allocation method was concealed from the primary investigator using sequentially numbered sealed opaque envelopes, generated by computerized table of random numbers method.

OUTCOME ASSESSMENT

Vibration perception threshold (VPT):

The VPT testing was done using Vibrotherm™ Biothesiometer[56] with the probe placed on the subject's skin. The therapist slowly increased the intensity of vibratory stimulus until onset of vibration sense is reported. Minimum intensity of vibration felt as a sensation reported by the subject was taken as the VPT. Both appearance and disappearance of the sensation of vibration were measured. Appearance of vibration was measured by turning up the vibration stimuli until the subject was just able to perceive vibration. Disappearance was measured by increasing the stimuli to above that of the appearance value, and then slowly reducing the stimuli to where the subject no longer felt the stimulus.[50] The therapist

who performed the VPT testing using the equipment was trained prior and intra-rater reliability was established in five healthy subjects prior to the study. The ICC was found to be .91. The test was conducted after providing standardised instructions to the subjects, and was performed in a designated, quiet room without distractions (as per American Academy of Neurology guidelines).[57] The sites of measurement of VPT were shown in figure. The two (b, c) out of three sites of measurement coincided with the areas of cutaneous innervation by the two branches- medial and lateral plantar nerve and the third (a) with the main trunk of tibial nerve in the sole of foot. The total average score of the three values in volts was taken as the final value of the test for VPT in the tested foot. The procedure is then repeated on the other foot by the same therapist. The testing therapist was not aware of the treatment technique employed on the leg, during post-test measurement of VPT. The total contact duration was maintained to be less than 30 seconds to prevent adaptation and interval between two trials was maintained at 4 mins to facilitate recovery of cutaneous mechanoreceptor afferents to vibratory stimulus.[58] Total duration of testing VPT per side was then 10 mins.

Thermal perception threshold(TPT)- Methods of levels (MLE)

Each degree was kept for 4 seconds since the minimum time duration of stimulus exposure to evoke a subjective sensation for thermal stimuli is three seconds.[59]

The procedure for testing thermal perception thresholds was done as per described by Malanda et al.[60] The Methods of Levels (MLE) was used in this study.

MLE is characterized by confirming or denying a well-defined temperature change. Starting from 32°C, temperature rises (warm sensation) or decreases (cold sensation) with a 2°C step (rate of change 1°C/s). Based on the subjects answer ("yes" or "no" sensation) the °C amplitude of the following temperature step is doubled ("no" answer) or halved ("yes" answer) until a minimal perceptive criterion is established. In this "yes/no" procedure post-stimulus speed of reaction and by that reaction time does not play a role. By doing so a complete MLE test consists of several single stimuli resulting in a finally acquired reaction-time free temperature threshold. Anticipation or prediction of stimuli is prevented by random inclusion of "dummies" (no temperature change after the auditory signal) and combining two separate sequences of levels stimuli in a single test sequence. In this study levels thresholds were determined by applying temperature stimuli directly after an auditory cue (change rate 1°C/s). The testing of cold sensation sequence preceded warm sensation. Return to adaptation temperature (32°C) started as soon as participant responded "yes" or "no" (return rate 4°C/s). The inter-stimulus interval was randomized between 4 and 6 s and the minimal perceptive criterion was set to 0.1°C. Final MLE threshold for either cold or warm sensation was considered the mean of the last "yes" and "no" answered temperature step value.

The outcome measures were taken in random order, (selected by a toss of a coin method) for each leg separately both pre and post interventions by another physiotherapist who was blinded to intervention method applied. All subjects were seen at the same time of the day (preferably afternoons) to minimize the effects of diurnal influence on the thermal sensitivity in the subjects.[61]

INTERVENTIONS

The intervention consisted of one of the following two techniques on the first side lower limb and the next on the other side lower limb of the same subject. Thus subjects acted as their own controls with control side receiving the sham treatment and experimental side receiving nerve slider technique with nerve massage.

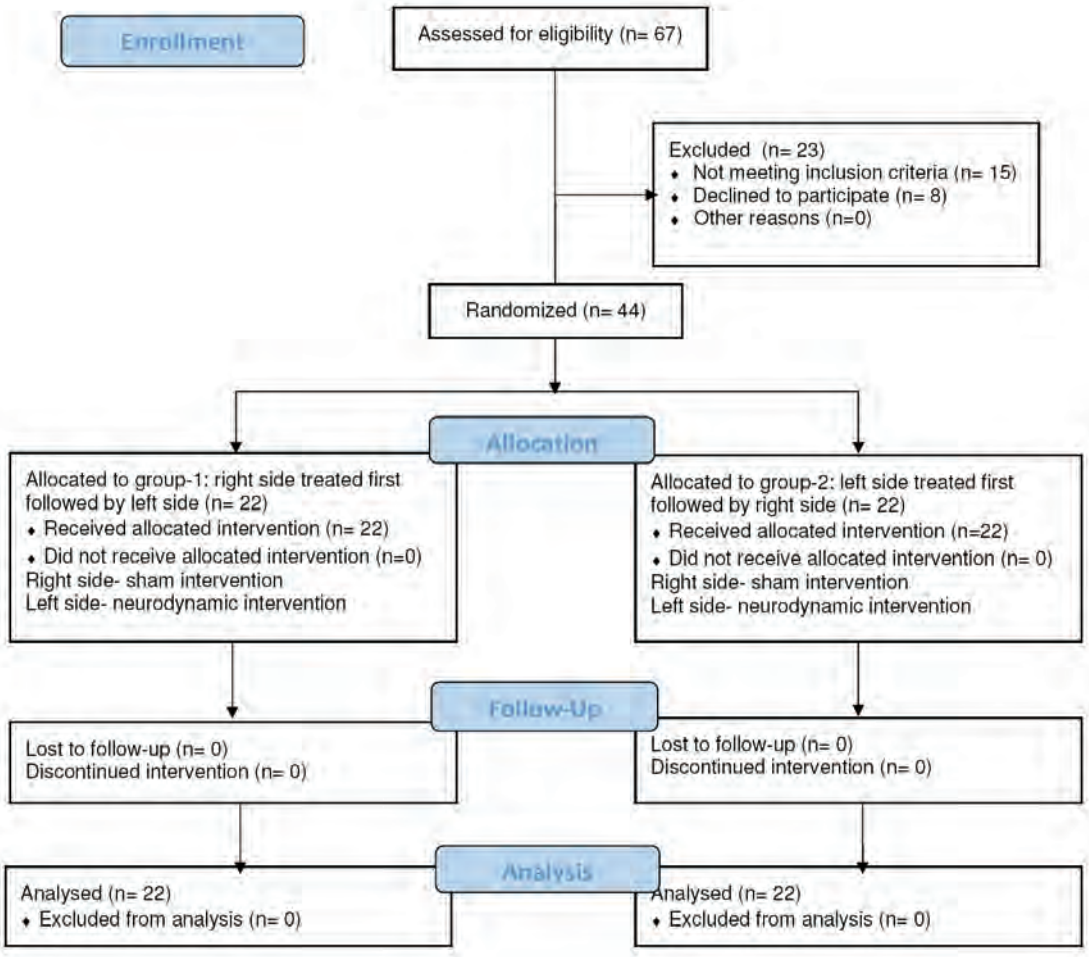
Control side- sham intervention

The sham intervention consisted of mid-range rhythmic passive joint movements performed by a physiotherapist at .5Hz, each movement for 5 repetitions, at ankle, subtalar, midfoot, forefoot and toes.[62] The control intervention hence was chosen with an intention to maximally influence tissues other than the nervous system like nociceptive structures.

Experimental side- neurodynamic intervention

The experimental intervention consisted of nerve sliders performed for the positive tested nerve on neurodynamic testing at level-2b examination as described by Shacklock.[63] The second part of the experimental intervention comprised of transverse nerve massage along the nerve trunk found tender on manual palpation

Figure 1: Consort flowchart of participants in this study



(sciatic, common peroneal and tibial nerves).[64] Both the experimental techniques were performed by a physiotherapist trained in neurodynamics under Neurodynamic solutions Inc., Australia with a post-graduate qualification and a clinical experience of eight years in manual physical therapy assessment and treatment methods. Slider dysfunction of the nerve was to be identified when mid-range symptom provocation during neurodynamic tests and decrease in symptom provocation during successive addition of neural tissue loading components.

Intervention duration was kept constant for both the sides to ensure adequate patient-blinding from experience bias. It took ten minutes per side. Total duration of both interventions together per patient was thus 20 mins.

The schematic representation of the study procedure was given in figure-1 as a CONsolidated Standards Of Reporting Trials (CONSORT) 2010 statement.[65]

DATA ANALYSIS

The data was analyzed using repeated measures analysis of variance at 95% confidence interval using SPSS 12.0.1 for Windows. Secondary analysis was done using independent t-test for comparison between gender and the

groups based on choice of first side for treatment. Pearson correlation coefficient was used for relationship between changes in outcome measures.

RESULTS

Sample size estimation

Estimation of sample size for our study was done based on minimum clinically important difference

Table 1: Overall baseline patient characteristics and between-group comparisons

	Group-1 (RL)	Group-2 (LR)	Between-group comparison- p value
Age (years)	53.45 ± 9.91	54.27 ± 10.01	.787 (NS)
Gender- male (female)	12 (10)	14 (8)	.551 (NS)
Duration of diabetes (years)	5.63 ±2.30	6.00 ± 2.30	.604 (NS)
Duration of neuropathic pain (years)	3.45 ±1.43	3.95 ± 1.91	.333 (NS)
Vibration perception thresholds (in volts)	46.25 ± 2.21	46.38 ± 2.71	.856 (NS)
Heat perception thresholds (in degree Celsius)	15.59 ± 1.90	16.09 ± 1.90	.389 (NS)
Cold perception thresholds (in degree Celsius)	15.75 ± 2.24	16.09 ± 1.90	.590 (NS)

NS: Not significant at $p<.05$

Table 2: Overall baseline findings of neurodynamic assessment in the patients

Nerves tested positive, N (%)	Neurodynamic testing		Nerve trunk palpation	
	Right	Left	Right	Left
Sciatic nerve	1 (2.3%)	1 (2.3%)	0	0
Tibial nerve	2 (4.5%)	5 (11.4%)	4 (9.1%)	8 (18.2%)
Common peroneal nerve	6 (13.6%)	7 (15.9%)	6 (13.6%)	10 (22.7%)
Sciatic + tibial nerve	9 (20.5%)	9 (20.5%)	5 (11.4%)	5 (11.4%)
Sciatic + common peroneal	3 (6.8%)	4 (9.1%)	2 (4.5%)	2 (4.5%)
Tibial + common peroneal	6 (13.6%)	6 (13.6%)	9 (20.5%)	9 (20.5%)
Sciatic + tibial + common peroneal	17 (38.6%)	12 (27.3%)	18 (40.9%)	10 (22.7%)

Table 3: Between-side comparison of changes in three outcome measures measured on three occasions (pre-treatment, immediate post-treatment and 15-min post-treatment) for both the interventions

	Control side- Sham intervention			Experimental side- Neurodynamic mobilization		
	T-1	**T-2**	**T-3**	**T-4**	**T-5**	**T-6**
VPT (volts)	45.88 ± 2.22	45.47 ± 2.68	46.20 ± 2.40	46.75 ± 3.21	32.31 ± 3.45	34.65 ± 4.04
HPT	15.72 ± 2.67	15.81 ± 2.77	15.40 ± 2.78	15.95 ± 2.77	7.79 ± .851	8 ± .835
CPT	15.63 ± 2.73	16.06 ± 3.16	15.59 ± 3.12	16.20 ± 3.23	7.93 ± .94	8.13 ± .90
	T-12	**T-23**	**T-13**	**T-45**	**T-56**	**T-46**
VPT (volts)	.40 ± 3.65	-.72 ± 4.00*	-.31 ± 3.41	14.43 ± 4.34*	-2.34 ± 6.04	12.09 ± 5.48*
HPT	-.09 ± 2.58	.40 ± 3.64	.31 ± 3.88	8.15 ± 3.18*	-.20 ± 1.06	7.95 ± 2.96*
CPT	-.43 ± 3.22	.47 ± 3.69	.04 ± 4.17	8.27 ± 3.52*	-.20 ± 1.13	8.06 ± 3.42*

in vibration perception thresholds between-treatments at 5 ± 2 volts and alpha level at 5% and a power of 90%, to get a sample of 22 per group. We thus multiplied into two to arrive at our present sample size 44. There were no expected drop-outs since the study was in a single session.

Patient characteristics

Of the 63 patients screened, 46 fulfilled the inclusion criteria and 44 volunteered to participate in our study. The study population of 44 patients was of age 53.86 ± 9.85 years, 26 male and 18 female, with diabetes duration of 5.81 ± 2.28 years and neuropathic pain duration of 3.7 ± 1.69 years. The patients' overall pre-treatment VPT was 46.31 ± 2.44 volts, HPT was 15.84 ± 1.89 degrees Celsius, and CPT was 15.92 ± 2.06 degrees Celsius. The overall patient demographic characteristics for patients' age, duration of diabetes, duration of neuropathic pain, VPT, HPT and CPT were shown in table-1 with between-group comparisons. Table-2 shows the overall baseline neurodynamic assessment (neurodynamic testing and nerve trunk palpation) findings for all three lower limb nerves (sciatic, tibial and common peroneal).

- : Negative sign indicates increase in values.

*- mean differences (changes) between-treatments were significant at p<.05 level.

(T-1 & T-4: pre-treatment; T-2 & T-5: immediate post-treatment; T-3 & T-6: 15-min post-treatment; T-12 & T-45: comparison between pre-treatment and immediate post-treatment; T-23 & T-56: comparison between immediate post-treatment and 15-min post-treatment; T-13 & T-46: comparison between pre-treatment and 15-min post-treatment).

COMPARISON BETWEEN INTERVENTIONS

The table-3 showed between-treatment comparison for the pre-post change in three outcome measures.

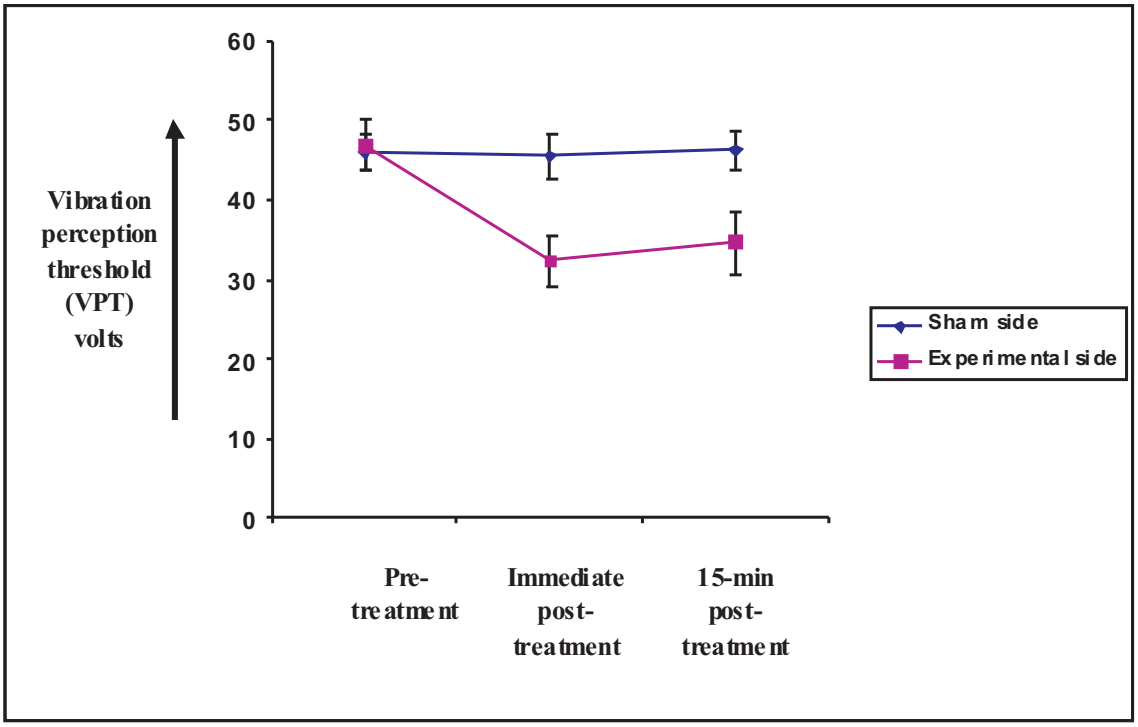
The experimental side had a greater reduction of VPT of about 14.02 ± 5.15 volts from pre-treatment to immediate post-treatment compared to the sham side (p<.05). The experimental side had a slightly greater increase in VPT of about 1.61 ± 6.83 volts from immediate post-treatment to 15-min post-treatment compared to the sham side (p>.05). The experimental side had a greater reduction of VPT of about 12.40 ± 4.90 volts from pre-treatment to 15-min post-treatment compared to the sham side (p<.05).

The experimental side had a greater reduction of HPT of about 8.25 ± 4.41 degree Celsius from pre-treatment to immediate post-treatment compared to the sham side (p<.05). The

experimental side had a slightly greater increase in HPT of about .61 ± 3.68 degree Celsius from immediate post-treatment to 15-min post-treatment compared to the sham side (p>.05). The experimental side had a greater reduction of HPT of about 7.63 ± 5.18 degree Celsius from pre-treatment to 15-min post-treatment compared to the sham side (p<.05).

The experimental side had a greater reduction of CPT of about 8.70 ± 5.62 degree Celsius from pre-treatment to immediate post-treatment compared to the sham side (p<.05). The

Figure 2: Comparison of changes in vibration perception thresholds (in volts) between sham-treated side versus neurodynamic-treated side at pre-treatment, immediate-post treatment and 15-min post-treatment



experimental side had a slightly greater increase in CPT of about .68 ± 3.94 degree Celsius from immediate post-treatment to 15-min post-treatment compared to the sham side (p>.05). The experimental side had a greater reduction of CPT of about 8.02 ± 5.97 degree Celsius from pre-treatment to 15-min post-treatment compared to the sham side (p<.05).

Comparison of change in VPT

Pre-treatment and immediate post-treatment-

The between-treatment difference (14.02 ± 5.15 volts) was statistically significant (p=.000) with greater decrease in VPT observed for the experimental side compared to the sham side.

Immediate post-treatment and 15-min post-treatment-

The between-treatment difference (1.61 ± 6.83 volts) was not statistically significant (p=.125) with greater decrease in VPT observed for the experimental side compared to the sham side.

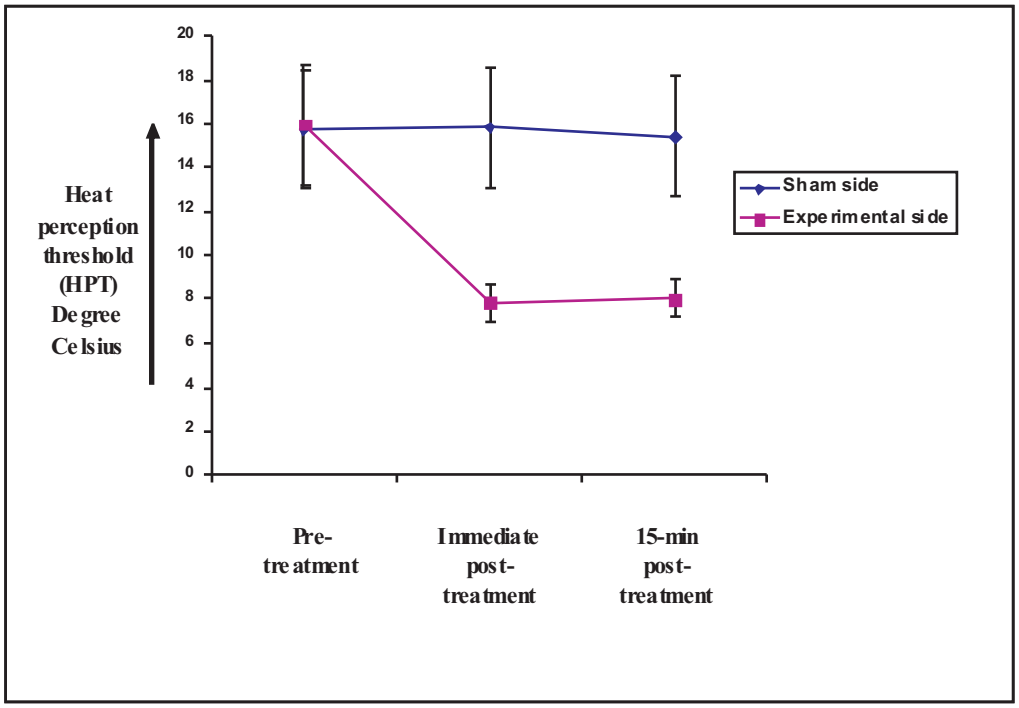
Pre-treatment and 15-min post-treatment-

The between-treatment difference (12.40 ± 4.90 volts) was statistically significant (p=.000) with greater decrease in VPT observed for the experimental side compared to the sham side.

Comparison of change in HPT

Pre-treatment and immediate post-treatment-
The between-treatment difference (8.25 ± 4.44 degree Celsius) was statistically significant (p=.000) with greater decrease in HPT observed for the experimental side compared to the sham side.

Figure 3: Comparison of changes in heat perception thresholds (in degree Celsius) between sham-treated side versus neurodynamic-treated side at pre-treatment, immediate-post treatment and 15-min post-treatment



Immediate post-treatment and 15-min post-treatment-

The between-treatment difference (.61 ± 3.68 volts) was not statistically significant (p=.275) with greater decrease in HPT observed for the experimental side compared to the sham side.

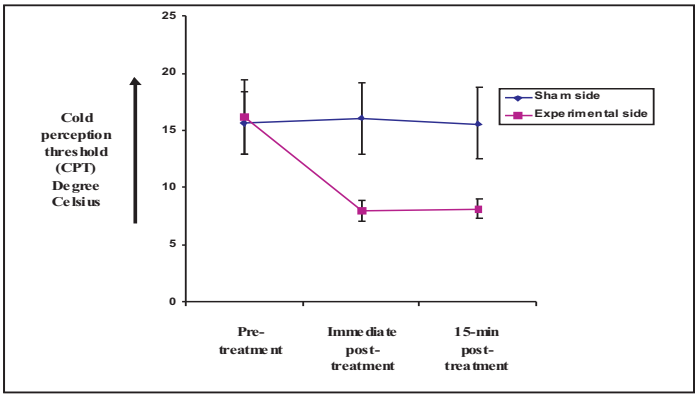
Pre-treatment and 15-min post-treatment-The between-treatment difference (7.63 ± 5.18 volts) was statistically significant (p=.000) with greater decrease in HPT observed for the experimental side compared to the sham side.

Comparison of change in CPT

Pre-treatment and immediate post-treatment-The between-treatment difference (8.70 ± 5.62 volts) was statistically significant (p=.000) with greater decrease in CPT observed for the experimental side compared to the sham side.

Immediate post-treatment and 15-min post-treatment-The between-treatment difference (.68 ± 3.94 volts) was not statistically significant (p=.257) with greater decrease in CPT observed

Figure 4: Comparison of changes in cold perception thresholds (in degree Celsius) between sham-treated side versus neurodynamic-treated side at pre-treatment, immediate-post treatment and 15-min post-treatment



for the experimental side compared to the sham side.

Pre-treatment and 15-min post-treatment-

The between-treatment difference (8.02 ± 5.97 volts) was statistically significant (p=.000) with greater decrease in CPT observed for the experimental side compared to the sham side.

DISCUSSION

Our study is the first of its kind reporting beneficial effects of nerve sliders and nerve massage in patient population of painful diabetic peripheral neuropathy. One study[66] earlier evaluated tibial nerve neurodynamic mobilization techniques for neuropathic pain in type-2 diabetic patients and another study[67] for sciatic nerve, both were conference presentations by Kumar et al. Published studies evaluating the techniques' effects were recently shown by Kumar et al[68] who studied nerve massage influence on the vibration and thermal perception in asymptomatic subjects when they tested the effects for tibial nerve. The authors concluded beneficial therapeutic effects for transverse nerve massage that made us to choose it as a part of experimental intervention. Another study by Kumar et al[69] on comparison between nerve sliders and tensioners for tibial nerve on their effects on vibration and temperature thresholds in asymptomatic subjects found slider techniques to be clinically useful that necessitated the inclusion of sliders into our experimental group.

Despite the existed controversy[70] about nerve mobilization and neurodynamics, the concept of specific nerve mobility and mobilization is growing in evidence.[48] Thus we based our patient selection not only based on clinical examination findings[71] to suit neurodynamic interventions but also based on evidence-informed clinical decision-making.[72]

The peripheral nerve trunks and their connective tissue sheaths have viscoelastic mechanical properties[73] and hence they can easily adapt to changes in their length by minimal metabolic and circulatory adjustments that manifest as neurophysiologic effects.[74] Of the reasons for rejection of null hypothesis, the contribution of clinical reasoning[75] in subject selection cannot be overemphasized in that all subjects had positive neurodynamic tests with mechanosensitivity on tibial nerve palpation.

One alternative explanation for the observed effects of the neurodynamic techniques could be due to the movement components which might have also induced afferent kinesthetic impulses from ankle and foot muscles which in turn could possibly influence the cutaneous receptor afferents thus altering perception of sensory thresholds.[76] This effect and possible acceptance of null hypothesis had been minimized by having a control side, where sham neurodynamic technique[77] was done including only ankle and foot movement components to stress local non-neural tissues. Such a sham intervention have enabled us to study the effects of cognitive-perceptual influences and the role of placebo associated with manual therapy interventions.[78] Caution should be exercised in that our study sample was small in size and it was a pilot study prior to start of a large-scale randomized controlled trial in patients with diabetic peripheral neuropathic pain.

The reason for choosing vibration perception threshold (VPT) and thermal perception thresholds (TPT) as outcome measures only instead of tactile threshold, current perception threshold, pressure pain threshold or thermal pain threshold is that VPT and TPT can be conveniently measured and they both in themselves depict an accurate measure of peripheral nerve function in neuropathies.[79]

The within-subject experimental design of our study eliminated the influence of confounding factors on sensory perception thresholds like age,[80] gender,[81] psychophysical factors,[82] room temperature,[83] skin temperature,[84] probe cross-sectional area[85] thus proving that the generalizability of the findings for the observed difference was due to the effects of techniques per se. Within-side skin temperatures can vary from 18-35^{o}C when noticed in a normal hand at a room temperature of 35^{o}C[85] measuring which was not under the scope of our study. Also within-side adaptation for vibratory stimulus[86] was best prevented in our study by selecting appropriate recovery times between successive stimuli.

The duration of thermal stimulus exposure used in our study was 4 min per degree Celsius (greater

than 3 min duration), which was shown to be the best duration to minimize the spatial summation effect of the sequential stimuli.[87] The other factor like frequency of stimuli was under control once the rate of exposure was maintained. The end-organ distribution[88] or cutaneous innervation[89] in the feet, if there was a difference between sides, which could influence thermal perception to a large extent, however was not under the control of our study.

The method of assessment used for measurement of thermal perception thresholds in our study was Method of Levels (MLE). Of the three methods of assessment[90], the Methods of Limits (MLI) was considered better than Methods of Levels (MLE) and Methods of Forced Choice (MFC) since it is inclusive of reaction time but is not suitable for distal body parts like feet since it is dependent on the distance of the part from the brain and hence the stimulus' conduction velocity.[91] For use in single part or a region, hence MLE method was widely preferable to MLI method. We hope this justifies our use of MLE method for thermal perception threshold testing.

The other significant implication of this study was the value of measuring the threshold for warming and cooling separately, since it is held that the two modalities are conveyed by different peripheral nerve fibres: sensations of warming in unmyelinated peripheral nerve fibres and those of cooling in small myelinated fibres. Estimation of thresholds can therefore be used to examine the functional integrity of these fibres which are inaccessible to clinical electrophysiological investigations.[92]

One of the acceptable limitations of this study was it was on immediate effects of the two techniques, the same when applied in a different duration and dosage might produce very different results. Post-intervention 15 min measurement of thresholds showed a trend towards reversibility of the effects of both the techniques, hence these techniques can be safely applied in patient population in that they are not detrimental to nerve function.[50] Of the major role in the effects of the techniques was the application of clinical reasoning in the selection criteria in that restricted tibial nerve mobility was confirmed with tibial nerve neurodynamic test and random selection of treatment side with blinded observer recording eliminated the bias to a large extent.

Another limiting factor of our study not controlled was the probable presence of anatomic variations in the tarsal tunnel[93] and also in both the course[94] and divisions[95,96] of tibial nerve which might have been present in subjects' either side lower limb which could not be ruled out. According to Shacklock,[63] presence of anatomical anomalies would mislead clinicians into misinterpretation of responses to neurodynamic testing. The effects of neurodynamic techniques were not attributed only to the peripheral mechanisms but also to the central neuromatrix.[97] The role of central neuromatrix in altering the sensory perception thresholds was a subject not yet studied so far.

There is scope for further research in patient populations with lower extremity peripheral neuropathic pain syndromes after knowledge of central and peripheral mechanisms for the symptoms,[98] with in-vivo non-invasive measurement techniques for outcome measurement such as real-time Spectral Doppler ultrasonography[99,100] for nerve mobility during the application of the two neurodynamic mobilization techniques. The techniques could also be studied in combination and/or comparison to other treatment techniques for peripheral neuropathic pain such as pharmacotherapy[101] and/or other physiotherapy treatment methods.[102] The effects of such treatment combinations should be evaluated using well established and validated clinical assessment scales[103] for PDPN patients.

CONCLUSION

Neurodynamic mobilization comprising of nerve sliders and nerve massage to sciatic , tibial and common peroneal nerves reduced vibration perception thresholds, heat perception thresholds and cold perception thresholds in the treated side significantly compared to the sham-treated side lower extremity in painful diabetic peripheral neuropathy patients in this study.

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