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A Systematic Review on Neurodynamics and Neuropathic Pain in Diabetic Peripheral Neuropathy: Revisiting the Evidence for "Chicken or Egg?

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Abstract

Background: Neurodynamics is the concept based on a close interaction of mechanics and physiology of the nervous system which is focused on mechanical properties of peripheral nerves to be considered while assessing and treating patients' neuropathic symptoms via nervous system mobilization and manual therapy. **Purpose:** The objective of this study was to evaluate the existing evidence for neurodynamics in Diabetic peripheral neuropathy (DPN) from a research-informed perspective. **Methods:** A systematic review using search terms "neurodynamics and diabetic neuropathy" in PubMed, CINAHL and Google Scholar was done and the obtained articles were descriptively synthesized into examination and treatment of neurodynamics in DPN population. **Results:** Out of the 12 included studies, there were four studies on healthy subjects which found neurodynamic techniques to have desirable neurophysiological effects and they were safe to use without any reported major detrimental effects on neurological function. The three evaluation studies, unanimously found altered responses to lower extremity neurodynamic testing in DPN population when tested to initial pain, in terms of range of motion changes during structural differentiation, and these studies found that neural mechanosensitivity was high among people with painful diabetic neuropathy compared to painless DN, or type-2 diabetes or normal persons, and correlated to neuropathic pain, sensory perception thresholds and quality of life. The five intervention studies (one on all three nerves, two on tibial nerve, one each on tibial and sciatic nerves) that studied community-based weekly intervention of neurodynamic mobilization in addition to standard care demonstrated beneficial effects in favor to the NDM group compared to standard care and/or sham intervention. **Conclusion:** There is limited evidence for altered neurodynamics in DPN population, and that neurodynamic mobilization was an effective therapeutic adjunct to standard care, although population-based pragmatic clinical trials are yet to done to provide effective recommendations for practice.

Keywords: Diabetic peripheral neuropathy; Neurodynamics; Nerve palpation; Nerve massage; Nerve mobility.

Introduction

Neurodynamics is the concept based on a close interaction of mechanics and physiology of the nervous system which is focused on mechanical properties of peripheral nerves to be considered while assessing and treating patients' neuropathic symptoms via nervous system mobilization and manual therapy.[1]

Neurodynamics is a relatively newer term considering that the very origin of the concept was involved with use of misnomers such as nerve rubbing,[2] nerve-stretching,[3] adverse neural tension,[4] neural tissue provocation,[5] neural tissue extensibility,[6] neural

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mobilization[7] which were suggested to be better replaced by the term "neurodynamics" much later.[8]

Neurodynamic assessment techniques were aimed at identifying the nerve and its adjacent structures as the source of dysfunction in patients who presented with positive/ painful neuropathic symptoms through nerve palpation and neurodynamic testing.[9] Presence of mechanical allodynia during the former and reproduction of patients' symptoms with symptom alterations in structural differentiation maneuvers during the latter were considered as important clinical signs that would direct intervention goals in neurodynamic mobilization.[10]

Techniques used for neurodynamic mobilization included nerve sliders and nerve tensioners, and nerve massage.[11] Nerve sliders were aimed at improving gliding of nerve on its undersurface whilst tensioners were aimed at elongating the nerve.[12] The former was shown tobe more beneficial due to its unique ability to produce increased longitudinal excursion of peripheral nerves thereby mobilizing the nerve against its nerve bed, without compromising microneurocirculation when compared to tensioners.[13]

There is growing evidence for neurodynamic mobilization as an effective manual intervention for many musculoskeletal conditions14 and for neuropathic pain in general,[15] but recommendations for its use in peripheral neuropathic pain could be derived based upon clinical reasoning and neurobiological evidence.[16]

Peripheral nervous system dysfunction clinically manifest as peripheral neuropathies in a large proportion of diabetic patients, presenting either as painful or painless neuropathies.[17] Painful neuropathies often present clinically as a combination of symptoms that involve nerve trunk pain and dysesthetic pain.[18] 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).[19] Dysesthetic pain is often characterized as an unfamiliar or abnormal sensation such as burning, tingling, electric, searing, drawing, or crawling,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).[20]

The foundation of knowledge behind neural tissue mechanosensitivity[21,22] in painful diabetic neuropathies arose from the fact that peripheral nerve trunks exhibited mechanical allodynia and mechanical hyperalgesia in animal and human experimental models of diabetic peripheral neuropathic pain (DPNP). [23,24,25]

Altered neurodynamics could be a cause or an effect of chronic neuropathic (nerve trunk) pain and vice versa, the question of chicken or egg, which is the need for this study. The nerve trunk pain present in DPNP may be assessed for its mechanosensitivity using neurodynamic examination and henceforth suitably addressed using neurodynamic mobilization techniques if evidence for neurodynamics could be unearthed in DPNP. The objective of this study was to evaluate the existing evidence for neurodynamics in DPNP from a research-informed perspective.

Methodology

A systematic review using search terms "nerve mobility, neurodynamics, manual therapy, neurophysiology and diabetic neuropathy"in PubMed, CINAHL and Google Scholar was done through parallel independent blinded search by two testers who resolved their disagreements with third tester by mutual consensus at every stage of review. The obtained citations were scrutinized by their title, abstract and full-text content, so that data extraction and descriptive synthesis was done to organize the evidence

under effects of lower extremity neurodynamics on neurophysiology in healthy subjects; lower extremity neurodynamic examination in diabetic neuropathy; and, effects of lower extremity neurodynamic mobilization in diabetic neuropathy.

Results

A total of 12 studies were included in the final list for data extraction and synthesis which are described as follows:

Neurodynamic Mobilization Effects on Neurophysiological Parameters in Healthy Subjects

Neurophysiological effects of SLR test was studied by Ridehalgh *et al*[26] 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*[27] on ten healthy subjects, demonstrated longer tibial nerve F-wave latencies when measured in straight leg raise position, supposedly 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.

In another preliminary randomized clinical trial comparing tibial nerve transverse massage and longitudinal massage on their effects on vibration perception thresholds (VPT), heat perception thresholds (HPT) and cold perception thresholds (CPT) in 48 asymptomatic volunteers, the three sensory thresholds were measured pre-technique, immediate post-technique and 15-min post-technique. The choice of first side of longitudinal/transverse nerve massage was selected randomly. Longitudinal massage was given to the tibial nerve along the length of the nerve from the foot to the popliteal fossa, and transverse massage was applied across the length of the nerve. The study found immediate decrease in VPT and HPT with an increase in CPT in the side of leg given transverse massage. Changes in HPT and CPT were not statistically significant, and the changes were reversible in 15-min post-technique.[28]

In another pilot study (parallel-group comparison), tibial nerve sliders and tensioner techniques were compared for their effects on VPT, HPT and CPT in 138 healthy volunteers who were randomly assigned to receive either of two techniques. The selected technique was applied to both the legs and between-sides averaged VPT, HPT and CPT were taken for outcome assessment. Tibial nerve slider technique was applied with performing movements beginning with ankle dorsiflexion/eversion and knee flexion to ankle plantarflexion/inversion and knee extension, in a 600 hip flexed position. The tibial nerve tensioner technique involved movements from ankle plantar flexion/inversion and knee flexion to ankle dorsiflexion/eversion and knee extension in the similar position. Pre-technique measurement was done first, and then following the technique application, immediate post-technique and 15-min post-technique measurements were taken. The authors found significant reductions in all the three measures immediately post-intervention for tibial nerve slider technique compared to the tensioner technique. The changes were reversible and were also statistically significant at 15-min post-treatment.[29]

To summarize from the above four studies on healthy subjects, it is fairly evident that neurodynamic techniques have desirable neurophysiological effects and they were safe to use without any reported major detrimental effects on neurological function.

Neurodynamic Examination Findings in PDPN Patients

Comparison with Other Populations

Boyd *et al*[30] studied 43 people with T2DM and peripheral neuropathy where the authors performed straight leg raise neurodynamic tests with ankle plantar flexion (PF/SLR) and dorsiflexion (DF/SLR) while they measured hip flexion range of motion (ROM), lower extremity muscle activity and symptom profile, intensity and location of symptoms at rest, first onset of symptoms (P1) and maximally tolerated symptoms (P2). The authors found that the addition of ankle dorsiflexion during SLR testing reduced the hip flexion ROM. Individuals in the T2DM group with signs of severe DSP had no difference in hip flexion ROM between PF/SLR and DF/SLR at P1 or P2. The authors concluded that P1 is an appropriate test end point for SLR neurodynamic testing in people with T2DM. However, their findings also suggested that people with T2DM and severe DSP have limited responses to SLR neurodynamic testing and increased neural tissue mechanosensitivity.

A cross-sectional study was on 164 subjects which included 38 normal subjects; 51 with type-2 diabetes mellitus; 30 with painless peripheral neuropathy and type-2 DM; and 45 with T2DM and PDPN. The study compared the neurodynamic examination findings between the above four groups. Upon performing neurodynamic testing and nerve trunk palpation to bilateral lower limb nerves, findings of pain/ resistance/ muscle spasm with range of motion at initial pain (P) and grade of mechanical allodynia were measured respectively for sciatic, tibial and common peroneal nerves. The authors found that the PDPN group had the greatest abnormalities in neurodynamic examination findings compared to diabetic group. The painless neuropathy group was similar to normal group in their findings. Sciatic and tibial nerves were commonly involved together in positive neurodynamic tests and all three nerves were mechanosensitive to nerve trunk palpation in PDPN group. We concluded that abnormal neurodynamic findings in PDPN patients were demonstrated in terms of positive sciatic and tibial neurodynamic tests and by mechanosensitivity during nerve trunk palpation for all three nerves tested.[31]

Relationship with Other Outcome Measures

In another cross-sectional study on 112 PDPN patients, that assessed neuropathic pain using neuropathic pain questionnaire (NPQ); neurodynamic testing- NDT (range of motion in degrees) and nerve trunk palpation- NTP (presence of mechanical allodynia by clinical scoring) of sciatic, tibial and common peroneal nerves; quantitative sensory testing that comprised of vibration perception thresholds (VPT), heat perception threshold- HPT and cold perception threshold- CPT using biothesiometer; and quality of life using neuropathy-specific quality of life (NeuroQoL) instrument. The study found a statistically significant positive correlation found between neuropathic pain, neurodynamic testing, neuropathy-specific quality of life in patients with PDPN. Also there was a good positive correlation found between NDT and NTP. There was a fair positive correlation found between NPQ and HPT; NPQ and CPT. There were a fair negative correlation found between NPQ and NeuroQoL; VPT and CPT. The study concluded that the observed relationship confirmed the then existed hypothesis of the inter-relationship between neuromechanics and neurophysiology existing among PDPN patients.[32]

Neurodynamic Mobilization as a Treatment Method in PDPN Patients

Sciatic, Tibial and Common Peroneal Nerves

The first observer-blinded pilot randomized sham-controlled clinical trial with concealed allocation was reported in 34 PDPN patients who were administered nerve sliders and nerve massage to one lower limb while sham intervention of passive joint movements was performed for the other limb. The three outcomes of VPT, HPT and CPT were assessed

pre, immediate post and 15 min-post intervention on both feet using a biothesiometer. The experimental side had a greater reduction of VPT, HPT and CPT from pre-treatment to 15-min post-treatment compared to the sham side.[33]

Sciatic Nerve

A randomized clinical trial studied thirty two PDPN patients who were randomized to receive either of two interventions - control and experimental. The control group received sham treatment, drugs for glycemic control, amitriptyline for neuropathic pain, diet-lifestyle modification and walking exercise prescription. The experimental group received in addition, sciatic nerve neurodynamic mobilization consisting of nerve massage and nerve sliders. The treatment session was of 45 min duration on five sessions (one session per week) for total study duration of five weeks. Patients were instructed to perform self-mobilization once daily and were given patient log to ensure compliance. Data was collected twice- pre and post intervention. The experimental group showed significant improvements post treatment in all the four study outcomes. The between-group mean differences for NPQ, neurodynamic range of motion, vibration threshold and NeuroQoL were in favor of experimental group which suggested efficacy of sciatic nerve neurodynamic mobilization in PDPN population.[34]

Tibial Nerve

A randomized controlled trial studied thirty two patients of age who were randomized to receive either of two interventions- control and experimental. The control group received drugs for glycemic control, analgesics for neuropathic pain, lifestyle modification and walking exercise prescription. The experimental group received in addition, tibial nerve neurodynamic mobilization consisting of nerve massage, sliders and tensioners. The treatment session was of 45 min duration on five sessions (one session per week) for total study duration of five weeks. Patients were instructed to perform self-mobilization once daily and were given patient log to ensure compliance. Data was collected twice- pre and post intervention. The experimental group showed significant improvements post treatment in all the four study outcomes. The between-group mean differences for neuropathic pain questionnaire (NPQ), neurodynamic range of motion, vibration threshold and neuropathy-specific quality of life (NeuroQoL) were in favor of experimental group which demonstrated beneficial effects for tibial nerve neurodynamic mobilization in DPN population.[35]

Singh *et al*[36] in their randomized controlled trial compared the effects of tibial nerve mobilization versus no-treatment on VPT in 30 male subjects with DPN who were treated for 21 days, and found that the nerve mobilization group had better reductions in VPTs post-intervention.

Common Peroneal Nerve

Kumar *et al*[37] evaluated the efficacy of common peroneal neurodynamic mobilization (CPNM) as an adjunct to standard physical therapy (SPT) in treatment of people with painful diabetic distal symmetric polyneuropathy (PDDSP) in theirparallel-group randomized clinical trial of 32 adults who were randomly assigned to receive either a combined SPT (walking exercise prescription, diet and lifestyle modification) with CPNM (sliders and nerve massage) or SPT alone, for once-weekly 30-min treatment sessions for 5-weeks. The combined group (SPT+CPNM) had better improvements for between-group mean differences in pain severity and pain interference on brief pain inventory- diabetic peripheral neuropathy (BPI-DPN), vibration perception thresholds (VPT), heat and cold perception thresholds (HPT, CPT) and neuropathy-specific quality of life (NeuroQoL) than the SPT group.

Discussion

This study was primarily aimed at establishing evidence in a direction-specific cause-to-effect inter-relationship between neurodynamics and neuropathic pain, and although longitudinal cohort studies were absent in DPN population, the randomized controlled trials had attempted to answer in one direction- altered neurodynamics could be a cause for neuropathic pain since effective improvements in neurodynamic range of motion during testing were associated with better symptom relief in patients with DPN.

However, the other direction is still unanswered, which indicates future trials on medical management for pain relief, to assess effects on neurodynamics. The second aspect is partially addressed however by the control group responses in the three RCTs that showed significant improvements in all outcomes. Mainstay in management of diabetes and its complications is a comprehensive multidisciplinary biopsychosocial team approach[38] which was evidently demonstrated in the treatments provided in the control groups of the three studies- a combination of anti-hyperglycemic drugs, analgesics for neuropathic pain, lifestyle modification and walking exercise prescriptions.

Validity and reliability of neurodynamic examination tests and procedures was not established prior to the included studies, and more recently nerve trunk palpation was validated using pressure algometry for sciatic, tibial and common peroneal nerves by Walsh and Hall.39Modifications of the straight leg raise test through different combinations of ankle and foot movements was shown to differentially induce nerve-specific strains in sciatic, tibial and plantar nerves which validated their use in clinical testing.[40]

The two evaluation studies, unanimously found altered responses to lower extremity neurodynamic testing in DPN population when tested to initial pain, in terms of range of motion changes during structural differentiation, and these studies found that neural mechanosensitivity was high among people with painful diabetic neuropathy compared to painless DN, or type-2 diabetes or normal persons. Future evaluation studies should explore the reliability and validity of test components in DPN population, and their relationship to clinical examination findings[41] and clinical assessment scales.[42]

The five intervention studies(one on all three nerves, two on tibial nerve, one each on tibial and sciatic nerves) that studied community-based weekly intervention of neurodynamic mobilization in addition to standard care demonstrated beneficial effects in favor to the NDM group compared to standard care and sham intervention. Future intervention studies should combine medical,[43] surgical,[44] physiotherapeutic[45] and acupuncture[46] treatments and evaluate their efficacy in a pragmatic manner. The five intervention studies- one pilot study and four randomized clinical trials on patients with PDPN have shown beneficial clinical effects which indicated a much larger well-designed large-scale clinical trial, with improved treatment dosage parameters and recommended outcome measures with long-term follow-up.

Recently, measurement of longitudinal nerve motion using ultrasonography is gaining popularity[47] and its reliability was reported in previous studies both at rest[48] and during neural mobilization.[49] In DPN population, ultrasonography of the tibial[50] and sural[51] nerves were shown to detect early changes of nerve fiber dysfunction and were recommended as effective non-invasive diagnostic techniques[52] that could be used for decision making in decompressive surgery.[53] Future studies thus could incorporate in-vivo nerve motion measurements for studying efficacy of neurodynamic-based interventions.

Another therapeutic advancement in the field of pain and its management is the mechanism-based classification of pain,[54] and clinicians and researchers involved with DPN population should emphasize a

mechanism-based approach while deciding evidence-informed treatments for mobilizing patients with DPN.[55,56]

Conclusion

The evaluation studies found that neural mechanosensitivity was higher among people with painful diabetic neuropathy compared to painless DN, or type-2 diabetes or normal persons. This altered neurodynamic examination was related to neuropathic pain, sensory perception thresholds and quality of life in people with DPN. From the intervention studies on neurodynamic mobilization in PDPN patients, it is now evident that NDM has beneficial effects both immediate and short-term, when applied to all three nerves- sciatic, tibial and common peroneal either individually or in combination.

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