Effect of Low Frequency Transcutaneous Magnetic Stimulation on Sensory and Motor Transmission

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Peripheral nerve injury diminishes fast conducting large myelinated afferent fibers transmission but enhances smaller pain transmitting fibers firing. This aberrant afferent neuronal behavior contributes to development of chronic post-traumatic peripheral neuropathic pain (PTP-NP). Non-invasive dynamic magnetic flux stimulation has been implicated in treating PTP-NP, a condition currently not adequately addressed by other therapies including transcutaneous electrical nerve stimulation (TENS). The current study assessed the effect of low frequency transcutaneous magnetic stimulation (LFTMS) on peripheral sensory thresholds, nerve conduction properties, and TENS induced fast afferent slowing effect as measured by motor and sensory conduction studies in the ulnar nerve. Results indicated sham LFTMS with TENS (Sham + TENS) significantly ($P = 0.02$ and 0.007, respectively) reduces sensory conduction velocity (CV) and increases sensory onset latency (OL), and motor peak latency (PL) whereas, real LFTMS with TENS (Real + TENS) reverses effects of TENS on sensory CV and OL, and significantly ($P = 0.036$) increases the sensory PL. LFTMS alone significantly ($P < 0.05$) elevates sensory PL and onset-to-peak latency. LFTMS appears to reverse TENS slowing effect on fast conducting fibers and casts a selective peripheral modulatory effect on slow conducting pain afferent fibers. Bioelectromagnetics. © 2015 Wiley Periodicals, Inc.

Key words: peripheral neuromodulation; neuropathic pain; non-invasive neuromodulation; TMS; TENS

INTRODUCTION

After a peripheral nerve injury, fast conducting large myelinated afferent A-beta fiber transmission diminishes over time. On the other hand, firing of smaller pain transmitting fibers such as A-delta and C-fibers is enhanced. This aberrant afferent neuronal behavior is thought to be one of the main neuronal mechanisms leading to development of chronic post-traumatic peripheral neuropathic pain (PTP-NP) [Puig and Sorkin, 1996]. Clinically, this persistent peripheral neuropathic pain state is often refractory to invasive interventions or medication [Sorkin and Yaksh, 2009; Rajput et al., 2012]. Non-invasive neuromodulation offers an appealing alternate therapeutic option in treating this often debilitating chronic pain condition. While it is known that transcutaneous electrical nerve stimulation (TENS) may slow afferent nerve conduction, particularly in large afferent fibers, and provide temporary pain relief [Walsh et al., 1995b; Koga et al., 2005], its application in managing patients with PTP-NP has been limited due to either on-site or surrounding tissue pain sensitivity to TENS electrodes and actual electrical stimulation. Recently, technology involving dynamic magnetic flux, derived from basic electromagnetic coupling principles [Lisanby et al., 2000], has been applied both centrally

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and peripherally for pain relief. Centrally, high frequency (>1Hz) transcranial magnetic stimulation (TMS) at the motor cortex or prefrontal cortices can produce analgesic benefits for various neuropathic pain conditions [Leung et al., 2009]. Peripherally, although dynamic magnetic flux use for pain relief is still limited, initial publications have suggested this technology can successfully be applied to treat pain of peripheral nerve origins as well [Smania et al., 2005; Weintraub and Cole, 2008; Khedr et al., 2012]. Aside from its non-invasiveness, treatment involving dynamic magnetic flux requires no skin contact with potentially longer duration of relief, making it a perfect candidate for treating PTP-NP. Based on the authors' accumulated clinical experience, while high frequency (>1 Hz) TMS has not been well tolerated in patients with PTP-NP, they reported better and prolonged pain relief with low frequency transcutaneous magnetic stimulation (LFTMS) as described in a recent case series [Leung et al., 2014]. While conducting randomized controlled studies will further validate the treatment modality in managing PTP-NP, it is equally important to assess mechanistically how LFTMS may affect neuronal functional changes. Here, the authors hypothesized that LFTMS could reverse slowing effect of TENS on large myelinated afferent fibers and LFTMS alone would not affect normal peripheral sensory thresholds but modulate slower transmitting pain fibers. To test these hypotheses, a sham-controlled study was conducted to assess LFTMS effect on peripheral sensory thresholds and peripheral sensory and motor functions, and its effect on TENS induced neuronal functional changes.

MATERIALS AND METHODS

Healthy subjects were enrolled for the study. Inclusion criteria included: age 18–60; male and female; no surgical procedure done to upper extremities for past 2 months; and no analgesics for past 2 weeks. Exclusion criteria included: history of psychological illness; history of peripheral neuropathy; lack of ability to understand experimental protocol or adequately communicate in English; pregnancy; pending litigation; history of trauma or surgery to upper extremities; and history of cardiac pacemaker or defibrillator implant.

Study Interventions and Assessments

The study consisted of 2 phases. In Phase I, two studies were performed as follows: (i) LFTMS/sham stimulation was provided in two randomized sessions at the right index finger with quantitative sensory testing (QST) conducted pre and post the stimulations; (ii) real LFTMS with TENS (Real + TENS)/sham LFTMS with TENS (Sham+TENS) were provided in two randomized sessions at the left forearm with sensory and motor nerve conduction studies (NCS) conducted pre and post stimulations. The Phase II study was conducted to assess whether LFTMS alone consisted of any effect on sensory and motor NCS (Fig. 1).

At the beginning of the Phase I study, QST was conducted at the volar surface of the right index finger before and after the study LFTMS treatment. Subjects were randomized to receive real or sham LFTMS at tested location of the right index finger at least one week apart. Following QST studies at the right index finger, NCS were then conducted at the left arm before and after Real + TENS or Sham + TENS at least one week apart. During the study session, ambient temperature was kept at 25°C and subjects were asked to put their hands in a pair of thermal controlled gloves between assessments. A skin temperature measuring strip (Redi-Temp, St. Louis, MO) was placed on subjects' study hands to ensure skin temperature was near 32(±0.5) °C. All subjects were blindfolded during study interventions. The locations of LFTMS, TENS, and NCS electrodes are illustrated in Figure 2.

TENS

TENS was provided by a 6 V square-wave stimulator (ITO ES-160, Tokyo, Japan; http://www.lhasaoms.com/ITO-ES-160) for blinding sensation of LFTMS as well as its active neuronal modulatory effect in afferent fibers. TENS electrodes were placed 1.5 cm apart and 3 cm distal to the medial epicondyle of the left forearm. Prior to LFTMS, intensity of TENS was adjusted until mild left 5th finger flexion movement was noted. During either Real + TENS or Sham + TENS, synchronized TENS was provided at .5 Hz with a pulse width of 400 us (Fig. 2).

Real LFTMS

Right index finger. The volar side of the index finger tip was first cleaned with alcohol and testing site marked on the center of distal phalanx. For study treatment, the finger was placed 1 cm away from the center of figure-of-eight TMS coil (Magpro B65, Magventure, Atlanta, GA) with the rest of the right hand resting on a supporting frame. A total of 400 pulses at 0.5 Hz were delivered via biphasic waveform at the marked testing site via TMS coil center. QST was repeated at the testing site afterwards. This LFTMS intervention setting was based on a recent published case series documenting the analgesic benefit of LFTMS in patients with PTP-NP [Leung et al., 2014a, b].

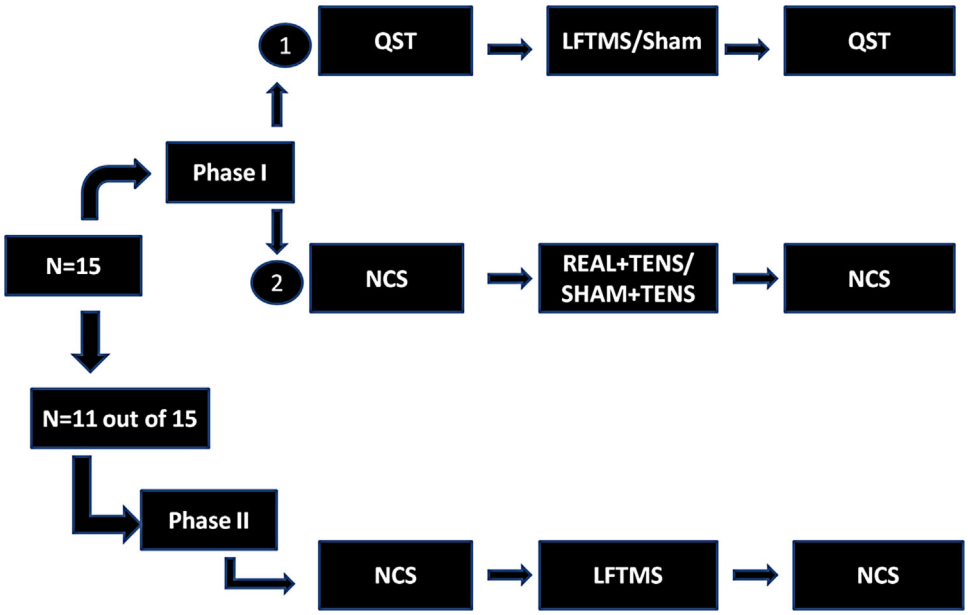

Fig. 1. Flow chart for 2-phase study. Duration between assessments including quantitative sensory testing (QST) and nerve conduction studies (NCS), and stimulations including Low Frequency Transcutaneous Magnetic Stimulation (LFTMS) alone, or LFTMS/sham with TENS (LFTMS + TENS or Sham + TENS) was about 10 min.

Left forearm. A total of 400 pulses at 0.5 Hz, 60% of maximal amplitude, were delivered via the center of TMS coil at 4 cm distal to the motor NCS stimulation site. Skin to magnetic coil distance was 1 cm and treatment setting based on a recent published case series [Leung et al., 2014a, b].

Sham LFTMS

Sham LFTMS was provided with TMS coil treatment site turned 180° away from targeted intervention site and non-treatment site covered with a magnetic shield molded to the coil shape to completely block the magnetic field [Leung et al., 2014a, b]. The effectiveness of the magnetic shield in blocking magnetic flux was tested with a gauss meter prior to the study to ensure no magnetic flux was present on the non-treatment side of the coil. However, clicking noises of pulses was still audible to subjects.

Study Assessments

Quantitative neurosensory testing. Non-noxious thermal sensations including cold and warm, and noxious thermal sensations including cold and heat pain thresholds were measured using a Thermal Sensory Analyzer (Medoc Advanced Medical Systems, Durham, NC). This device consisted of a thermode measuring 46 × 29 mm. Thermode temperature could either rise or fall (at a rate of 1.2°C/s for cold and warm sensations, and 3°C/s for cold and heat pain), depending on sensations being tested. The subject signaled the onset of feeling the tested sensation by pressing a switch, which in turn reversed the temperature change and returned thermode temperature to the 32°C baseline. The computer then recorded thermode temperature when the switch was pressed. The average value of testing result would be automatically calculated by the computer and displayed on the screen. This method of peripheral sensory testing has been well established in literature and has been used extensively in pain-related studies [Leung et al., 2001; Leung et al., 2005]. After the thermal sensory testing, a 6 s subject threshold specific heat pain stimulation was given at the testing site. The subject was then asked to rate intensity of heat pain stimulation on a mechanical visual analogue scale (M-VAS) [Price et al., 1994]. Tactile sensation was measured using von Frey (VF) hair filaments of varying sizes. Testing was done in descending fashion. Each filament was tested three times. Each test lasted about 5 s with a 10 s break in between. Tactile threshold was defined as force at which patient felt at least two of the three consecutive stimuli and none from the next smaller size filament [Leung et al., 2006; Leung et al., 2008].

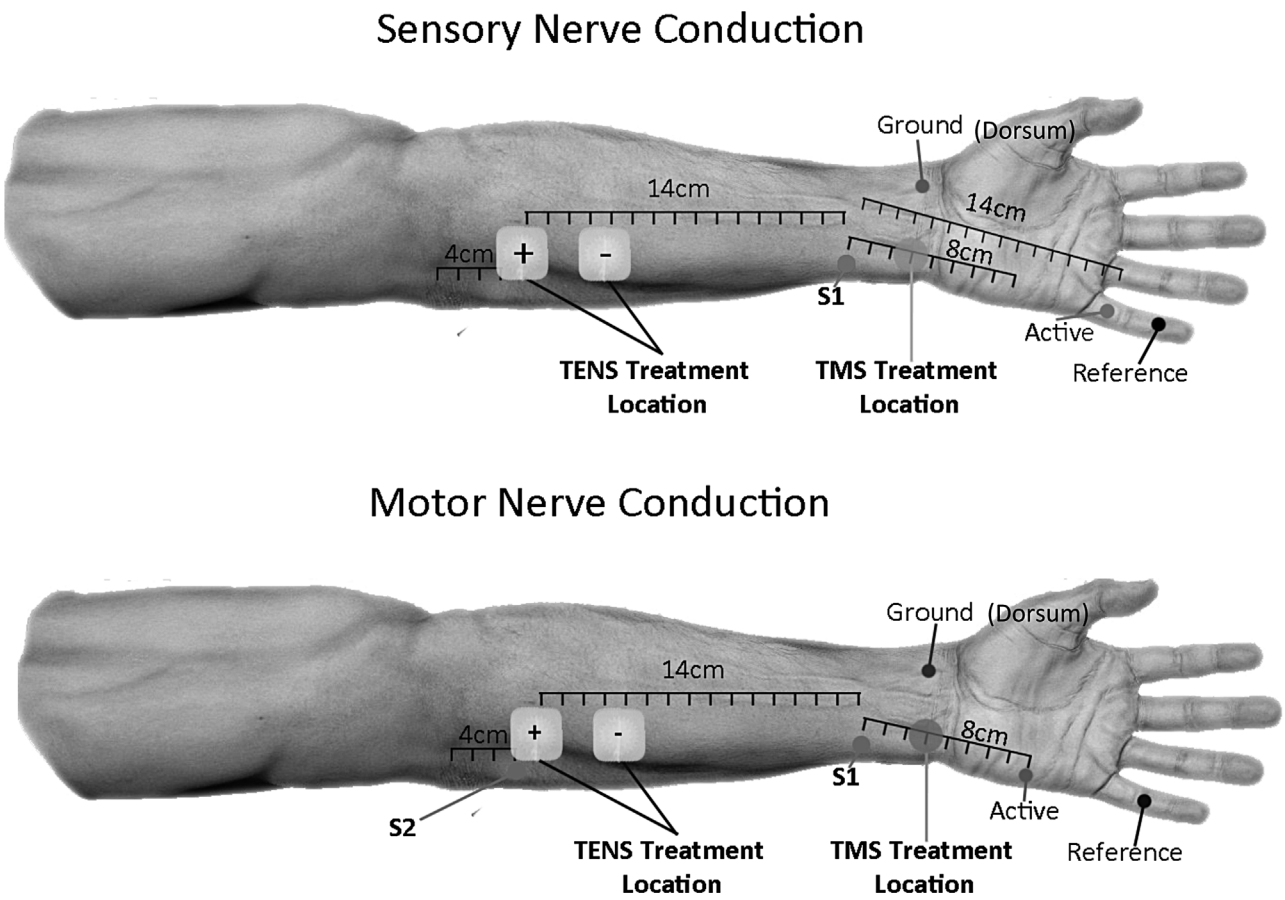

Fig. 2. Locations of Transcutaneous Electrical Nerve Stimulation (TENS) and Low Frequency Transcutaneous Magnetic Stimulation (LFTMS) in relation to motor and sensory nerve conduction study electrodes and stimulation sites. S1: Stimulation site 1; S2: Stimulation site 2.

NCS. The NCS (XLTEC NeuroMax 1004, Oakville, Canada) was conducted to assess effect of LFTMS on left ulnar nerve motor and sensory functions according to a widely used and established protocol [Buschbacher and Prahlow, 2005; Nacir et al., 2012; Thanakiatpinyo and Srisawasdi, 2013; Yurrebaso et al., 2014].

Ulnar sensory nerve to the 5th digit. Subjects were first placed in a sitting position. An active ring electrode was placed in contact with radial and ulnar sides of the 5th digit, slightly distal to digit base. A reference ring electrode was placed in contact with radial and ulnar sides of the 5th digit, 4 cm distal to the active electrode (or in small fingers as far distally as possible). A ground electrode was placed on the dorsum of the hand. For stimulation point 1 (S1), the subject was asked to straighten fingers. Then the stimulation cathode (with anode placed proximally) was placed 14 cm proximal to the active ring electrode over the ulnar nerve at the wrist, slightly radial to the tendon of the flexor carpi ulnaris (Fig. 2). Stimulus output was initially set at 10 mA and was increased in 5 mA increments until optimal waveform trace was achieved. Then five measurements were obtained and results averaged for analysis. Machine settings for sensory NCS were as follows: Sensitivity 20 μV/division, Low frequency filter 20 Hz, High frequency filter 2 kHz, Sweep speed 1 ms/division; 40 mA (maximal output), and 0.25 ms pulse duration.

Ulnar motor nerve to the digiti minimi. The subject's left arm was positioned in a 45° abducted angle and externally rotated posture. The elbow was flexed to 90° with the forearm in a neutral position (thumb pointing toward ear). An active flat electrode (1 × 1 cm) was placed on the ulnar surface of the hypothenar eminence, halfway between the level of the pisiform bone and the 5th metacarpophalangeal joint. A reference electrode (1 × 1 cm) was placed slightly distal to the 5th metacarpophalangeal joint. A ground electrode was placed on the dorsum of the

hand. For stimulation point 1 (S1), the cathode was placed distal to the anode (A) and 8 cm proximal to the active electrode, in a line measured slightly radial to the tendon of the flexor carpi ulnaris (Fig. 2). Machine settings for the motor NCS were: Sensitivity 5 mV/division, Low frequency filter 2-3 Hz, High frequency filter 10 kHz, Sweep speed 2 ms/division; 80 mA (Maximal output), 0.1 ms pulse duration. For stimulation point 2 (S2), cathode was placed approximately 4 cm distal to the medial epicondyle with the anode located proximally. To optimize response, stimulus output was initially set at 10 mA and increased in 5 mA increments until maximal S2 amplitude was achieved.

Post-study blinding assessment. At the conclusion of each study session, the subjects were asked whether they perceived the LFTMS treatments received as real or sham.

Data Analysis

Descriptive statistics were obtained for all variables and tests of normality of continuous measures and homogeneity of variance were performed. Different statistical processes such as square root or log transformation were applied [Tabachnick and Fidell, 1989] for data distribution examination. All variables were then subjected to parametric analyses. If any variables failed the normal distribution examination, an additional method of non-parametric analysis (McNemar's test) was applied to confirm the result of the parametric analyses. For parametric analyses, comparability of two study treatments (Real + TENS vs. Sham + TENS for Phase I, and LFTMS vs. Sham for Phase II) and on baseline demographic and pre-intervention (Pre) outcomes was tested using analyses of variance (ANOVAs). The two study treatments from pre to post intervention were compared using repeated measure ANOVA with two within factors of study intervention (Real + TENS and Sham + TENS) and time (Pre- and Post-intervention). Both sensory and motor NCS domains (Fig. 3) included onset latency (OL), peak latency (PL), onset to peak amplitude (OPA) and conduction velocity (CV). QST domains included sensory thresholds (°C) of cool, warm, cold pain, and heat pain sensations, manual heat pain stimulation temperature (°C), manual heat pain stimulation intensity M-VAS, and von Frey tactile threshold. The two-way interaction of study treatments and time were followed by pre- to post- intervention comparisons per study treatment groups. Furthermore, gender effect was tested by adding it to the model as a covariate. Analyses were performed using the SPSS version 19 (Chicago, IL). All analyses were two-tailed, where applicable, with $\alpha = .05$.

RESULTS

With approval from Veteran Administration San Diego Healthcare System Human Subject Protection Review Committee, 17 healthy subjects were enrolled and completed the Phase I study. However, due to an error in initial data recording, the first two subjects' data were not included in data analysis. Of data from 15 subjects (average age = 21.0 ± 3.3 years old), there were no significant differences between male ($N = 9$) and female ($N = 6$), and between the two study sessions in their pre-intervention assessments. For the Phase II study, 11 subjects were able to return. Due to relocation issues, the remaining 4 subjects were not available for the Phase II study. Furthermore, four variables (CV at pre Real+TENS, PL and cool threshold at post Real + TENS, and heat pain at post Sham + TENS) failed the initial data distribution examination due to their skewness and were re-analyzed with a non-parametric analytical method (McNemar's test). The outcome of the non-parametric analyses for these four variables confirmed the result of the parametric analyses.

For sensory NCS in the Phase I study ($N = 15$), the main effect of Time (Pre vs. Post-intervention) was significant for OL and CV. A significant ($P < 0.05$) Time effect (Pre- vs. Post-intervention) was noted within the Sham + TENS group on OL and CV. In these two assessments, the Sham + TENS was found to significantly elevate ($P < 0.05$) sensory OL ± SD from 2.76 ± 0.22 to 3.02 ± 0.35 ms and reduce ($P < 0.01$) CV from 49.57 ± 5.16 to 45.80 ± 5.03 m/s. There was a significant time effect within the Real + TENS group on PL ± SD, which was elevated from 3.52 ± 0.28 to 3.64 ± 0.36 ms ($P < 0.05$). For the sensory NCS in the Phase II study ($N = 11$), LFTMS alone was found to significantly elevate PL ($P = 0.013$) from 3.15 ± 0.36 to 3.67 ± 0.50 ms and OPA ($P = 0.043$) from 42.4 ± 29.5 to 55.9 ± 25.5 μV (Fig. 4).

For motor NCS in the Phase I study ($N = 15$), the two-way (Time × Treatment) interaction was significant only for the OL. Within the Sham-TENS group there was a significant ($P = 0.009$) Time effect in PL with an elevation from 9.02 ± 0.64 to 9.34 ± 0.73 ms and a strong increasing trend ($P = 0.052$) for OL from 3.37 ± 0.33 to 3.52 ± 0.35 ms, which just missed significance. No significant time effect was found in

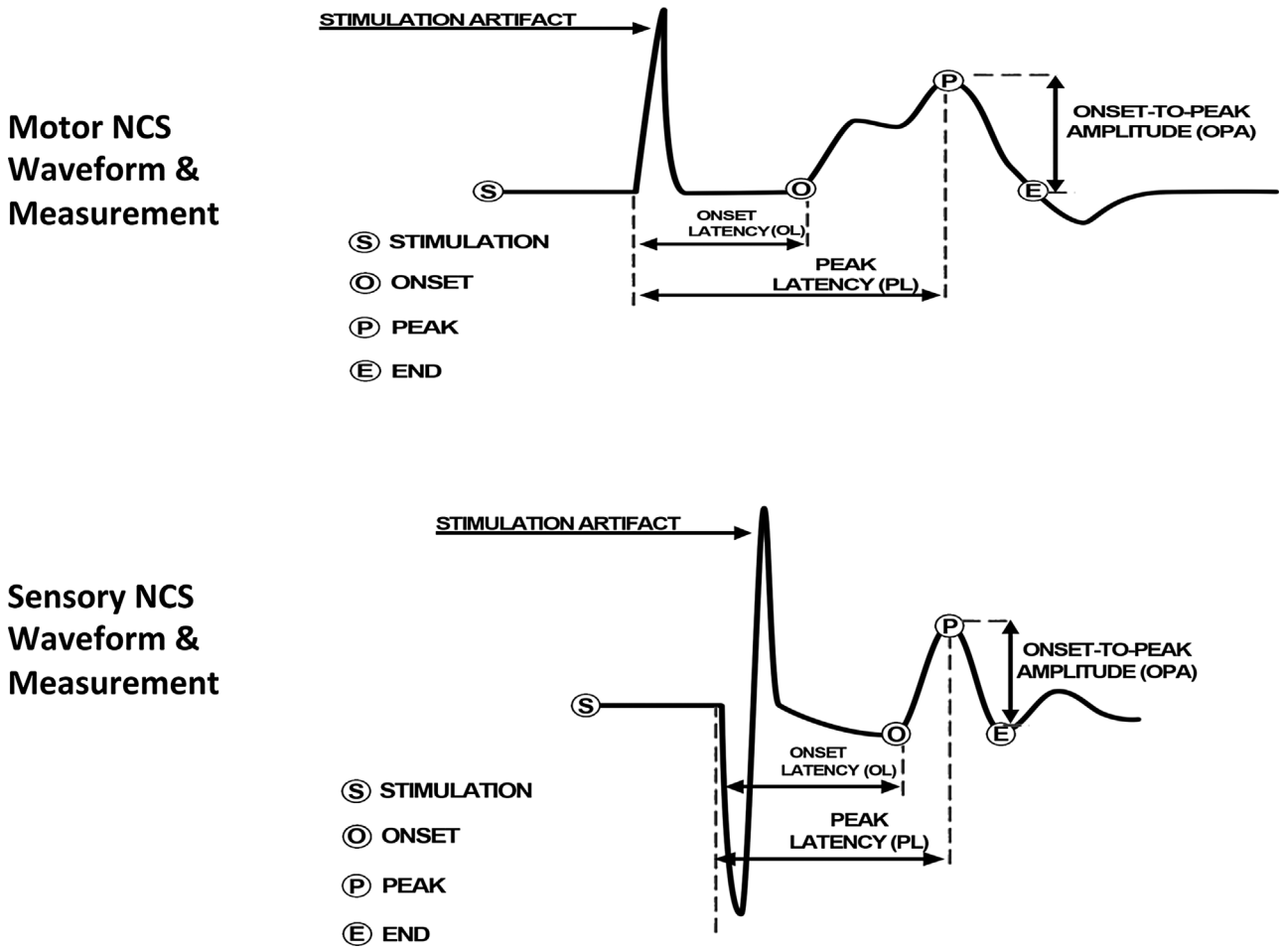

Fig. 3. Examples of typical waveforms observed with sensory and motor nerve conduction studies (NCS) and locations of measurement taken.

the Phase II study ($N=$) for motor NCS with LFTMS alone (Fig. 5).

For QST, two-way interaction was significant only for the manual heat pain M-VAS. However, there were no individual treatment effects associated within each group. For the cool sensation, this main effect of Time was not significant within either treatment group, whereas, for the warm sensation, it was significant within both groups (Table 1). Post study blinding assessments showed no significant difference between real and sham treatment groups in perceiving study treatments.

DISCUSSION

PTP-NP is a common debilitating condition occurring after physical trauma to the nerve. In some surgical procedures, the prevalence of post-surgical PTP-NP can exceed 60% [Hsu and Cohen, 2013]. Preclinical studies have demonstrated that after peripheral nerve injury, large myelinated A-beta fiber afferent firing diminished over time whereas smaller pain transmitting fibers including A-delta and C-fibers had enhanced firing [Puig and Sorkin, 1996]. Clinically, a significant degree of pain with altered sensitivity at the scar area or within distribution of the peripheral nerve is the clinical hallmark of PTP-NP. This chronic pain state is sometimes accompanied by a condition known as allodynia in which noxious perception occurs with non-noxious stimuli such as light stroking [Koplovitch et al., 2012] and with morphological changes including formation of neuroma [Zimmermann, 2001; Rajput et al., 2012]. In addition, spontaneous electrical activities at the site can also enhance sensitivity of nociceptors and augment conduction of nociceptive impulses toward the central nervous system. Therefore modulating afferent sensory input at injury site without physically irritating or contacting the area of neuronal injury provides an excellent alternative in

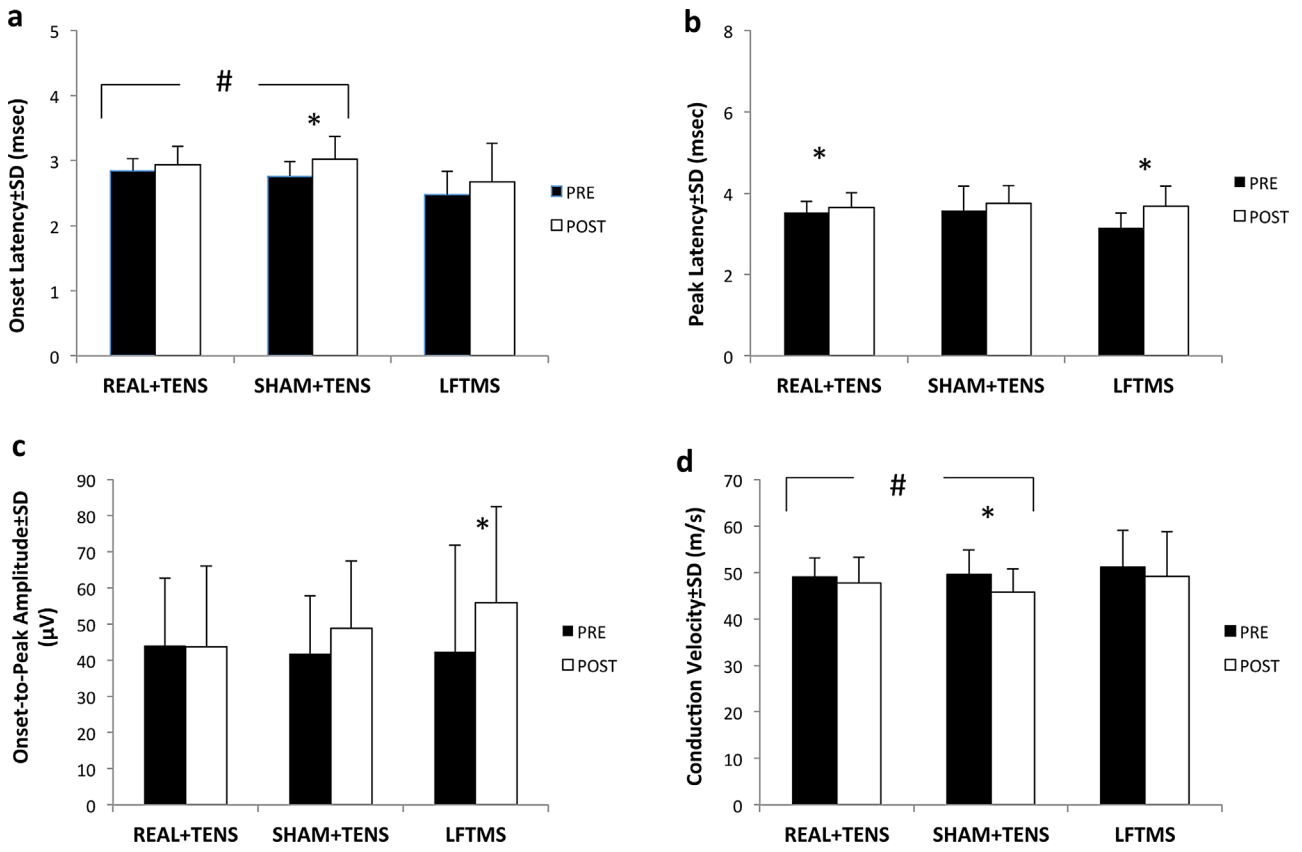

Fig. 4. Sensory Nerve Conduction Studies (NCS). Real + TENS: Real Low Frequency Transcutaneous Magnetic Stimulation with transcutaneous electrical Nerve Stimulation (TENS); Sham + TENS: Sham Low Frequency Transcutaneous Magnetic Stimulation with transcutaneous electrical nerve stimulation (TENS); **a**: Onset Latency; **b**: Peak Latency; **c**: Onset-to-Peak Amplitude; **d**: Conduction Velocity; $*P < 0.05$ for Time (pre and post intervention) effect; $\#P < 0.05$ for Treatment (Real vs. Sham) effect.

managing PTP-NP with a potential long testing analgesic effect.

Specific populations of sensory afferents are characterized by well-defined stimulus-response properties. Broadly speaking, high frequency and low-threshold mechano-stimulation is transmitted by the heavily myelinated A-beta fibers. Cool and well-localized pain is carried by the less myelinated A-delta fibers, whereas warm, hot and cold pain sensations are carried by the unmyelinated C-fiber [Yarnitsky and Ochoa, 1991; Verdugo and Ochoa, 1992]. Previous electrical stimulation and nerve block studies suggested that cold-specific A-delta afferent activity can attenuate C-fiber mediated cold pain sensation [Fruhstorfer, 1984; Wahren et al., 1989; Ochoa and Yarnitsky, 1994]. In addition, fast conducting non-pain specific A-beta afferent activity can compete and modulate slow conducting pain specific C-fiber input [Staud et al., 2011; Yalcin et al., 2011].

In the context of non-invasive peripheral pain neuromodulation, low frequency TENS ($\leq$5 Hz) appeared to undiscrimitively diminish both large and small afferent fibers input as it diminished mechanical pain and tactile thresholds, and reduced PL. On the other hand, high frequency TENS at 250 Hz appeared to predominantly activate pain transmitting A-delta afferent inputs [Walsh et al., 1995a; Koga et al., 2005]. The analgesic effect of low frequency ($\leq$5 Hz) TENS is usually not sustained once stimulation is stopped [Chesterton et al., 2002]. While TENS reduces hyperalgesia and pain, tolerance to treatment effects may develop with prolonged stimulation and a high intensity of stimulation is required to counteract the tolerance effect and produce optimal analgesia [Sato et al., 2012]. In patients with PTP-NP, a direct high intensity electrical stimulation over injury site is often not tolerated by patients with some degree of tactile allodynia, making direct electrotherapy not an ideal therapy for this patient population.

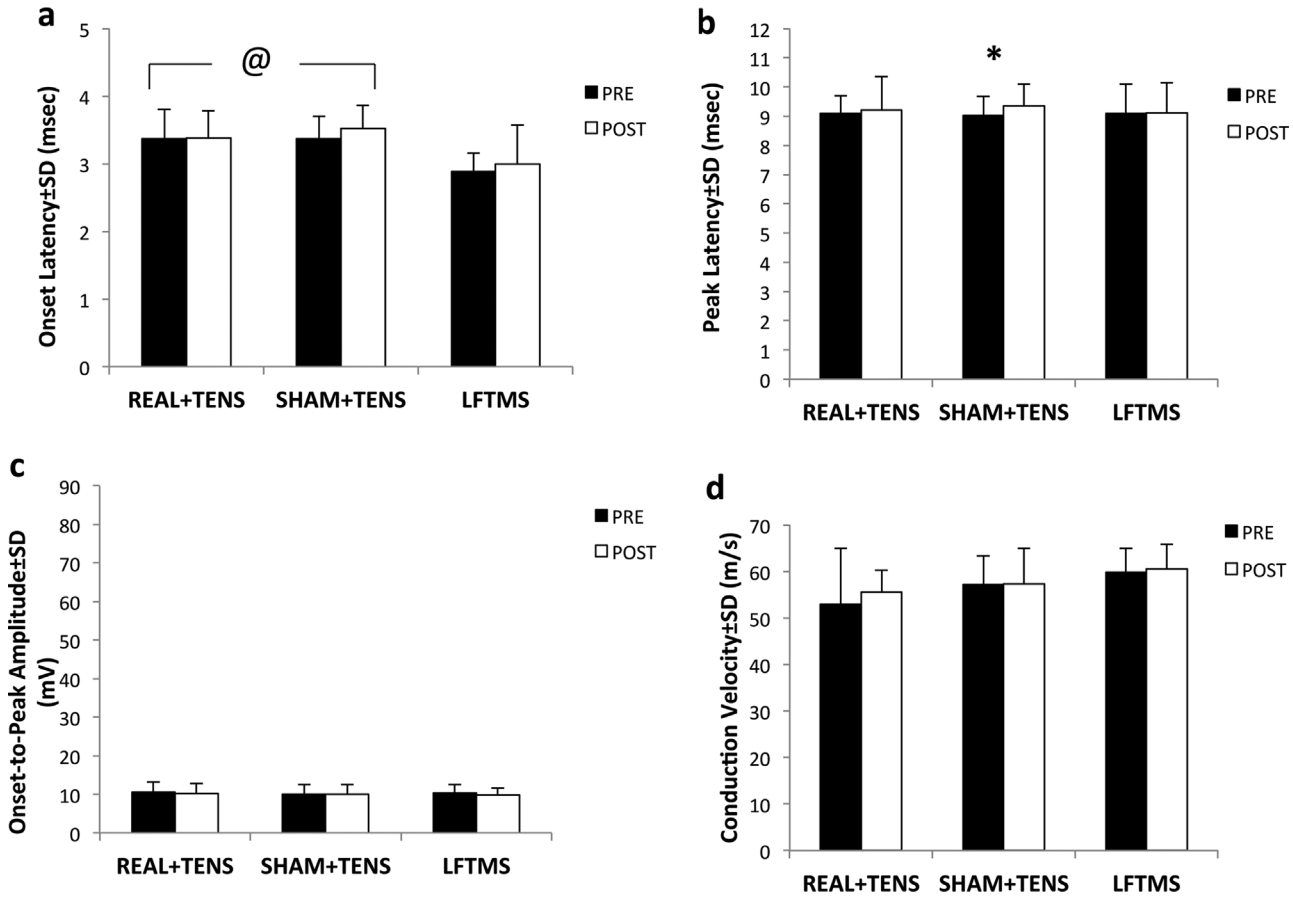

Fig. 5. Motor Nerve Conduction Studies (NCS). Real + TENS: Real Low Frequency Transcutaneous Magnetic Stimulation with transcutaneous electrical nerve stimulation(TENS); Sham + TENS: Sham Low Frequency Transcutaneous Magnetic Stimulation with transcutaneous electrical stimulation(TENS); **a**: Onset Latency; **b**: Peak Latency; **c**: Onset-to-Peak Amplitude; **d**: Conduction Velocity; $^{*}P < 0.05$ for Time (Pre- and post-intervention) effect.; $^{@}P < 0.05$ for the Time × Treatment interaction.

Dynamic magnetic flux is thought to affect neuronal functions by inducing localized neuronal depolarization [Griskova et al., 2006]. This treatment modality offers several advantages over electrical stimulation. One major advantage is that with appropriate coil design, dynamic magnetic flux stimulation provides a higher degree of spatial resolution than electrical stimulation, thus increasing specificity of the intervention [Binkofski et al., 1999]. Other comparative studies also indicated faster conduction velocity, thus a quicker neuronal response with magnetic stimulation in comparison to electrical stimulation [Similowski et al., 1997]. In clinical applications, dynamic magnetic flux can provide neuromodulation to patients with PTP-NP without contacting the patients' sensitive skin. Initial evidence suggests that this analgesic effect can be long lasting [Leung et al., 2014a, b]. In addition, it has been demonstrated that dynamic magnetic flux may facilitate nerve repair/regeneration [Fujiki and Steward, 1997]. While dynamic magnetic flux has been applied centrally as transcranial stimulation to treat depression and pain for the past several decades, its peripheral application for pain relief has only been explored recently. Preliminary studies indicated that peripheral dynamic magnetic stimulation may have positive therapeutic effects on motor recovery and pain relief in patients with traumatic brachial plexopathy [Khedr et al., 2012]. Other studies suggested it might be used for treating myofascial pain syndrome and chronic low back pain [Smania et al., 2005; Masse-Alarie et al., 2013]. In peripheral stimulation, magnetic stimulation is much better tolerated than TENS in minimizing pain related to muscle contraction [Kremenic et al., 2004; Han et al., 2006]. This observed analgesic benefit can be derived from several possible mecha-

TABLE 1. Thermal and Tactile Threshold Measurements With Low Frequency Trancutaneous Magnetic Stimulation (LFTMS) and Sham Stimulation

	Thermal thresholds					
	LFTMS			Sham		
	Pre ± SD (°C)	Post ± SD (°C)	*P*-Value	Pre ± SD (°C)	Post ± SD (°C)	*P*-Value
Cold	27.2 ± 2.8	26.4 ± 2.6	0.072	26.0 ± 3.1	24.8 ± 3.4	0.145
Warm	36.4 ± 2.5	38.0 ± 2.3	0.011*	38.1 ± 2.1	39.3 ± 3.0	0.033*
Cold Pain	3.2 ± 5.7	5.7 ± 5.7	0.216	5.8 ± 5.9	4.8 ± 5.5	0.960
Heat Pain	48.6 ± 1.8	48.6 ± 2.1	0.960	48.4 ± 1.9	49.0 ± 2.4	0.126
	Tactile thresholds					
von Frey	3.29 ± 0.34	3.36 ± 0.22	0.388	3.26 ± 0.34	3.35 ± 0.19	0.251

*$P < 0.05$.

nisms. Centrally, low frequency (1Hz≤) TMS has been shown to be neuronal inhibitory whereas high frequency TMS is neuroexcitatory [Funke and Benali, 2011]. Therefore, it is possible in peripheral stimulation that similar direct inhibitory response can occur in damaged neurons. Alternately, stimulation may preferentially stimulate myelinated pain inhibiting fast conducting large fibers and reverse aberrant neuronal functions associated with PTP-NP.

Current study results indicated that Sham + TENS significantly reduced sensory CV ($P = 0.02$) and increased OL ($P < 0.01$) whereas, Real + TENS reversed the effect of TENS on sensory CV and OL and significantly ($P = 0.036$) increased sensory PL. In addition, LFTMS alone appeared to significantly ($P = 0.01$) increase sensory PL and OPA. As OL is mainly related to fast conducting myelinated large fibers [Kimura, 2013; Kasius et al., 2014], this current observation confirms the previous one that TENS alone exerts an overall inhibitory effect on peripheral sensory afferent fibers, particularly in fast conducting large myelinated fibers. On the other hand, TENS alone did not appear to alter PL whereas, both Real + TENS and LFTMS alone induced significant increase in sensory PL, suggesting the TENS inhibitory effect was less significant on the slow conducting C-fibers than faster conducting myelinated fibers, and LFTMS has a direct slowing effect on slow conducting C-fibers. In addition, LFTMS was able to reverse TENS induced slowing effect on fast conducting fibers by reversing enhanced OL and reduced sensory CV induced by TENS. This modulatory effect of LFTMS also appeared to have a statistically significant effect on sensory PL, suggesting a possible either direct or indirect inhibitory effect on slow conducting C-fibers. Overall, the modulatory effect of LFTMS does not appear to have any profound effect on normal thermal sensory, pain and tactile thresholds. The transient warm threshold increase observed in both real and sham LFTMS studies is likely caused by an adaptation phenomenon.

In short, TENS appeared to have a slowing effect on sensory afferents, especially, fast conducting pain modulatory fibers. LFTMS appears to reverse the TENS slowing effect on fast conducting fibers, thus facilitating the peripheral modulatory effect on slow conducting pain fibers.

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