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Adel M. Alshahrani

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LOMA LINDA UNIVERSITY
School of Allied Health Professions
in conjunction with the
Faculty of Graduate Studies

The Effects of a Novel Therapeutic Intervention in Diabetic Peripheral
Neuropathy Patients

by

Adel M. Alshahrani

A Dissertation submitted in partial satisfaction of
the requirements for the degree
Doctor of Science in Physical Therapy

September 2015

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Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Science.

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ABBREVIATIONS

INF	Intra-Neural Facilitation
DPN	Diabetic Peripheral Neuropathy
CDP	Computerized dynamic posturography
SOT	Sensory Organization Test
LOS	Limits Of Stability
RT	Reaction Time
EPE	Endpoint Excursion
MXE	Maximum Excursion
DCL	Directional Control
ABC	Activities-Specific Balance and Confidence
DSPN	Chronic sensorimotor distal symmetric polyneuropathy
mTNS	Modified Total Neuropathy Scale
COG	Center Of Gravity

ABSTRACT OF THE DISSERTATION

The Effects of a Novel Therapeutic Intervention in Diabetic Peripheral Neuropathy Patients

by

Adel M. Alshahrani

Doctor of Science, Graduate Program in Physical Therapy
Loma Linda University, September 2015
Dr. Eric Johnson, Chairperson

Diabetes mellitus (DM) is a common disorder affecting individuals in the United States and in the world. The prevalence of DM has increased noticeably over the last three decades with an estimated 380 million people currently diagnosed with this disease. DM is associated with numerous systemic complications that affect the retina, heart, brain, kidneys, and nerves. The most common complication of DM is diabetic peripheral neuropathy. Diabetic peripheral neuropathy causes reduced sensation, reflexes, proprioception, and strength in lower limbs that leads to balance problems. Various manual therapy techniques have not approached a pilot study for the efficacy of a manual therapy technique to evaluate symptom alleviation in patients with diabetic peripheral neuropathy in order to improve balance.

The purpose of this study is to look at the impact of a novel intervention called Intra-neural facilitation (INF) on objective static, objective dynamic, subjective balance measures, and a peripheral neuropathy scale in patients with Diabetic Peripheral Neuropathy (DPN).

Balance will be assessed using VSR Computerized Dynamic Posturography Sensory Organization Test (SOT, objective static balance measure), VSR Computerized Dynamic Posturography Limits of Stability (LOS, objective dynamic balance measure),

and Activities-Specific Confidence in Balance Scale (ABC, subjective balance measure) and neuropathy will be assessed using modified total neuropathy scale (mTNS).

Evaluation will be conducted at baseline (pre intervention) and (post intervention). The results of this study showed that subjects showed significant improvement in the SOT, one component in the LOS (movement velocity, MVL), and mTNS ($P < .05$).

In conclusion, intraneural facilitation improved objective balance measures and neuropathy symptoms in patients with diabetic peripheral neuropathy. Further study is needed to determine long-term benefits of this intervention.

CHAPTER ONE

INTRODUCTION AND REVIEW OF THE LITERATURE

Diabetes Epidemiology

Diabetes has assumed epidemic proportions in the United States (US), with 9% of the population having the disease. [1]. According to the American Diabetes Association (ADA), the cost of diagnosed diabetes in the US for the year 2012 was \$245 billion, signifying a 41% increase from \$174 billion in 2007 [2]. The bulk of diabetes spending is attributed to direct medical costs including: inpatient care, prescription medications, diabetes supplies and anti-diabetic agents, physician office visits, and residential facility stays [2]. A person with diabetes is likely to spend \$7,900 out of pocket in diabetes-related treatment[2]. This cost is projected to be higher since diabetes increases one's risk for cardiovascular diseases and ocular, renal, and neural complications. [3].

Diabetic Neuropathy Epidemiology

The global prevalence of diabetes has increased dramatically in the last three decades. It is estimated that nearly 380 million people worldwide live with diabetes mellitus[1]. The most common symptomatic complication of diabetes mellitus is diabetic neuropathy. Fifty percent of patients with diabetes have neuropathy [4]. The diabetic peripheral neuropathy (DPN) is a heterogeneous condition that affects different parts of the body. The chronic sensorimotor distal symmetric polyneuropathy (DSPN) is the most common type of peripheral neuropathy in diabetic patients [5]. DPN is known to cause deterioration of the nervous system in the lower limb, which might have a negative impact on the sensory system [6, 7]. Owing to the lack of true proprioceptive

information, patients with DPN are more likely to lose balance during static and dynamic conditions [7-12]. This can lead to an impairment in physical function as a result of reduced standing and walking activities, usually because the patient is afraid of falling [13].

Physiological Effects of Diabetic Peripheral Neuropathy

Due to chronic hyperglycemia, normal cellular communication is weakened, initiating a signaling cascade through the production of protein kinase C and advanced glycation end products, leading to potential nerve damage. Nerve damage occurs as a result of poor nerve perfusion and endoneurial hypoxia caused by reduced capillary blood flow due to thickening of the axons. [14]. The first pathological change in microvascular disease is vasoconstriction. This condition results from the thickening of the capillary basement membrane and hyperplasia, and subsequent decrease in blood flow to the endothelial cells leading to neural hypoxia. Consequently, patients with DPN demonstrate delayed reflex responses when their limbs are positioned in various ways due to limited blood flow to the [15]. These physiological occurrences show that DPN patients are more likely to demonstrate balance problems and are at a higher risk of falling [16].

Balance and Diabetic Peripheral Neuropathy

Postural stability and balance are coordinated by the central nervous system through the integration of three systems, visual, vestibular, and somatosensory [17]. An anomaly on any one of these systems has a potentially disastrous impact on balance. For patients with DPN, postural instability and loss of balance is normally as a result of

discrepancies in the somatosensory system [6, 7]. Due to lack of true proprioceptive information, patients with DPN are more susceptible to balance loss during static and dynamic conditions [7-12]. This can lead to impairment in physical function caused by less standing and walking, usually because the patients fears they may fall [13, 18]. Numerous studies show that patients with DPN have lower balance abilities according to balance indices [9, 12, 16, 19-23].

Intervention for Diabetic Peripheral Neuropathy in Physical Therapy

Treatment for DPN takes on many forms, and prevention of complications can be done through excellent blood glucose control. Whereas there are many pharmacological interventions for DPN symptoms, physical therapy interventions can play an important role in the management of DPN. It is possible to restore balance by restoring the health of the neurons, sensory integration, and compensatory strategies. Management of DPN in physical therapy ranges from using strength exercises and stretching modalities, orthotic devices, and assistive devices, or the combination of two or more of these interventions [13].

Numerous studies have been conducted on patients with diabetic peripheral neuropathy and balance problems. In these studies, physical therapy management ranged from modalities, exercises, stretching, and assistive device. In one such study, Leonard et al, [24] divided patients with DPN into two groups. One group used Monochromatic Infrared Energy (MIRE) and the other group used sham treatment to one leg. Subjects were then asked questions about balance and perception of falls risk. The investigators found decreased perceptions of falls risk in both groups. Also, Kochman et al, [25]

studied the use of MIRE plus strengthening, stretching, and balance exercises on patients with DPN to improve balance. They found an improvement in Tinetti balance measure and a reduction in number of falls. Elsewhere, Powell et al, also found a reduction in number of falls and improvement in fear of falling in a retrospective study of patients with DPN treated with MIRE unit for home use [26]. Pripalta et al, [27] divided his subjects into two groups. One group received vibration insoles that delivered sub-sensory vibration and the other group with no vibration insoles. They found reduction in all sway parameters. Richardson et al, [28] divided the subjects into two groups. One group received open and closed chain ankle strengthening, wall slides, and single-leg stance and the other group neck flexion and scapular stabilization exercises. They found significant improvement on tandem stance, single-leg stance, and functional reach. Ashton-Miller et al, [29] divided the subjects into two groups. One group used single-end cane and the other group with no cane. They found reduction in failure fall. Mueller et al, [30] studied weight bearing exercises versus non weight bearing exercises on patients with DPN. The weight-bearing group showed significance improvement over the non-weight bearing group in the 6-minute walk distance and daily step counts.

Intraneural Facilitation (INF)

The INF intervention is a manual physical therapy approach that was invented and developed by physical therapists at Loma Linda University's east campus rehabilitation services. The intervention is used together with anecdotal evidence in reducing peripheral neuropathy symptoms. The main concept of this approach is the use of two holds. The first hold is called facilitation hold. It entails putting the joint in the other side of the

targeted limb in full loose packed position. For instance, we would put the ankle joint in full planter flexion and inversion and this position would be sustained during the whole session with a stretch strap. We hypothesized that with the joint in this position, the nerve will move more than the artery because the artery has more elastin in it. In this case the nerve is more mobile. The nerve would have more excursions that would stretch the nutrient vessels that are clustered in the joint. the nutrient vessels would have larger opening than the cardiovascular system and more consistent opening [31]. The nutrient vessels in the epineurium will bifurcate in two directions up and down. When they reach the perineum, they will feed the neural connective tissue and we will have more consistent blood flow in the outside of nerves system. By putting consistent pressure in these nutrient vessels, the blood flow will be biased from the cardiovascular system into the nerves and it continues process.

Now, the second hold is a stretch, which slightly stretches the perineurium, potentially unweighting the pressure on the transperineurial vessels allowing circulation to proceed from the epineurial arterioles to the endoneurial capillaries. An example would be a hamstring stretch that would put more blood supply into the sciatic nerve. The purpose of the second hold is to open the perinirium that is the tough middle layer of the neural connective tissue. When the opening happens, we propose this would decompress and allow more blood supply from the outside into the inner part of nerve facicle then into endoneurial capillaries. When the endoneurial capillaries gets more consistent blood flow, it can produce nitric oxide by compressing the pressurized red blood cells into the inflamed capillaries which will lead to vasodilation of endoneurial capillaries [32].

Sensory Organization Test (SOT)

This tool can help researchers to obtain objective scores for static balance. It can assess the ability to utilize vision, somatosensory, and vestibular systems to maintain balance. The NeuroCom[®] Smart Balance Master system computerized dynamic posturography (CDP) was utilized in the present study. This apparatus consists of two force plates. The force plates can be pitched up and down as well as in the anterior-posterior direction. For this test, the patient wore a safety harness while two researchers surrounded the patient to minimize the risk of falling. The researchers asked patient to stand upright on the center of the force plates in a standardized position with shoes on. The patient faced a monitor enclosed by visual surround on three sides.

The test itself consists of six conditions and each condition has three 20-second trials. It identifies abnormalities in three sensory systems that help in postural control: somatosensory, visual, and vestibular. In condition 1, the patient is required to stand still and all sensory information is available. In condition 2, the patient is required to stand still with eyes closed. In condition 3, the surround moves as the patient moves on the force plates. In condition 4, the force plates move as the patient moves. In condition 5, the patient is required to close their eyes and the force plates move as the patient moves. In condition 6, the surround and force plates move as the patient moves. We took the composite equilibrium score and considered static balance score.

The equilibrium score represents the average center of gravity sway for each trial in the six conditions. The normal limit of the Anterior/Posterior (AP) sway angle is 12.5 degrees. We can obtain the equilibrium score from the following equation, $([12.5\text{deg} - (\text{the taMAX} - \text{the taMIN})] / 12.5\text{deg}) * 100$. The total score of this test is 100. Subjects

with little AP sway will acquire scores close to 100, whereas subjects with enormous AP sway will receive scores near zero. In the screen after finishing the test, the green bars represents the range within normal limits and red the range outside the normal limits.

Limits of Stability (LOS)

This tool can help researchers to obtain objective score for dynamic balance. It measures the maximum distance the COG can be moved while maintaining postural stability. The NeuroCom[®] Smart Balance Master system computerized dynamic posturography (CDP) was utilized for this purpose. This apparatus consists of two force plates. The force plates can be pitched up and down as well as in anterior-posterior direction at a frequency of 100 Hz. During this test the patient wore safety harness and two researchers were surrounding the patient to minimize the risk of falling. The researchers asked subjects to stand upright on the center of the force plates in a standardized position with shoes on. The subject faced a monitor enclosed by visual surround on three sides.

For it to quantify control of the center of gravity (COG), the patient is required to voluntarily sway to eight directions without losing their balance spaced at 45 degrees intervals, as represented in computer screen in front of the subject. These eight directions include pure forward, forward-right, pure right, back-right, pure back, back-left, pure left, and forward-left. The LOS report includes reaction time (RT, the time in seconds between the command and the movement of the subject), movement velocity (MVL, the average speed of COG in degrees per seconds), endpoint excursion (EPE, the distance achieved toward a target on the first movement), maximum excursion (MXE, maximum

distance achieved), and directional control (DCL, the difference of amount of movement towards the target to away from the target). We took the composite scores of RT, MVL, EPE, MXE, and DCL from the eight directions. In the screen after finishing the test, the green bars represents the range within normal limits and red the range outside the normal limits.

Activities-Specific Balance Confidence Scale (ABC)

Activities-Specific Balance Confidence Scale (ABC) [33], is a subjective measure of confidence in performing several activities without losing balance or suffering a sense of wobbliness. It is a 16-item self-report measure in which subjects rate their balance confidence for performing activities. Each item ranges from 0 – 100. Score of zero implies falling and a score of 100 implies patient's confidence of stability. We can get the total score of this scale by adding all items together then dividing by 16. The equation for the ABC is: $(\text{overall score of the 16 items} / 16) * 100$. Studies showed that the ABC has excellent test-retest reliability ($r=0.92$, $p<0.001$) [33].

Modified Total Neuropathy Scale (mTNS)

The San Antonio Consensus meeting recommended assessing the peripheral neuropathy with combining quantitative vibrations threshold, quantitative touch threshold, nerve conduction, and patients' report [34]. The total neuropathy scale was first used 1994 [35]. It demonstrated its reliability (interrater reliability, .94; intrarater reliability, .97) [36] although it included nerve conduction studies, which makes it hard to use in a clinical setting. Another version called modified Total neuropathy Scale (mTNS)

developed in 2006, does not include nerve conduction studies [37]. The mTNS is scored from 0 to 24 with each neuropathy rated from 0 to 4 (0 being normal, 4 being severe neuropathy). The higher the score, the more severe the neuropathy. The mTNS severity levels are 3: 0-8 (mild), 9-16 (moderate) and 17-24 (severe). Usually the clinical testing for the mTNS includes muscle strength, vibration sense, pin level, and reflexes [38]. Wampler et al [37], found positive correlations between the mTNS and the TNS ($r = 0.99$; $P < 0.001$).

Summary

Diabetes continues to be a major health burden in the US. In addition to the cost of treatment, diabetes also affects quality of life through debilitating conditions such as diabetic retinopathy, cardiomyopathy, and neuropathy [5, 39]. Of these complications, the diabetic peripheral neuropathy (DPN) which affects peripheral nerves and circulation, can lead to impairment in balance [9, 12, 16]. Patients with DPN are more likely to lose balance during static and dynamic conditions as a result of impaired proprioceptive input. [7-12]. This often results in impairment in physical function caused by limited activity since patients stand and walk less for fear of falling [13, 18]. The current study was a clinical trial approach to determine the effectiveness of INF on objective static measures, dynamic balance measures, and a subjective balance measure. We used quantitative posturography balance measures given their objectivity and utilization in many previous studies [40-43]. We also measured the effect of INF on a neuropathy scale.

CHAPTER TWO

**THE EFFECT OF INTRA-NEURAL FACILITATION ON BALANCE ON
PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY**

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Abstract

Objective: To determine the effect of a novel therapeutic intervention called intraneural facilitation (INF) on balance measures and a neuropathy scale in patients with diabetic peripheral neuropathy.

Design: Prospective pre- and post-test, single group clinical trial.

Setting: Outpatient physical therapy clinic.

Participants: Thirteen patients with diabetic peripheral neuropathy.

Intervention: Subjects received ten sessions of INF.

Main Outcome Measures: The modified total neuropathy scale (mTNS), the NeuroCom[®] Smart Balance Master system computerized dynamic posturography (CDP) that includes the sensory organization test (SOT) and the limits of stability (LOS), and the activities-specific balance and confidence (ABC) scale.

Results: Subjects in this study showed significant improvement in the mTNS, SOT, and one component in the LOS (movement velocity, MVL). There were no significant differences in the ABC or in 4 components of the LOS, which were reaction time (RT), endpoint excursion (EPE), maximum excursion (MXE), and directional control (DCL).

Conclusion: Intranural facilitation improved objective balance measures and neuropathy symptoms in patients with diabetic peripheral neuropathy. Further study is needed to determine long-term benefits of this intervention.

Keywords: Balance, Postural; Diabetes Mellitus, Diabetic Neuropathies, Manual Therapies.

Abbreviations

INF	Intraneural Facilitation
DPN	Diabetic Peripheral Neuropathy
CDP	Computerized Dynamic Posturography
SOT	Sensory Organization Test
LOS	Limits of Stability
RT	Reaction Time
EPE	Endpoint Excursion
MXE	Maximum Excursion
DCL	Directional Control
ABC	Activities-Specific Balance Confidence Scale
DSPN	Sensorimotor Distal Symmetric Polyneuropathy
mTNS	Modified Total Neuropathy Scale
COG	Center of Gravity
DM	Diabetes Mellitus

Introduction

Diabetes mellitus (DM) is a common disorder affecting individuals in the United States and in the world [1]. The prevalence of DM has increased noticeably over the last three decades with an estimated 380 million people currently diagnosed with this disease [1]. DM is associated with numerous systemic complications that effect the retina, heart, brain, kidneys, and nerves [5, 39].

The most common symptomatic complication of DM is diabetic polyneuropathy (DPN), estimated to occur in 50 percent of patients with DM [4]. Despite therapeutic advances of diabetes care over the past decade, there are few known interventions that appropriately address the progression and treatment of DPN [44]. DPN can occur in many forms but most commonly presents as a painless sensorimotor distal symmetric polyneuropathy (DSPN) [5].

Diabetic DSPN causes deterioration of the peripheral nervous system in a length-dependent fashion and can negatively impact the sensory system [6, 7]. Impaired proprioceptive input renders these patients more susceptible to loss of balance during static and dynamic conditions [7-12]. This can impair physical function by reducing standing and walking activities as many patient experience fear of falling [13, 18].

The pathogenesis of DPN is multifactorial and mediated by alterations in the polyol pathway, aldose reductase inhibitors, advanced glycolation products, disordered biochemistry consequences, essential fatty acids, neurotrophic factors and oxidative stress. The common pathological endpoint is endoneurial microangiopathy and subsequent nerve ischemia and hypoxia [14, 45]. As such, DPN patients are more likely

to develop an array of peripheral nerve disorders, balance problems, and a higher risk of falling [9-12, 16, 19-23, 45].

The proposed study utilizes an innovative approach termed intraneural facilitation (INF) in the treatment of diabetic DSPN. This approach aims to bias blood flow into the neural fascicle, improve endoneurial capillary circulation, and reverse intrafascicular ischemia. This passive technique includes stretching muscles, mobilizing joints, tractioning skin, distending visceral structures, and distorting blood vessels to reroute blood to the ischemic nerves [32]. We sought to determine the effectiveness of INF in DSPN using validated neuropathy scales, objective static measures, dynamic balance measures, subjective balance measure, and quantitative posturography balance measures [40-43].

Methods

This IRB-approved study was conducted at Loma Linda University (LLU), which is a tertiary teaching hospital with an outpatient physical therapy clinic providing care to a diverse group of patients. Study subjects were screened from our clinic between October 2014 and February 2015. Informed consent was obtained and the assessment and intervention procedures were conducted in our physical therapy area.

Inclusion criteria for this study included:

1. Male and female patients with DPN from 18 to 85 years of age,
2. DSPN form of DPN confirmed by a medical doctor,
3. Ability to hold static balance for a minimum of 5 minutes.

Potential subjects were excluded if they had co-morbidities such as open wounds, cardiac disease, or other forms of progressive neurological disease or peripheral polyneuropathy impacting balance.

Modified Total Neuropathy Scale (mTNS)

The mTNS is scored from 0 to 24 with each neuropathy rated from 0 to 4 (0 being normal, 4 being severe neuropathy). The mTNS severity levels are divided into 3 levels: 0-8 (mild), 9-16 (moderate) and 17-24 (severe). The clinical testing for the mTNS includes muscle strength, vibration sense, pin sensation level, and muscle stretch reflexes [38].

Static and Dynamic Balance Scales

The NeuroCom[®] Smart Balance Master system computerized dynamic posturography (CDP) was utilized. This apparatus consists of two force plates that can be pitched up and down as well as in an anterior-posterior plane. During this test our subjects wore safety harnesses and supported by two researchers to minimize the risk of falling. The subjects stood upright on the center of the force plates in a standardized position. In this machine two tests were utilized:

1. The Sensory Organization Test (SOT) assesses three sensory systems that affect postural control (visual, somatosensory, and vestibular) (Figure.1A). Six different conditions are tested consecutively with three 20-second trials: in step 1 the patient is required to stand still with eyes open (all sensory information available); in step 2 the patient is required to stand still with their eyes closed; in step 3 the

surround moves as the patient moves; in step 4 the force plate moves as the patient moves; in step 5, the patient closes their eyes and the force plates move as the patient moves; in step 6, the surround and force plate move as the patient moves. We assessed the composite equilibrium and static balance scores (Figure. 1B). [46-48]



Figure 1A. Computerized Dynamic Posturography Sensory Organization Test (SOT)







		VISUAL CONDITION		
		FIXED	EYES CLOSED	SWAY-REFERENCED
S U P P O R T C O N D I T I O N	F I X E D	1 	2 	3 
	S W A Y R E F E R E N C E	4 	5 	6 

Figure 1B. Subjects performed six conditions in the SOT. They stood still on a forceplate with their feet positioned according to a standardized grid and arms by the side.

2. Limits of Stability (LOS) quantifies control of the center of gravity (COG) (Figure 2A). The patient is required to voluntarily sway to eight directions without losing their balance (Figure 2B). The LOS report includes reaction time (RT), movement velocity (MVL), endpoint excursion (EPE), maximum excursion (MXE), and directional control (DCL). We took the composite scores of RT, MVL, EPE, MXE, and DCL from the eight directions.



Figure 2A. Computerized Dynamic Posturography Limits of Stability (LOS)

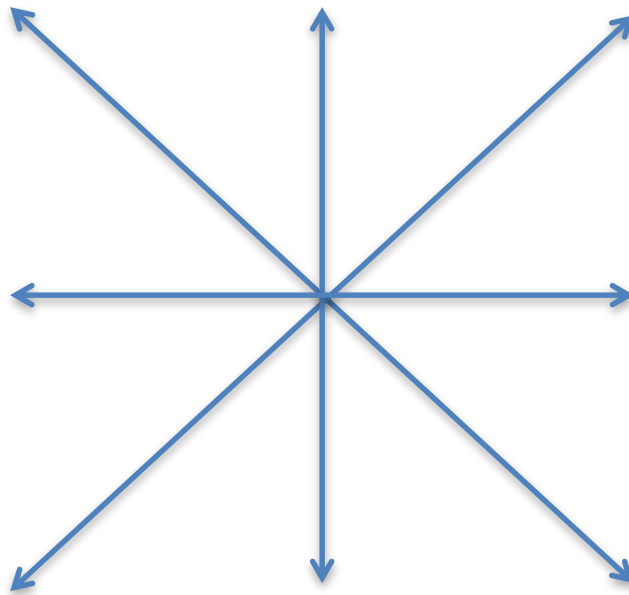


Figure 2B. Subjects in LOS went through leaning in eight directions as the arrows represent it. They stood still on a forceplate with their feet positioned according to a standardized grid and arms by the side.

Activities-Specific Balance Confidence (ABC) Scale

The ABC Scale [33] is a subjective measure of confidence in performing several activities without losing balance or suffering a sense of wobbliness. It is a 16-item self-report measure in which subjects rate their balance confidence for performing certain activities. Each item ranges from 0 – 100. A score of zero implies falling and a score of 100 implies patient's confidence of stability. The total score of this scale is derived by adding all items together then dividing by 16.

Data Collection

Pre-treatment assessment included baseline demographic data, the mTNS, SOT & LOS scores, and the ABC scale.

Post-treatment data was collected for these same measures following 10 sessions of INF treatment.

Data Management and Analysis

Data Management: Two researchers conducted data management using coding manuals for all study measures. All study data was initially reviewed to identify missing values. Methods for missing value adjustment included imputation, list-wise deletion or case-wise deletion. All modifications were recorded in the data-coding manual for future missing data analysis.

Data Analysis: data were analyzed using statistical package SPSS for Windows version 22.0 (SPSS, Inc., Chicago, IL). Means and standard deviations were calculated for the outcome measures separately for pre-intervention and post-intervention. Paired t-

test was used to detect significant change in SOT, RT, MVL, EPE, MXE, and DCL between pre-intervention and post-intervention. Wilcoxon signed was used to compare differences in DCL and mTNS between pre-intervention and post-intervention. A p of .05 or less was considered significant.

Results

Of 25 subjects screened for our study, 17 met inclusion criteria and were enrolled. Of these, 13 completed the study (Figure 3). Four subjects did not complete the study: one developed a foot infection, one had insurance problems that prevented ongoing therapy, and two elected to exit the study due to time restraints. Subject demographics are listed in the Table 1.

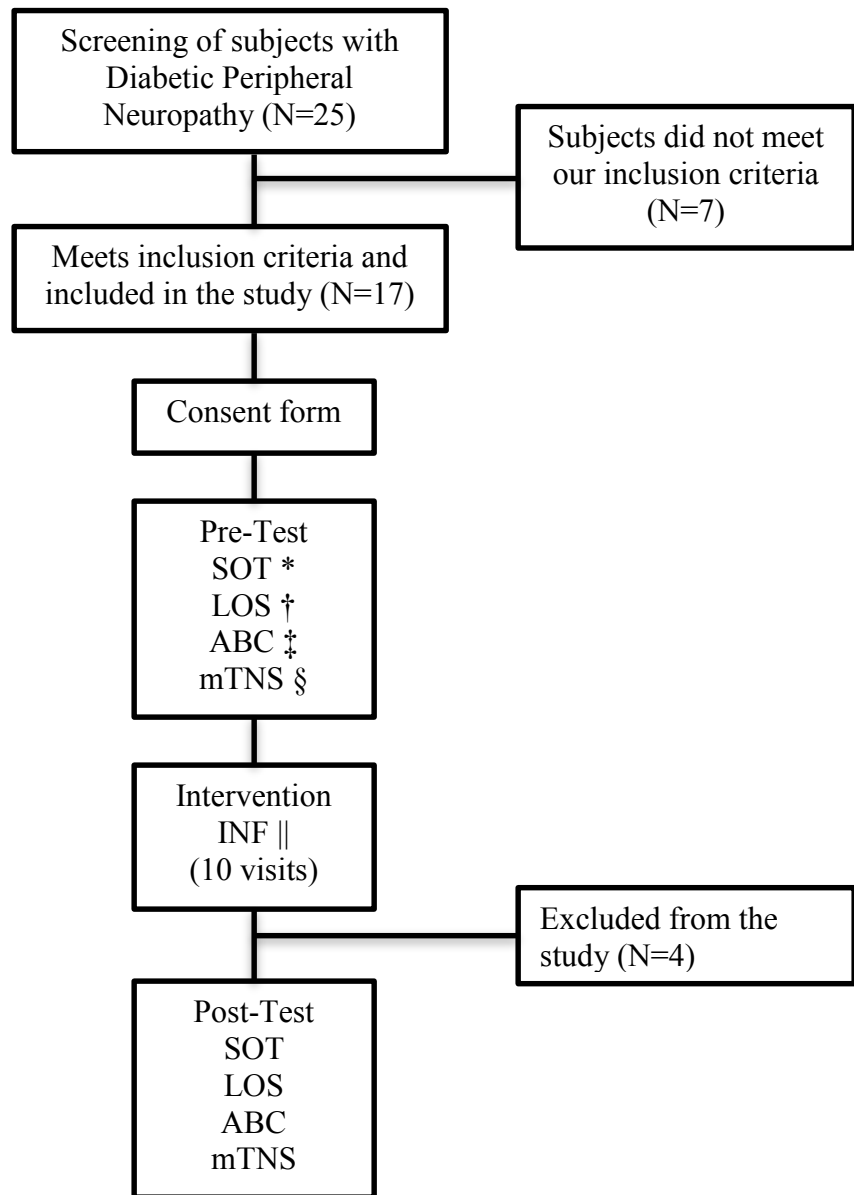


Figure 3. Subject screening and completion.

* Sensory organization test.

† Limit of stability

‡ Activities of balance confidence

§ Modified total neuropathy scale

|| Intra-neural facilitation

Table 1: Patients' demographics

	N	Minimum	Maximum	Mean	Std. Deviation	Male	Female
Age	13	49	73	65.15	7.548		
Gender						7	6

The mTNS showed significant reduction from pre and post treatment measurements ($p = .001$) (Table 2). For changes in SOT, we found a significant increase from pre- and post-treatment measurements ($p = .012$) (Table 3). For LOS components, the MVL showed a significant increase from pre to post-treatment measurements ($p = .023$) (Table 4). The remaining measures of RT, DCL, EPE, MXE, and ABC showed a trend towards improvement but did not show statistically significant differences before or after INF (Tables 4 & 5).

Table 2: Changes in modified total neuropathy scale (mTNS)

	N	Pre Mean	Pre SD*	Post Mean	Post SD*	Mean Difference	<i>P</i> value
mTNS	13	10.62	4.37	7.77	4.19	-2.85	.001

P value from Wilcoxon signed rank test

* Standard deviation

Table 3: Changes in sensory organization test (SOT)

	N	Pre Mean	Pre SD*	Post Mean	Post SD*	Mean Difference	P value
SOT	13	53.77	21.81	66.00	14.32	12.23	.012

P value from paired t-test

* Standard deviation

Table 4: Changes in limits of stability (LOS)

	N	Pre Mean	Pre SD¶	Post Mean	Post SD¶	Mean Difference	<i>P</i> value
RT*	13	0.91	0.62	0.81	0.36	-0.10	.544 ^a
DCL†	13	55.44	32.57	63.15	20.45	7.71	0.834 ^b
EPE‡	13	39.68	23.61	48.31	17.15	8.62	.334 ^a
MVL§	13	1.99	1.25	3.28	1.26	1.29	.023 ^a
MXE	13	54.31	31.87	68.46	24.14	14.15	.249 ^a

a *P* value from paired t-test

b *P* value from Wilcoxon signed rank test

* Reaction time

† Directional control

‡ End point excursion

§ Movement velocity

|| Maximum excursion

¶ Standard deviation

Table 5: Changes in activities-specific of balance confidence (ABC)

	N	Pre Mean	Pre SD*	Post Mean	Post SD*	Mean Difference	P-value
ABC	13	71.42	25.78	78.02	17.01	6.60	.119

P value from paired t-test

* Standard deviation

Discussion

The results of our study are consistent with previous reports indicating that patients with DSPN are more susceptible to falls during static and dynamic conditions [19, 49, 50]. In addition, our results show that INF can improve neuropathy symptoms as measured by the mTNS ($p = .001$), static balance or SOT ($p = .012$), and dynamic balance or MVL ($p = .023$) scores. All other LOS components (RT, DCL, EPE, and MXE) showed a trend towards post-treatment improvement but were not statistically significant.

We chose to use the mTNS in our study because it was easy to use and is a valid tool [37]. The CDP has been used extensively in the literature for different conditions as a validated tool to measure static and dynamic balance [51-53]. Whitney et al [54], looked at the relationship between falls history and CDP scores. They found that scores of < 38 increased the likelihood ratio for recognizing repeated fallers in the past 6 months. On diabetic subjects, Simmons et al [42], measured postural instability in two groups: those with or without cutaneous sensory discrepancies and a control non-diabetic group. They found that CDP scores are less for subjects with cutaneous sensory discrepancies so they are more likely to postural instability. In another study Di Nero et al [55], found that CDP distinguished between DM subjects with and without peripheral neuropathy.

While many interventions have tried to mitigate the impact of DPN through exercises, it remains a progressive disease with few effective interventions. There are few systematic physical therapy approaches that are typically used in treating patients with DPN. For instance, Kochman et al, [25] studied the use of monochromatic infrared energy (MIRE) plus strengthening, stretching, and balance exercises on patients with

DPN to improve balance. They reported improved balance and reduction in number of falls. Mueller et al [30] investigated weight-bearing exercises versus non-weight bearing exercises on patients with DPN. The weight-bearing group revealed significant improvement over the non-weight bearing group.

The effects of therapeutic rehabilitation on balance in patients with DPN have included modalities [24], combining modalities with exercises [25], exercises [28, 30], and assistive devices [29]. Ashton-Miller et al [29] divided subjects into two groups. One group used a single-point cane and the other group did not use a cane. They found a reduction in failure rate during weight transfer to unipedal stance. Richardson et al [28] divided the subjects into two groups. One group received open and closed chain ankle strengthening, wall slides, and single-leg stance and the other group neck flexion and scapular stabilization exercises. They found significant improvements in tandem stance, single-leg stance, and functional reach. Mueller et al [30] studied weight bearing exercises versus non-weight bearing exercises on patients with DPN. The weight bearing group showed significance improvement over the non-weight bearing group in the 6-minute walk distance and daily step counts. Exercises may play an important role on patients with DPN. On the other hand, exercises usually need weight bearing and utilization of painful limbs. Also, recent studies highly recommended minimal physical activity for patients with DPN to prevent adverse events [56, 57]. In order to decrease pain, parasthesia, and lesions associated with DPN through physical therapy, we should limit patient participating with exercise activities in order to enhance functional outcomes [56, 57]. The present study demonstrates decreased neuropathic symptoms and improved balance using INF. By reducing patient neuropathic symptoms, INF may enhance patient

participation in therapeutic exercise programs and form a bridge between the inactive painful diabetic patient and the active non-painful diabetic patient who can exercise.

The INF intervention is a novel manual physical therapy approach with anecdotal evidence in reducing peripheral neuropathy symptoms. The main concept of INF is the use of two manual holds. The first hold is called facilitation hold (Figure 4). It includes putting the contralateral joint in a maximal loose-pack position. For example, the ankle joint in contralateral side will be in full planter flexion and inversion. This position will be sustained during the whole session with a stretch strap. We hypothesize that with the joint in this position the nerve will move further than the artery as the artery has more elastin. With increased neural excursion in relation to the artery, the nutrient vessels that are clustered at the joint will be stretched. This stretch may enlarge the opening at the junction of the artery and bridging nutrient vessel, thus consistently creating a vascular bias into the neural epineurial capillaries. Theoretically, this creates increased epifasciular vascular pressure. [31].

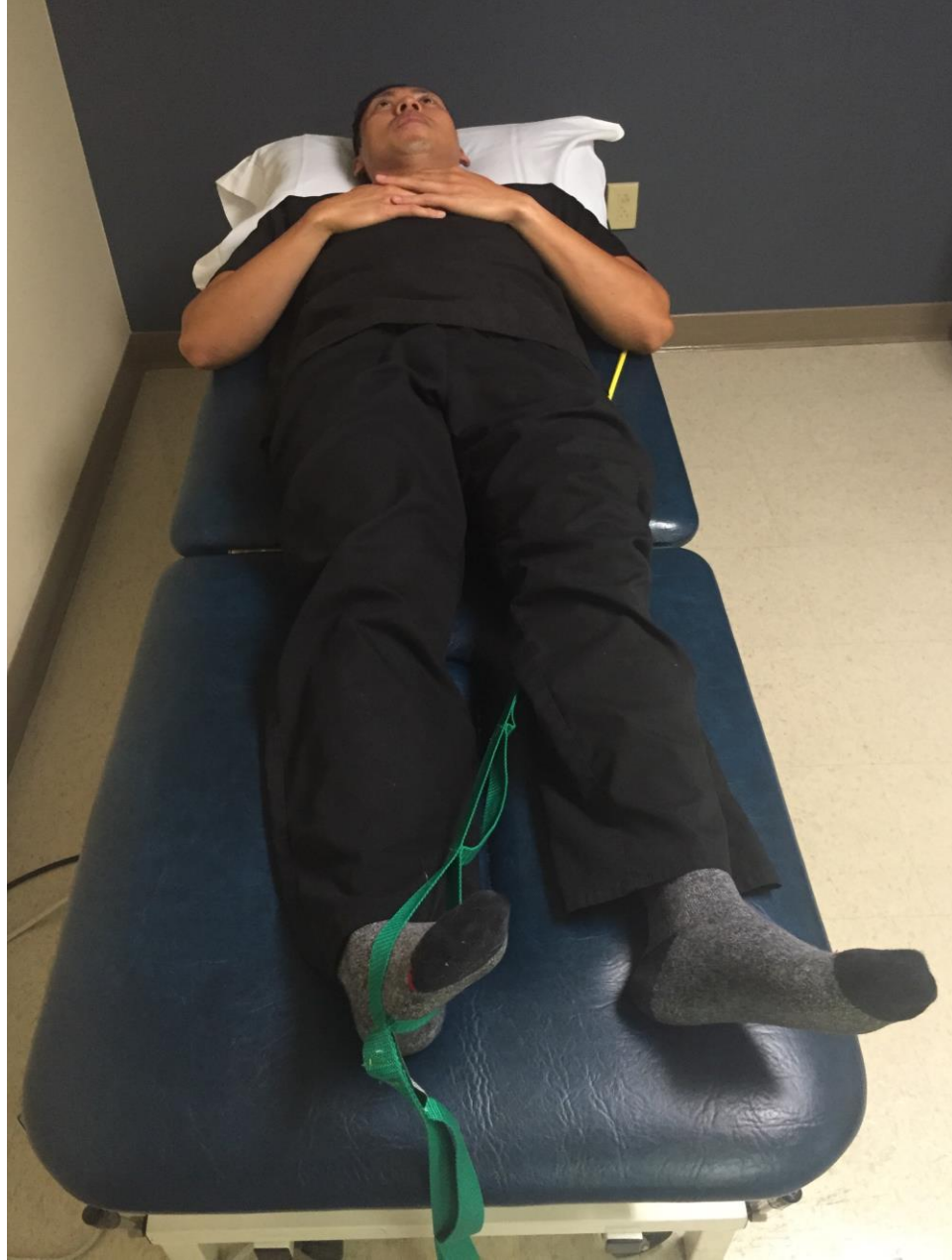


Figure 4. Facilitation hold includes positioning the contralateral ankle joint in a maximal loose-pack position of plantar flexion and inversion. This position is maintained throughout the entire session.

With increased endoneurial edema and a strong perineurium, the pressurized blood flow may not push through the transperineurial vessels that cross the perineurium into the endoneurial capillaries. A second hold or mild stretch is necessary to bias the increased epineurial blood flow past the perineurium into the endoneurial capillaries. This hold potentially provides an unweighting pressure. The second hold or stretch will also enable the therapist to bias circulation in the neural structures that appear to be most affected. For example a hamstring stretch would bias blood flow into the sciatic nerve microvasculature (Figure 5). Previous studies demonstrated short-term exercise effects on endoneurial capillaries including stimulating endothelial vasodilation, enhancing endoneurial blood flow, improving abnormal nerve perfusion, increasing the release of nitric oxide, and enhancing the concentration of Na/K ATPase [58-62]. We hypothesize that improvements in the mTNS of our subjects were due to these immediate vascular changes that occurred in the treated extremities although more research is need to substantiate this [32].

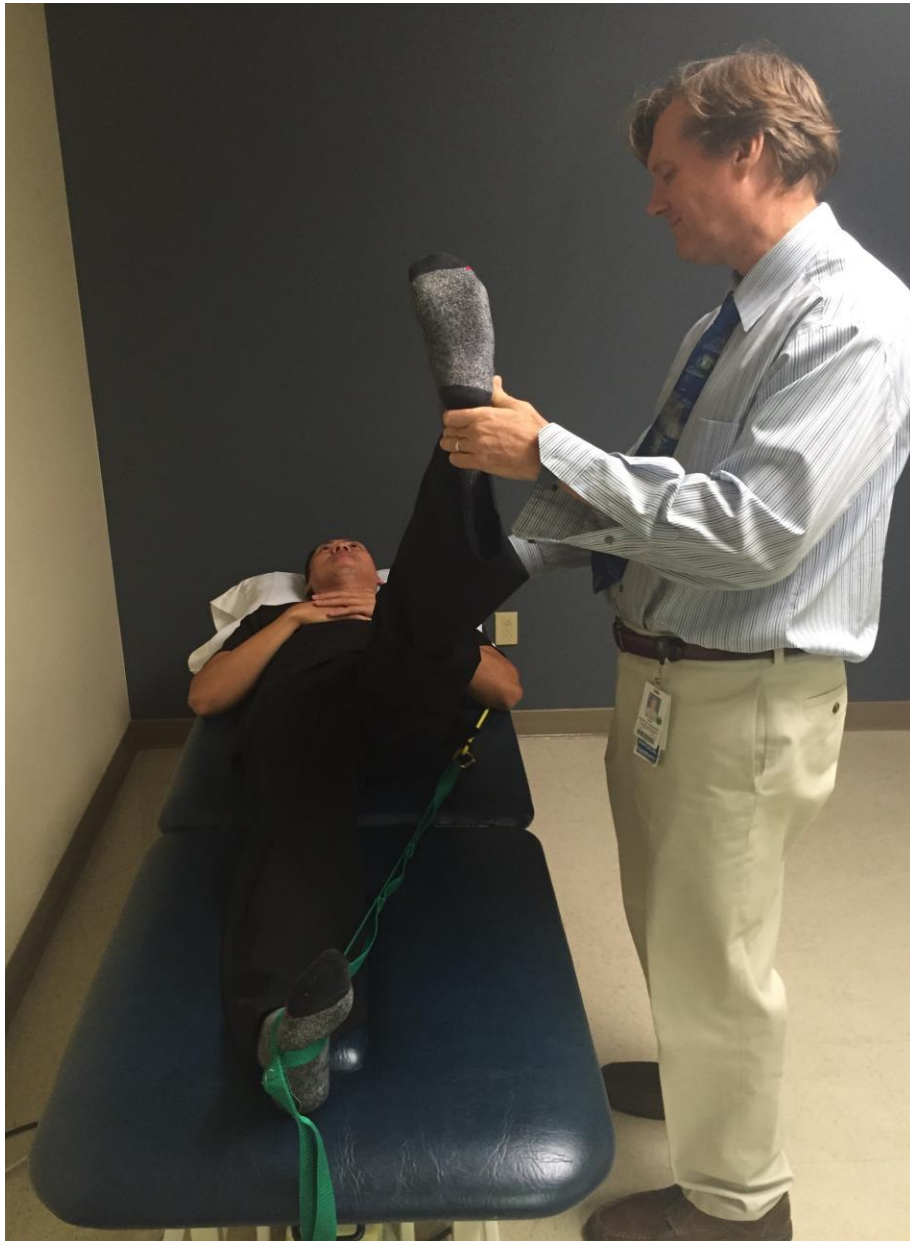


Figure 3. Secondary hold. In case of impaired sciatic nerve, a hamstring stretch bias's blood flow into the sciatic nerve microvasculature.

Study limitations

Our study limitations include the potential for bias with mTNS assessment as the clinician who provided the treatment also assessed the mTNS pre and post intervention. Other limitations were not having a control or sham group and the small sample size that does not allow for generalization of our study findings. Moreover, the present study only measured short-term benefits of the intervention.

Conclusion

This pilot study showed that INF improves static and dynamic balance measures as well as neuropathy symptoms using validated measures in patients with diabetic DSPN. Whether the improvements in balance measures noted in the intervention subjects translate into decreased fall risk in daily life is uncertain. However, given the minimal risk associated with INF, we believe our results warrant further study of this technique in patients with diabetic and idiopathic DSPN to establish long-term benefits, measure the effect of INF on pain measures, and if possible employ a control or sham group.

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CHAPTER FOUR

DISCUSSION

The prevalence of diabetes has increased noticeably over the last three decades. It is estimated that 380 million people worldwide live with diabetes mellitus. Diabetes mellitus is a progressive disease process which can result in numerous health complications. [1]. It places a significant burden on the healthcare system, not to mention debilitating conditions associated with it (diabetic retinopathy, cardiomyopathy, and neuropathy) [5, 39]. Diabetic peripheral neuropathy (DPN) is known to affect peripheral nerves and circulation and may lead to impaired balance [9, 12, 16]. As a result of impaired proprioceptive input, patients with DPN are therefore more susceptible to loss of balance during static and dynamic conditions [7-12]. This may lead to impairment in physical function due to a reduction in standing and walking activities as many patients experience fear of falling [13, 18].

The current study was a clinical trial designed to test the effectiveness of intraneural facilitation (INF) on objective static measures, dynamic balance measures, and a subjective balance measure. The INF is an innovative approach which aims to bias blood flow into the neural fascicle improving endoneurial capillary circulation and reversing intrafascicular ischemia in an attempt to improve neural blood flow. This passive techniques may involve stretching affected muscles, mobilizing joints, tractioning skin, distending visceral structures, and distorting blood vessels to reroute blood to the ischemic nerves [32]. . We used quantitative posturography balance measures given their objectivity and utilization in many previous studies [40-43].

Also, we measured the effect of INF on a neuropathy scale. The INF intervention is a novel manual physical therapy approach with anecdotal evidence in reducing peripheral neuropathy symptoms. The main concept of INF is the use of two manual holds. The first hold is called facilitation hold. It comprises placing the contralateral joint in a maximal loose-pack position. For example, the ankle joint in contralateral side will be in full plantar flexion and inversion. This position will be sustained during the whole session with a stretch strap. We hypothesized that with the joint in this position the nerve will move further than the artery as the artery has more elastin. With increased neural excursion in relation to the artery, the nutrient vessels that are clustered at the joint would be stretched. This stretch may enlarge the opening at the junction of the artery and bridging nutrient vessel, thus consistently creating a vascular bias into the neural epineurial capillaries. Theoretically, this creates increased epifasciular vascular pressure. [31].

With increased endoneurial oedema and a strong perineurium, the pressurized blood flow may not push through the transperineurial vessels that cross the perineurium into the endoneurial capillaries. A second hold or mild stretch is necessary to bias the increased epineurial blood flow past the perineurium into the endoneurial capillaries. This hold potentially provides an unweighting pressure. The second hold or stretch will also enable the therapist to bias circulation in the neural structures that appear to be most affected. For example a hamstring stretch would bias blood flow into the sciatic nerve microvasculature. When the endoneurial capillaries gets more consistent blood flow, it produces nitric oxide by compressing of the pressurized red blood cells into the inflamed capillaries which will lead to vasodilation of endoneurial capillaries [32].

The results of this study are consistent with those of previous studies indicating that patients with DPN are more susceptible to falls during static and dynamic conditions [19, 49, 50]. The current study was conducted to determine the effect of a novel therapeutic approach, INF, for patients with DPN. Our results suggest that INF can improve static and dynamic balance, and neuropathy symptoms including reduced muscle strength, vibration sense, pin level (sharp/dull), and reflexes in patients with DPN.

Subjects in this study increased their composite equilibrium score between pre-intervention and post-intervention by 22.47% ($p = .012$). In the LOS components, RT, DCL, EPE, and MXE also improved but were not statistically significant. However, MVL component in LOS showed significant difference $p = .023$. The ABC was not significantly improved. This may be the result of a ceiling effect which has been previously reported in the literature [63].

There was a significant reduction 44.17% ($p = .001$) in the mTNS. We chose to use the mTNS in our study because it was easy to use and is a valid tool [37]. The San Antonio Consensus meeting recommended assessing peripheral neuropathy by combining quantitative vibrations threshold, quantitative touch threshold, nerve conduction, and patients' report [34]. The TNS is a reliable tool used to assess peripheral neuropathy in diabetic patients[36]. However, it is an expensive and time-consuming tool. The mTNS was proposed as an alternative for the TNS in the clinical settings and it showed its effectiveness. Wampler et al [37], found positive correlations between the mTNS and the TNS ($r = 0.99$; $p < .001$).

The effects of therapeutic rehabilitation on balance in patients with DPN have been previously reported in the literature. These studies include modalities [24],

combining modalities with exercises [25], exercises [28, 30], and assistive devices [29]. Ashton-Miller et al [29] divided subjects into two groups. One group used a single-point cane and the other group did not use a cane. They found a reduction in failure rate during weight transfer to unipedal stance.

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Exercises might play an important role on patients with DPN. On the other hand, exercises usually need weight-bearing and utilization of painful limbs. Also, recent studies highly recommended minimal physical activity for patients with DPN to prevent adverse events [56, 57]. In order to decrease pain, paresthesia, and lesions associated with DPN through physical therapy, we should limit patient participation in exercise activities in order to enhance functional outcomes [56, 57]. The present study demonstrates decreased neuropathic symptoms and improved balance using INF. By reducing patient neuropathic symptoms, INF may decrease patience towards participating in a therapeutic exercise program. Thus, forming a bridge between the inactive painful diabetic patient and the active non-painful diabetic patient who can exercise.

This study was limited by the potential for bias with mTNS assessment since the clinician who provided the treatment also assessed the mTNS pre and post intervention. Our study's greatest limitation was not having a control group to compare our results with. Also, the small sample size does not allow for generalization of our study findings. Furthermore, the present study only measured short-term benefits of the intervention. Future studies should look at long-term benefits of this intervention with a larger sample size.

In conclusion, this pilot study showed that INF improves static and dynamic balance measures as well as neuropathy symptoms using validated measures in patients with diabetic DSPN. Whether the improvements in balance measures noted in the intervention subjects translate into decreased fall risk in daily life is uncertain. However, given the minimal risk associated with INF, we believe our results warrant further study of this technique in patients with diabetic and idiopathic DSPN to establish long-term benefits, measure the effect of INF on pain measures, and if possible employ a control or sham group.

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APPENDIX A

ACTIVITIES-SPECIFIC BALANCE CONFIDENCE (ABC) SCALE

For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the following rating scale:

0% 10 20 30 40 50 60 70 80 90 100%

No confidence

Completely confident

“How confident are you that you will not lose your balance or become unsteady when you...

1. ...walk around the house? ____%
2. ...walk up or down stairs? ____%
3. ...bend over and pick up a slipper from the front of a closet floor ____%
4. ...reach for a small can off a shelf at eye level? ____%
5. ...stand on your tiptoes and reach for something above your head? ____%
6. ...stand on a chair and reach for something? ____%
7. ...sweep the floor? ____%
8. ...walk outside the house to a car parked in the driveway? ____%
9. ...get into or out of a car? ____%
10. ...walk across a parking lot to the mall? ____%
11. ...walk up or down a ramp? ____%
12. ...walk in a crowded mall where people rapidly walk past you? ____%
13. ...are bumped into by people as you walk through the mall? ____%
14. ... step onto or off an escalator while you are holding onto a railing? ____%

15. ... step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing? ____%
16. ...walk outside on icy sidewalks? ____%

APPENDIX B

RESEARCH FLYER



Loma Linda University
Adventist Health Sciences Center
Institutional Review Board
Approved 9/5/2014
5140219 Chair R. L. Rioshino

Research Opportunity

**Adults ages 18-85
Needed for Balance Study**

**Loma Linda University
School of Allied Health Professions**

The Physical Therapy program is conducting a student research study Titled: **The Effect of Intra-neural Facilitation on Balance in Patients with Diabetic Peripheral Neuropathy**

The study will be held at the Loma Linda University Medical Center Department of Outpatient Physical Therapy and will require about 60 minutes of your time on each of 2 days. You must have a referral from your physician for Physical Therapy
Intra-neural Facilitation

√ You must be able to stand independently for at least 5 minutes without an assistive device such as a cane.

For More Information Contact:

Dr. Eric Johnson @ 909-558-4632 ext. 47471 / E-Mail: ejohnson@llu.edu or
Adel Alshahrani @ 412-979-3118 / E-Mail: amalshahrani@llu.edu

APPENDIX C
INFORMED CONSENT

Title: The effect of intra-neural facilitation on balance in patients with
diabetic peripheral neuropathy

Sponsor : Department of Physical Therapy, Loma Linda
University

Principal

investigaor: Eric Glenn Johnson, DSc, PT, MS-HPed, NCS
Professor, Physical Therapy Department
Loma Linda University, Loma Linda CA
School of Allied Health Professions
Nichol Hall Room #A-712
Phone: (909) 558-4632 Extension 47471
Fax: (909) 558-0459
Email Address: ejohnson@llu.edu

1. Why is this study being done?

The purpose of the study is to determine the effect of Intra-Neural Facilitation (INF) on balance.

INF is a Physical Therapy treatment approach that is prescribed by physicians for patients with diabetic peripheral neuropathy. There have been no research publications describing the effects of INF in patients with diabetic peripheral neuropathy.

You are invited to participate in this research study because you are an adult between the ages of 18-85 years with Diabetes (Type 1 or 2) diagnosed by a physician, have distal symmetrical lower extremity symptoms for greater than 3 months including impaired sensation and have been referred to physical therapy for intraneural facilitation (INF).

2. How many people will take part in this study?

Approximately 40 subjects will participate in this study.

3. How long will the study go on?

Your participation in this study will include 60 minutes on the first day of your Physical Therapy visit and another 60 minutes after 10 sessions of INF.

4. How will be involved?

Participation in this study involves the following:

Your date of birth, height and weight will be recorded. In addition to the INF that you were referred by your physician to receive, you will complete a questionnaire on your balance confidence that will take about 5-10 minutes. We will also measure your standing

balance with a computerized device that will take about 15-20 minutes. This device has a stable platform that records your body sway with eyes open then eyes closed. No special clothing is required. A safety harness will be placed on you and two researchers will be near you in case you lose your balance. The entire process will take approximately 60 minutes on the first and second days of data collection. All data collection will take place at your regularly scheduled physical therapy appointment times and location.

5. What are the reasonably foreseeable risks or discomfort I might have?

Participating in this study exposes you to minimal risk because you may lose your balance during the testing procedures. To prevent falling, you will be wearing a safety belt and two researchers will be standing beside you at all times. There is also a minimal risk of breach of confidentiality.

6. Will there be any benefit to me or others?

Although you will not benefit from this study, the information gathered from the study may benefit future patients with balance impairments resulting from diabetic peripheral neuropathy if INF is shown to improve balance.

7. What are my rights as a subject?

Participation in this study is voluntary. Your decision whether or not to participate or withdraw at any time from the study will not affect your ongoing relationship with Loma Linda Health and will not involve any penalty or loss of benefits to which you are otherwise entitled.

8. What happens if I want to stop taking part in this study?

You are free to withdraw from this study at any time. If you decide to withdraw from this study you should notify the research team immediately. The research team may also end your participation in this study if you do not follow instructions, miss scheduled visits, or if your safety and welfare are at risk.

9. How will information about me be kept confidential?

Your identity will not be recorded with the research data. We cannot guarantee absolute confidentiality. You will not be identified by name in any publications describing the results of this study. All electronic data will be maintained on an encrypted computer and paper data kept in a locked file cabinet in a locked office.

10. Will I be paid to participate in this study?

You will not be paid to participate in this research study but you will receive a \$25 gift card on each of the two days of data collection.

11. How do I call if I am injured as a result of being in this study?

If you feel you have been injured by taking part in this study, consult with a physician or call 911 if the situation is a medical emergency. No funds have been set aside nor any plans made to compensate you for time lost for work, disability, pain or other discomforts resulting from your participation in this research.

12. Who do I call if I have questions?

If you wish to contact an impartial third party not associated with this study regarding any questions about your rights or to report a complaint you may have about the study, you may contact the Office of Patient Relations, Loma Linda University Medical Center, Loma Linda, CA 92354, phone (909) 558-4647, e-mail patientrelations@llu.edu for information and assistance.

13. Subject's statement of consent

I have read the contents of the consent form and have listened to the verbal explanation given by the investigator. My questions concerning this study have been answered to my satisfaction. Signing this consent document does not waive my rights nor does it release the investigators, institution or sponsors from their responsibilities. I hereby give voluntary consent to participate in this study.

- I may call Eric Johnson during routine office hours at (909) 558-4632 extension 47471 or during non-office hours at (909) 658-5223 if I have additional questions or concerns.

I understand I will be given a copy of this consent form after signing it.

Signature of Subject

Printed Name of Subject

Date

14. Investigator's statements

I have reviewed the contents of this consent form with the person signing above. I have explained potential risks and benefits of the study.

Signature of Investigator

Printed Name of Investigator

Date

APPENDIX D

AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION



**Authorization for Use of
Protected Health Information (PHI)**

Per 45 CFR §164.508(b)

RESEARCH PROTECTION PROGRAMS

LOMA LINDA UNIVERSITY | Office of the Vice President of Research Affairs

24887 Taylor Street, Suite 202 Loma Linda, CA 92350

(909) 558-4531 (voice) / (909) 558-0131 (fax)/e-mail: irb@llu.edu

Title of study: The Effect of Intra-neural Facilitation on Balance in Patients with Diabetic Peripheral Neuropathy

PRINCIPAL INVESTIGATOR: Eric G. Johnson, DSc, PT, MS-HPED, NCS

Others who will use, collect, or share PHI: Adel Alshahrani
Shilpa Gaikwad
Mark Bussell

The study named above may be performed only by using personal information relating to your health. National and international data protection regulations give you the right to control the use of your medical information. Therefore, by signing this form, you specifically authorize your medical information to be used or shared as described below.

The following personal information, considered “Protected Health Information” (PHI) is needed to conduct this study and may include, but is not limited to name, birth date, phone number, and e-mail.

The individual(s) listed above will use or share this PHI in the course of this study with the Institutional Review Board (IRB) and the Office of Research Affairs of Loma Linda University.

The main reason for sharing this information is to be able to conduct the study as described earlier in the consent form. In addition, it is shared to ensure that the study meets legal, institutional, and accreditation standards. Information may also be shared to report adverse events or situations that may help prevent placing other individuals at risk.

All reasonable efforts will be used to protect the confidentiality of your PHI, which may be shared with others to support this study, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the PHI may share with others if they are required by law, and they may share it with others who may not be required to follow national and international “protected health information” (PHI) regulations such as the federal privacy rule.

Subject to any legal limitations, you have the right to access any protected health information created during this study. You may request this information from the Principal Investigator named above but it will only become available after the study analyses are complete.

- This authorization expires on August 15, 2015.

You may change your mind about this authorization at any time. If this happens, you must withdraw your permission in writing. Beginning on the date you withdraw your permission, no new personal health information will be used for this study. However, study personnel may continue to use the health information that was provided before you withdrew your permission. If you sign this form and enter the study, but later change your

mind and withdraw your permission, you will be removed from the study at that time. To withdraw your permission, please contact the Principal Investigator or study personnel at 909-558-4632 extension 47471.

You may refuse to sign this authorization. Refusing to sign will not affect the present or future care you receive at this institution and will not cause any penalty or loss of benefits to which you are entitled. However, if you do not sign this authorization form, you will not be able to take part in the study for which you are being considered. You will receive a copy of this signed and dated authorization prior to your participation in this study.

I agree that my personal health information may be used for the study purposes described in this form.

Signature of Patient
or Patient's Legal Representative

Date

Printed Name of Legal Representative
(if any)

Representative's Authority
to Act for Patient

Signature of Investigator Obtaining
Authorization

Date