Examination of parameters in transcutaneous electrical nerve stimulation effectiveness

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EXAMINATION OF PARAMETERS IN TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION EFFECTIVENESS

by

Carol Grace T Vance

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Physical Rehabilitation Science
in the Graduate College of
The University of Iowa

May 2013

Thesis Supervisor: Professor Kathleen A. Sluka

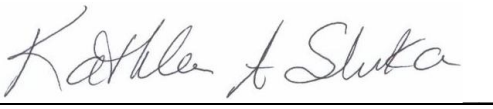
ABSTRACT

Pain is the oldest medical condition and has been referenced through the ages. TENS is a non-invasive treatment for pain. Despite conflicting reports of treatment outcomes, TENS has enjoyed widespread clinical utilization. Seminal work by Sluka and colleagues reported low frequency TENS produces anti-hyperalgesia through μ-opioid receptors and high frequency TENS produces anti-hyperalgesia through δ-opioid receptors in an animal model of inflammation. The experimental results suggested that pain can be reduced by both high and low frequency TENS but by differing opioid receptors. These important findings require translational experiments to be conducted in humans.

Providing an adequate placebo for experimental investigation of any physical intervention presents as a challenge. An improvement in the placebo intervention is critical to ascertain the true effects of TENS on painful conditions. Clinical TENS experiments often only examine a single outcome - resting pain. Recent work suggests TENS is less effective on resting pain as compared to movement pain. Investigation to determine which outcome measures (pain at rest, movement pain, pain sensitivity, and function) are most likely to be affected by TENS in human subjects with pain are critical to inform the design of future studies.

The least investigated parameter for application of TENS electrode site determination. One method of selection employs a technique of finding points on the skin with suspected lower impedance. To date, no literature exists to determine the effectiveness of this clinical practice and speculation has existed for decades regarding the existence of distinct electrical properties associated with specific points on the body.

This series of experiments accomplishes the goals of improving the TENS placebo, testing established parameters from basic science experiments in a patient population, testing multiple outcome measures to direct future investigation; and examined the effect of electrode site selection in TENS analgesia. These experiments were the first to establish a placebo that can 100% blind the TENS examiner, to test this placebo in a patient population, and to show that although there are differences in impedance between optimal and sham sites, that this difference had no effect in the amount of analgesia produced by TENS.

Abstract Approved: 
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CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph.D. thesis of

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To my ever supportive parents- Pete and Mimi Thompson

We all must die. But that I can save him from days of torture, that is what I feel is my great and ever new privilege. Pain is a more terrible lord of mankind than death itself.

- *Albert Schweitzer, MD, physician, humanitarian, theologian*
On the Edge of the Primeval Forest and More from the Primeval Forest: Experiences and Observations of a Doctor in Equatorial Africa

ACKNOWLEDGMENTS

I would like to express my deep gratitude to my thesis advisor Kathleen A. Sluka for her patient guidance, enthusiastic encouragement and useful critiques of this research work. I am grateful for the advice and encouragement given by my thesis committee members Drs. Amendola, Frey-Law, Rakel, and Segal toward the completion of this thesis.

My special thanks are extended to the staff of the Physical Therapy and Rehabilitation Science Department for technical assistance and encouragement, and to the faculty for their support of my research.

I wish to acknowledge Barb Rakel for providing research space, Glenn Williams for providing a critical piece of research equipment, and Jason Wu for providing invaluable technical support.

I am particularly grateful for the assistance given by Shannon Lehman, Dana Dailey, Jennifer Lee, and the past and present members of the Sluka laboratory. I am fortunate to be associated with these exceptional people.

Finally, I wish to thank my parents, my husband Gaylen and my children, Ben, Jacob, Sammy and Kari for their support and encouragement throughout my study.

ABSTRACT

Pain is the oldest medical condition and has been referenced through the ages. Transcutaneous Electrical nerve Stimulation (TENS) is a non-invasive treatment for pain. Despite conflicting reports of treatment outcomes, TENS has enjoyed widespread clinical utilization. Seminal work by Sluka and colleagues reported low frequency TENS produces anti-hyperalgesia through μ-opioid receptors and high frequency TENS produces anti-hyperalgesia through δ-opioid receptors in an animal model of inflammation. The experimental results suggested that pain can be reduced by both high and low frequency TENS but by differing opioid receptors. These important findings require translational experiments to be conducted in humans.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CMPT	Cutaneous Mechanical Pain Threshold
HF	High Frequency
HPT	Heat Pain Threshold
HTS	Heat Temporal Summation
LF	Low Frequency
OA	Osteoarthritis
OSS	Optimal Site Selection
P	Placebo
PPT	Pressure pain Threshold
SSS	Sham Site Selection
TENS	Transcutaneous Electrical Nerve Stimulation
TUG	Timed Up and GO test
USG	Urine Specific Gravity
VAS	Visual Analogue Scale

CHAPTER I

INTRODUCTION

Under normal circumstances pain is protective and critical to survival. However, there are numerous instances where pain presents as a limiting factor in recovery from illness or injury. When experienced or observed, pain is by nature a subjective experience. Because of the many dimensions of pain and its ability to affect function, outlook, and motivation it is a term difficult to define and measure. The International Association for the Study of Pain (IASP) definition of pain "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or defined in terms such damage" [189], provides a platform for clinicians and researchers to evaluate aspects of pain and the interventions utilized to address it.

Pain is the oldest medical condition and has been referenced through the ages in many civilizations. Sumerians clay tablets from 5000 BC contain the earliest written references to the utilization of opium as a method of pain reduction and early Egyptian medical documents (1500 BC) contain references to salicylates derived from the bark of the willow tree utilized in pain reduction [1].

In the 17th century Rene Descartes, first proposed a link between peripheral sensation and the brain. His simplistic model indicated that that peripheral sensation is conveyed directly to the brain, where perception occurs. This hard wired model persisted into the 19th century with few modifications [14]. In 1965, seminal work by Melzack and Wall challenged the concept of a hard-wired system. They proposed the gate control theory of pain indicating sensory information undergoes dynamic integration and modulation prior to arrival at the sensory cortex [120].

In direct response to the gate control theory, Wall and Sweet introduced Transcutaneous Electrical Nerve Stimulation (TENS). Their hypothesis was that large diameter fiber stimulation could reduce pain based on animal work suggesting

"presynaptic depolarization" in the substantia gelatinosa reduced the excitatory effectiveness of afferent nociceptive impulses on cells in the dorsal horn [180]. The authors reported their findings after executing 2 minute sensory TENS treatments using 100 μsec and 100 Hz in eight subjects ranging from 26-62 years of age with differing diagnoses. The outcomes were felt to be clinically important as several of the subjects experienced extended relief from their painful condition [180]. In the 20 years to follow, a significant interest in TENS for the management of pain was demonstrated by the great number of publications dedicated to this topic. This included case reports and clinical studies often with poor design and methodological quality. Despite conflicting reports of treatment outcomes, TENS has enjoyed widespread, ongoing clinical utilization. Recent advances in the basic mechanism of TENS action [26,46,71,82,87,111,164-167,178] over the last 25 years has provided additional insight into utilization of this pain management intervention.

Seminal work by Sluka and colleagues reported low frequency TENS produces anti-hyperalgesia through μ-opioid receptors and high frequency TENS produces anti-hyperalgesia through δ-opioid receptors in the spinal cord in an animal model of inflammation [164]. The experiment was conducted at a strong sensory intensity (motor minus 10%) and suggested that pain could be reduced by both high and low frequency TENS but by differing opioid receptors. This information was beneficial in several regards. First, the previously held belief that the endogenous opiates are released only at a motor level of stimulation using low frequency TENS was discounted. Secondly, this supports the rationale that the Gate Control Theory does not offer a complete explanation of pain reduction with electrical stimulation. Lastly, these findings suggest clinicians should try differing TENS parameters to best maximize pain relief in their clients. For example, opioid tolerance develops with repeated TENS application [26], and high frequency but not low frequency TENS is able to reduce hyperalgesia in morphine tolerant animals [166]. These findings suggest low frequency TENS may not be the first

choice when treating patients who are taking medications that activate the μ-opioid pathway or who have become tolerant to these types of medications.

Significance

Because pain is multidimensional in its definition, it stands to reason that not one discipline holds all the keys to treat and manage pain. The majority of patients who present to the physical therapy clinic will have a pain complaint, and pain is routinely referred to as the 5th vital sign. Interventions for pain management can be used alone or as adjunct to pharmacological treatment to decrease undesirable side effects such as nausea, constipation, dizziness and lethargy [69,148,154,155,170,170]. Importantly, when a patient presents with levels of pain that precludes them from participation in the active interventions (e.g. exercise and functional training) outlined by the therapist, it is imperative that the therapist be knowledgeable and capable of designing an intervention to address the pain and allow for appropriate progression toward the end goals. In support, an early study showed that both high and low frequency TENS reduce analgesic intake and increase the social activity of previously incapacitated patients suffering from chronic pain [57].

TENS investigations have been inconsistent in parameter selection with regard to intensity, frequency, stimulation site selection and pulse duration. The least investigated parameter is that of site selection. Typically clinicians choose a method of TENS electrode site selection and apply it to all patients. A common practice is to bracket above and below the painful area with four electrodes [73,125,136,150]. This approach can be further subdivided into setting the electrode pairs into proximal and distal to the pain, medial and lateral to the pain, or a in a crossed inferential placement. Other methods are to place electrodes at the spinal level suspected to be associated with the pain, over a peripheral nerve or at the dermatomal level. One method suggests using the unit to locate

points of decreased resistance to electrical stimulation to determine electrode placement [15,92,125].

Importantly, nearly all prior studies have been conducted with a traditional and obvious placebo. As is the case with any intervention which is actively perceived by the subject, the issue of providing an adequate placebo group in research investigations has been difficult. In addition, prior TENS studies use separate instructions for active and placebo TENS, which can influence patient expectations and have profound effect on treatment outcome [16,27,67,103,104]. For example, seminal work by Levine and colleagues shows a significant analgesia with a placebo drug when given in a completely blinded manner; the placebo had equivalent analgesia to that of low-dose morphine [103]. On the other hand, negative or neutral instructions result in less reduction in pain after spinal manipulation when compared to positive instructions [16].

In addition, conclusions based on differing outcome measures utilized to determine successful interventions impact the body of knowledge of TENS as an intervention. Early investigations have evaluated pain at rest [126,168,191], however, it may be the case that TENS is more effective for movement related pain [145]. Given the above, it is understandable why there are differing conclusions regarding the efficacy of TENS in treating patients with pain

The series of experiments outlined below demonstrate testing and validation of a new placebo TENS unit in healthy subjects (Experiment 1) and in subjects with documented painful knee OA (Experiment 2). The third experiment investigates an established method of site determination, points of least impedance, [15,92] against sham sites that are classified by perceived increased tissue impedance. Further, Experiment 2 examines the effects of TENS on multiple outcomes, pain and function, in the patients diagnosed with knee OA. Importantly, Experiment 2 will assist with determination of appropriate indicators of significant differences due to TENS intervention. Information from these experiments will be of benefit to further the evaluation of TENS treatment by

researchers via an improved placebo TENS validation. Clinicians and patients will benefit from any findings related to significant differences due to treatments and in outcome measurement tools.

Pain terminology

Hypoalgesia is defined as "Diminished pain in response to a normally painful stimulus [189]." To evaluate the effectiveness of an intervention in healthy subjects a painful stimulus is imposed before and after the intervention. Pressure Pain threshold (PPT) will be the instrument of choice to demonstrate the effectiveness of Transcutaneous Electrical Nerve Stimulation (TENS) when this intervention is applied to the body by differing strategies. In these experiments, the threshold to a painful pressure stimulus is expected to be increased during and following TENS. Otherwise stated, the subject will have the ability to endure more pressure before indicating the pressure stimulus is painful. PPT will be the primary outcome measure to assess TENS effectiveness in Experiments 1 and 3 involving healthy human volunteers.

Hyperalgesia is defined as "An increased response to a stimulus which is normally painful."[189] It can be further divided into primary hyperalgesia which occurs at the direct site of injury and secondary hyperalgesia which occurs outside of the direct area of insult. For example, pressure pain threshold could be decreased in patients with knee pain representing hyperalgesia. If the threshold was decreased at the medial joint line, it would be described as primary hyperalgesia. Decrements noted when testing at the anterior tibialis muscle would be indicative of secondary hyperalgesia. This delineation is important because primary hyperalgesia is thought to reflect changes in the peripheral nervous system and secondary hyperalgesia is thought to be mediated by changes in the central nervous system [162]. In the second experiment hyperalgesia will be measured in subjects with knee osteoarthritis with several instruments including: Pressure Pain

Threshold (PPT), Cutaneous Mechanical Pain Thresholds (CMPT), and Heat Pain threshold (HPT), and Heat Temporal Summation (HTS).

Transcutaneous Electrical Nerve Stimulation

Mechanisms

TENS is one of the non-invasive interventions used in the practice of physical therapy specifically to modulate pain. First presented as a potential treatment for chronic pain by Wall and Sweet in 1967 [180], these small battery powered units generate alternating current which is applied to the skin via conductive electrodes.

An animal model of inflammation demonstrated that analgesia with TENS was accomplished by different mechanisms depending on the stimulation frequency. In this effort, TENS was applied to at 4 Hz and 100 Hz while controlling all other parameters. Dorsal horn neuron sensitization was decreased by both 4 Hz and 100 Hz TENS [109] . Blockade of opioid receptors in the spinal cord and the brainstem show that 100 Hz TENS activates δ-opioid receptors and 4 Hz TENS activates μ-opioid receptors [165]. Similarly, in human subjects low frequency TENS is blocked by naloxone at low doses and high frequency TENS is blocked by naloxone at higher doses[102,161], further supporting different opioid receptors in low and high frequency TENS. Subsequent reports demonstrate similar effects of frequency in the acute inflammation model [164,166] and in opioid tolerant animals [26,166]. In translational work in humans, High frequency TENS but not low frequency TENS provided significant reduction in pain in opioid-treated patients when using visual analogue scales for pain intensity and unpleasantness [101].

Parameters

In addition to pulse frequency; pulse duration, stimulation intensity, treatment duration, and electrode sites are the parameters the therapist must choose to deliver TENS treatment. Evidence for proper stimulation intensity is established by several authors who

have found that a strong sensory stimulus provides increased hypoalgesia in healthy subjects [2,34,35,38,41,132,144].This is further supported by Sluka, et al in an investigation where TENS decreased hyperalgesia in an animal model of joint inflammation when the skin receptors were blocked in the area of TENS application, but not when the joint receptors were blocked [141]. It is noteworthy to report the stimulus intensity was "motor minus 10%", which would be representative of "strong sensory" sensation in humans. Interestingly, this stimulating intensity was used in the reports mentioned above and in numerous projects in the Sluka laboratory. This finding also demonstrates sensory stimulation [8,26,74,75,86,87,140,141,164-166] activates opioid pathways once thought only to be engaged by motor stimulation. Thus, clinicians should be striving to apply TENS at a strong but comfortable intensity, and as treatment progresses, the stimulus should be advanced if patients continue to have pain and no longer feel the same initial sensation. The parameter of pulse duration has received less attention. Gopalkiinshanon and Sluka, 2000 show no significant difference between groups of animals receiving 100 μs verses 250 μs stimulation [71]. Further inquiry into very low pulse durations such as 4-10 μs as is used in high voltage pulsed stimulation is warranted.

Because the clinician determines the pulse duration, pulsed frequency, stimulus intensity, duration and frequency of application, and electrode placement, a nearly infinite number of treatments can be delivered by various combinations of these parameters. Although this allows for individualization of treatment, it presents therapists with a dilemma in that until recently evidence for best practice application was nonexistent. For example; if there were 10 frequency choices, 5 pulse duration settings, 3 intensity choices, 3 methods to place electrodes, and 4 durations suggested, mathematical calculations indicate that there are 1,800 possible combinations of parameters available for treatment and a potential explanation for the variability in effectiveness reported in the TENS literature.

With regard to electrode placement for optimal treatment outcome, many applications have been described and utilized with textbooks confirming that there is not one superior method across all conditions including segmental, peripheral, or contralateral methods [73,125,136,150]. In a 1978 review article by Mannheimer, it is stressed that not all pain conditions will be best treated by using the same electrode selection method [113]. Two papers by Melzack and colleagues address acupuncture points and pain correlation [119] and acupuncture and TENS [121]. In 1977 authors compared trigger point charts by Travell and Rinzler [175] to coinciding acupuncture points associated with painful conditions by Mann [112] and Kao and Kao [83]. Spatial distribution and associated pain patterns of trigger points and acupuncture points were found to be correlated 71% of the time. This is of interest because both types of points are derived from different concepts of medicine and are located and labeled differently. Trigger and acupuncture points also demonstrate some similarity in that practitioners apply brief intense stimulation (needle, manual pressure, neuroprobe or injection) to the point to produce prolonged pain relief [119]. Melzack and Wall offer insightful commentary about TENS and acupuncture indicating that both methods produce analgesia by providing intense sensory input [121]. The term “hyperstimulation” is used to describe the highest possible intensity tolerated by patients (which may include noxious stimulation) to achieve temporary pain relief in chronic conditions. Two independent experiments comparing acupuncture and TENS in patients with chronic low back pain demonstrate equivocal results using the McGill pain questionnaire and 1-5 subjective pain scale as outcome measures [62,91]. These early publications on the topic of utilization of acupuncture points for pain management with TENS have contributed to the common practice of utilizing acupuncture points employed by therapists when selecting TENS electrode sites. The lack of attention to the parameter electrode site selection coupled with the contention that electrode site selection may differ dependent on the painful condition presenting to the clinician [113,121] indicates further

investigation remains warranted to address the methodology of site determination. Electronic searches for reports involving electrode site placement demonstrate the void pertaining to the topic. Although not specifically addressing the issue of how sites are selected, several articles describe concepts about electrodes and their placement. Cottell et al investigated the changes in microflora during repeated use of self-adhesive TENS electrodes and concluded that there were no infection control or safety concerns with daily electrode application over a four week period. An investigation into the modern self-adhesive electrodes suggests that at lower levels of stimulation, often used in TENS treatments, very little current is applied to the skin due to the high impedance of the electrodes. This problem is reduced as stimulation intensity increases; however current density becomes concentrated in the center of the electrode [134]. Reduced thermal allodynia was obtained in rats with neuropathic pain when electrodes were applied to the contralateral limb and when low frequency TENS was applied over acupoints [169]. Interestingly, in the same report, high frequency TENS applied over the paraspinal musculature reduced the development of mechanical allodynia. Examination of the effects of electrode site placement in healthy volunteers was examined in a series of experiments which also tested the effect of stimulation intensity and frequencies [34,35,39]. The experiments show hypoalgesia attained when using both segmental and extra segmental sites, but specifically when strong but comfortable or high intensity stimulation amplitudes were used [34,35]. When the investigators tested simultaneous stimulation of segmental and extra segmental sites with differing intensity and frequency combinations, they show dual-site stimulation (using different parameter combinations at each site) produces significantly greater hypoalgesic effects only when stimulation parameters include high-intensity segmental stimulation [39]. Together these findings suggest an overall importance of stimulation intensity regardless of site and frequency.

Brown et al. investigated electrode placement on the ipsilateral arm of induced ischemic upper limb pain compared to electrode placement at the contralateral leg in

healthy volunteers. They concluded no significant difference in pain intensity and McGill Pain Questionnaire ratings between TENS applied at the ipsilateral arm versus contralateral leg [20]. In contrast, opioid analgesic requirements were reduced in females with post-operative incisional pain when the electrodes were placed over acupoints or at the dermatomal level but not when placed over non-acupoints at the shoulder [33]. Patients with secondary dysmenorrhea treated with TENS over acupoints had significantly lower average pain scores compared to patients receiving TENS over non-acupuncture points [110]. Importantly, few studies report how electrode sites were located other than mentioning anatomical landmarks and measured distances. It is clear the methodology of how clinicians should proceed to determine exactly where to position the electrodes is under investigated.

Purpose

The primary purpose of the three independent yet related experiments in this proposal is to improve the clinical application of TENS for the management of pain. Specifically, testing a novel placebo unit, testing methods of electrode site selection, utilizing multiple outcome measures and translating the parameters utilized in basic science mechanistic studies to a study involving a painful human condition are the topics of inquiry. The first experiment involves testing a new placebo unit against active HF-TENS (100 Hz), LF-TENS (4 Hz) and a traditional placebo unit in healthy human subjects. The second experiment includes evaluation of the new placebo, HF-TENS and LF-TENS, in a chronic pain population, specifically subjects with a confirmed diagnosis of knee OA. Healthy human subjects are studied in the third experiment to evaluate different methods of electrode site selection.

Specific Aims and Hypotheses

Specific Aim 1: To determine if there is a difference in PPT, subject blinding, and examiner blinding when using active TENS, Traditional placebo TENS and Transient placebo TENS in healthy human volunteers.

Hypothesis 1: The Transient placebo TENS will result in significantly higher subject and investigator blinding than the Traditional placebo TENS therapy; and the Transient placebo TENS will not significantly increase PPT as expected for the active TENS intervention.(Figure 1.1. Conceptual Model-Experiment 1)[a]

Specific Aim 2: To determine the efficacy of HF-TENS and LF-TENS for subjects with chronic knee osteoarthritis pain and to determine which outcome measures (pain at rest, movement evoked pain, pain sensitivity, and function) are most likely to be affected by HF-TENS and LF-TENS in people with pain to inform the design of future studies.

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[a] Manuscript published: Rakel BA, Cooper N, Adams HJ, Messer BR, Frey Law, L, Dannen DR, Miller CA, Polehna AC, Ruggle RC, Vance CGT, Walsh DM, Sluka KA. A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. J Pain. 2010;11(3):230-238.

Hypothesis 2: HF-TENS and LF-TENS will reduce pain during movement, but not pain at rest, increase pain thresholds, and increase function in subjects with knee OA. (Figure 1.2. Conceptual Model-Experiment 2)[b]

Specific Aim 3: To determine if there is a difference in skin impedance and PPT when using electrode sites determined by optimal site selection (OSS) and sham site selection (SSS) when using HF TENS and compared to Transient Placebo TENS in healthy human volunteers.

Hypothesis 3: Skin impedance will be significantly lower at OSS sites as compared to SSS sites.

Hypothesis 4: PPT will be significantly increased when using electrode stimulation sites determined by the OSS method to deliver HF TENS as compared to HF TENS delivered over SSS and both will be greater than placebo TENS. (Figure1.3. Conceptual Model-Experiment 3)

[b] Manuscript published***:*** Vance CG, Rakel BA, Blodgett NP, Desantana JM, Amendola A, Zimmerman MB, Walsh DM, Sluka KA. Effects of Transcutaneous Electrical Nerve Stimulation on Pain, Pain Sensitivity, and Function in People with Knee Osteoarthritis: A Randomized Controlled Trial. Phys Ther. 2012; 92(7):898-910.

Figure1-1. Conceptual Model for Experiment 1

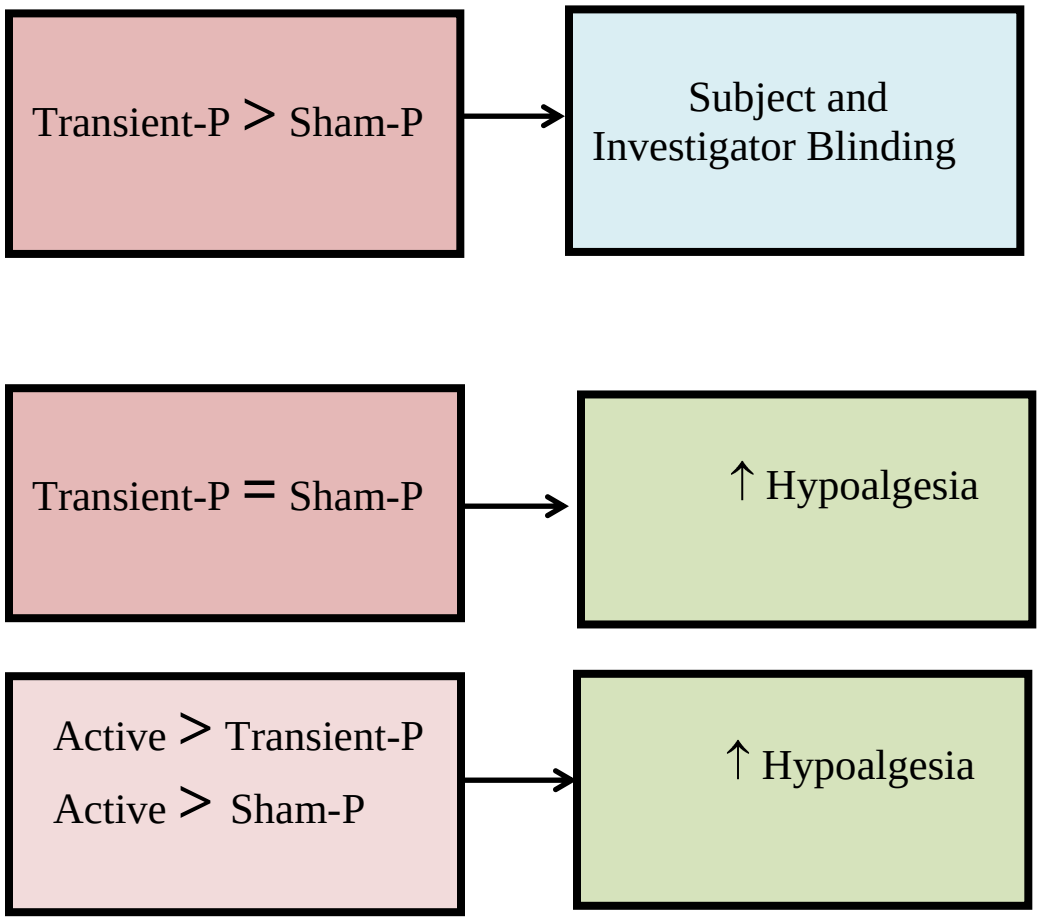


Figure 1-2 Conceptual Model for Experiment 2

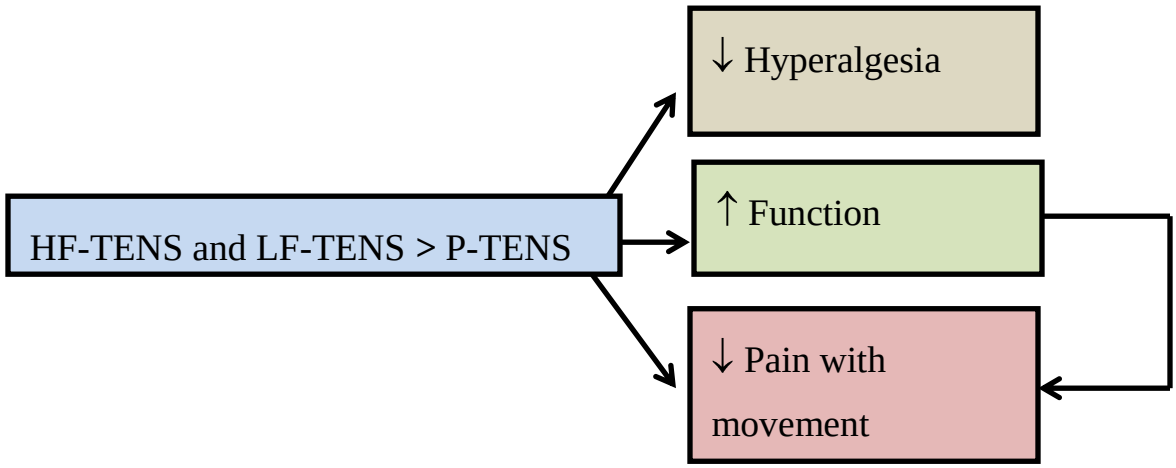
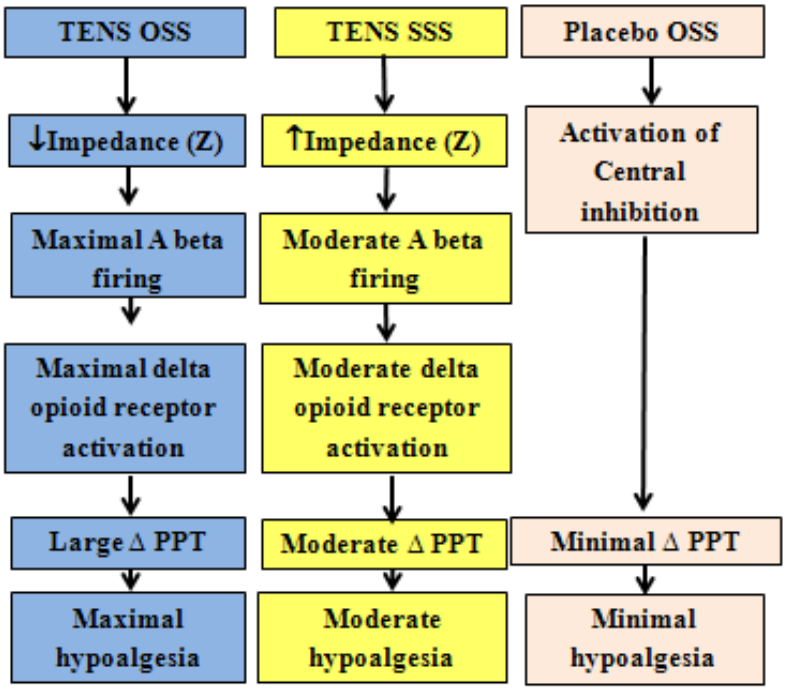


Figure1-3 Conceptual Model for Experiment 3



CHAPTER II

A NEW TRANSIENT SHAM TENS DEVICE ALLOWS FOR INVESTIGATOR BLINDING WHILE DELIVERING A TRUE PLACEBO TREATMENT[c]

Abstract

This study compared a new transient sham TENS that delivers current for 45 seconds to an inactive sham and active TENS to determine the degree of blinding and influence on pain reduction. Pressure pain thresholds (PPT), heat pain thresholds (HPT), and pain intensities to tonic heat and pressure were measured in 69 healthy adults before and after randomization. Allocation investigators and subjects were asked to identify the treatment administered. The transient sham blinded investigators 100% of the time and 40% of subjects compared to the inactive sham that blinded investigators 0% of the time and 21% of subjects. Investigators and subjects were only blinded 7% and 11% of the time, respectively, with active TENS. Neither placebo treatment resulted in significant changes in PPT, HPT, or pain intensities. Subjects using higher active TENS amplitudes (≥17mAs) had significantly higher PPTs and lower pain intensities to tonic pressure than subjects using lower amplitudes (<17mAs). HPTs and pain intensities to tonic heat were not significantly changed. Subjects with lower BMIs temporally summated to tonic heat or pressure significantly more often than those with higher BMIs. The transient TENS

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[c] Published as: Rakel BA, Cooper N, Adams HJ, Messer BR, Frey Law, L, Dannen DR, Miller CA, Polehna AC, Ruggle RC, Vance CGT, Walsh DM, Sluka KA. A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. J Pain. 2010;11(3):230-238.

completely blinds investigators to treatment and does not reduce pain, thereby providing a true placebo treatment.

Perspective

This article presents the benefits of a new transient sham TENS device for use in prospective, randomized, clinical trials. This device facilitates blinding of subjects and investigators to eliminate expectation bias and determine the true efficacy of TENS for use in clinical populations.

Introduction

Transcutaneous electrical nerve stimulation (TENS) is commonly used for the relief of acute and chronic pain. TENS delivers electrical current through the skin to produce pain relief. To examine efficacy of any treatment for pain, including TENS, it should be compared to an adequate placebo that allows evaluation of its physiological effect [188]. Placebo-induced expectancies decrease pain and modulate specific neural mechanisms [159,179,193]. In some studies, placebo TENS has shown similar effects to active TENS [22,129,147]. Thus, the evaluation of placebo treatment to discerning the true efficacy of active TENS treatment is essential. Historically, placebo methods have involved devices that use a battery and display an active indicator light but do not deliver current [18,34,35,39,129,145]. This method attempts to blind the subject but has the limitation of not blinding the investigator who is applying the treatment. Lack of investigator blinding can result in bias when recording outcome data and influence the findings of studies in favor of active TENS therapy or require a separate investigator to allocate treatment so the investigator assessing outcomes remains blinded. A new sham TENS device has been developed that delivers current for 30 seconds and then gradually ramps down to no current over the next 15 seconds. This approach has the potential of blinding the investigator as well as the subject to TENS treatment but whether this occurs

is currently unknown. Further, it is unclear if the short stimulus provided by this placebo device elicits a physiologic response that may result in a treatment effect.

The primary purpose of this study was to determine the degree of blinding that occurs with the new transient sham TENS device that delivers current for approximately 45 seconds. We hypothesized that this device would result in significantly higher subject and investigator blinding than the inactive sham TENS therapy. A secondary aim was to determine if the brief 45 seconds of stimulation provided by the new, transient TENS placebo influenced pressure and heat pain thresholds and pain intensities to tonic heat and pressure compared to active TENS therapy. We hypothesized that this short term stimulation would not significantly increase pain thresholds or decrease pain intensities as expected for the active TENS therapy.

Materials and Methods

Subjects

Sixty-nine healthy adults (mean age 27.19 ± 1.75 years) were tested. After approval from the Institutional Review Board, subjects were recruited through posters, campus e-mail, and advertisements in campus publications. Individuals were excluded if they had: 1) any current acute or chronic pain condition; 2) prior use of TENS; 3) myocardial infarction or stroke within the last 12 months; 4) pacemaker or other contraindication to TENS; 5) pregnancy; and 6) any known neuromuscular disorders or loss of sensation (defined by lack of sharp or dull sensations over any of 5 dermatomes on the extremity being tested). After providing written informed consent, the subjects were stratified by gender and randomized using a computer generated randomization list and SNOSE (sequentially numbered, opaque sealed envelopes) allocation concealment method described by Doig and Simpson [52]. The envelopes were stored in a secure area that only the allocation investigators had access to and were opened after consent was obtained. After data collection on the first 42 subjects, the effect of intensity seemed to be

important so the remaining subjects were randomized to either transient placebo or active TENS to further distinguish the effect of TENS amplitude.

Demographic information including age, gender, height, and weight were recorded. There were no significant differences between groups based on age, gender, or body mass index (BMI) (Table 2-1).

TENS Treatment

Subjects were randomized to receive one of three TENS treatments: 1) active TENS therapy (n=30); 2) a new, transient placebo TENS therapy using a custom made unit that is active for the first 30 seconds then ramps down to zero stimulus over 15 seconds (n=25); or 3) inactive placebo TENS therapy using a non-functional unit that appears to work but provides no stimulus (n=14) (Figure 2-1). All devices were Rehabilicare Maxima TENS units (DJO Global, Vista, CA).

Stimulation parameters were constant mode, 100 Hz pulse rate, and 100 μsec pulse duration. Pulse amplitude was determined for the active and transient placebo TENS in all cases as a strong, but comfortable intensity. In the first series of data collected, intensity was increased until a motor contraction was produced, and then the pulse amplitude was decreased to 10% below motor contraction (active n=15 or placebo n=12) as previously used in animal studies [164]. An interim analysis showed that those able to tolerate a greater intensity gave a greater degree of analgesia. We subsequently allocated the remaining subjects into a different protocol. This protocol was achieved by increasing pulse amplitude until reaching the maximum intensity that the participant could tolerate, regardless of muscle contraction (active n=15; transient placebo n=13). At all times, there was equal randomization between placebo and active TENS groups, and the randomization schedule did not change. The TENS units were calibrated using an oscilloscope prior to starting the study. For each pulse amplitude setting on the devices,

peak to peak voltage was measured across a 1 kΩ resistor to calculate the corresponding current in mAs.

Parameters were set within the first 30 seconds of stimulation. Pulse amplitude was recorded for each subject. The inactive placebo units were set at an amplitude of 25 mA. TENS was applied with two, 2-inch square, self-adhesive electrodes placed at two points on the posterior aspect of the non-dominant forearm: one distal to the elbow and the other above the wrist crease (Figure 2-2)**.** Treatment was applied by two investigators who did not participate in outcome assessments.

Pressure Pain Threshold

PPT was assessed using a digital pressure algometer (Somedic AB, Farsta, Sweden) with a 1 cm^2 tip and a controlled rate of stimulus delivery (40 kPA/s). Subjects were instructed to activate a button when the sensation of pressure clearly became one of painful pressure and were familiarized with the assessment by completing two practice trials on their dominant forearm. PPTs were assessed at three marked sites on the subject's non-dominant forearm, 2 cm apart over the wrist extensor muscle mass and distal to the elbow. With this method, mean pressure pain thresholds (PPT) of the knee average approximately 250 kPa[123]. Previous studies demonstrate that anesthetic blockade of the skin under the algometer has no effect on the PPT, thus this is a measure of deep tissue hyperalgesia [17,88].

Pain Intensities to Tonic Pressure

Pain intensities to tonic pressure were used to determine pressure temporal summation. Tonic pressure was applied using a custom built device incorporating a pressure transducer and a lever with a movable weight to grade the force delivered (see Figure 2-2). The forearm was secured in place with a vacuum pillow (VersForm, Sammons Preston, Bolingbrook, IL). The pressure stimulus was delivered through a 1 cm^2 probe over the extensor muscle mass proximal to the location of the PPT readings.

Pressure threshold was reassessed with this device and 130% of this threshold value was used as the tonic pressure stimulus for each subject. This same pressure was applied continuously for two minutes while subjects marked the intensity of their pain on a 100 mm visual analog scale (VAS) at 10 s intervals starting at initial application of the stimulus. The VAS has high reliability, validity, and sensitivity, particularly when attempting to determine the therapeutic effect of specific treatments [37,160].

Heat Pain Threshold

Heat pain threshold (HPT) was assessed using a TSAII NeuroSensory Analyzer (Medoc Ltd, Ramat Yishai, Israel) as previously described [54,187,187] with a 16 X16 mm stimulator. Use of a 16X16 mm stimulator was based on our preliminary work showing more consistent development of temporal summation with this smaller probe size compared to the larger (30X30mm) probe (unpublished). Temperature started at 37 °C and increased by 1 °C/s to a maximum of 52 °C. The thermal stimulus was terminated when the subject first perceived pain. If pain was not perceived by 52 °C, the test was stopped for subject safety and this temperature was recorded as the pain threshold. Subjects were familiarized with the assessment by completing two practice trials on their dominant forearm. HPTs were assessed at the same three marked sites as the PPTs on the subject's non-dominant forearm over the extensor muscle mass. Threshold occurs at temperatures of 44.5 to 45.0^{o}C on normal skin.

Pain Intensities to Tonic Heat

Pain intensities to tonic heat stimuli were used to determine heat temporal summation. Tonic heat was applied using the same TSAII NeuroSensory Analyzer and 16 X16 mm stimulator used for HPTs. A continuous stimulus of 46 °C was applied for 100 seconds on a marked site over the extensor muscle mass, adjacent to the testing sites for the heat and pressure pain thresholds on the non-dominant forearm. Subjects rated their pain response every 10 s on the 100 mm VAS described above, beginning with the

application of the thermal stimulus. Subjects were familiarized with this assessment by completing one trial on their dominant forearm. The room temperature was maintained between 20 and 23ºC. This method has been used by other investigators to successfully measure temporal summation [59,68,151].

Protocol

Pain measures were performed by an outcome assessor who was blind to group allocation in the following order: HPT, PPT, tonic heat, tonic pressure. Prior to each test, participants were familiarized with the assessment by completing practice trials as described above. The outcome assessor then left the room and another investigator randomized the subject to treatment. The assigned TENS treatment was applied to the subject's forearm by a third investigator. After a 20 minute treatment interval, the outcome assessor returned and repeated the four pain measures. The TENS device was then discontinued and the subject's height and weight were measured.

Blinding Assessment

At the conclusion of testing, the outcome assessor asked the subject "Do you think you received an active or placebo treatment?" The investigator applying the TENS treatment was asked "Do you think the subject received an active or placebo treatment?" Their responses to these questions were recorded and used to gauge the adequacy of subject and investigator blinding.

Statistical Analysis

Blinding was coded as 0 for correct group assignment and 1 for incorrect (blinded) group assignment. PPTs and HPTs were calculated as the mean of the three sites tested at each time point. Changes in PPT and HPT were calculated as % of baseline, where no change is equivalent to 0%. Changes in pain intensities for both tonic heat and pressure were calculated as a change in the area under the curve for the duration

of testing (i.e. 100 seconds for heat and 120 seconds for pressure) post-TENS to pre-TENS. Descriptive statistics were calculated for all variables. $\times^2$ tests were used to compare blinding between groups, and to compare against an expected result of 50:50 blinding (i.e. chance). One-way ANOVA compared differences between groups and repeated measures ANOVA was used to compare differences across time for treatment data (i.e. PPT, HPT, area under the curve for tonic heat and pressure). Post hoc testing was performed with a Tukey's test for differences between groups and with a paired t-test for differences across time. Pearson product-moment correlation coefficients were used to assess levels of associations between TENS pulse amplitudes and the pressure pain sensitivity measures: PPT and pain intensities to tonic pressure. Differences in BMI between summators and non-summators were compared with a t-test. All data are presented as mean +/- S.E.M; significance was set at $p<0.05$.

Results

Adequacy of Blinding

The new transient placebo TENS completely blinded the investigators to treatment. Investigators correctly identified the transient placebo TENS as a placebo treatment 0% of the time (0/25). In other words, they thought they were applying active TENS therapy 100% of the time when using this sham device. Investigators correctly identified the inactive placebo TENS as a placebo treatment 100% of the time (14/14) and correctly identified the active treatment 93% of the time (28/30). Investigator responses were significantly different when comparing the new transient placebo to both the inactive placebo and the active treatment ($p<0.0001$).

Subjects correctly identified the new transient placebo 60% of the time (15/25), the inactive placebo 79% of the time (11/14), and the active treatment 87% of the time (26/30). The new transient placebo was no different than chance (random 50:50 probability) suggesting adequate blinding. In contrast, the inactive placebo and the active

TENS were more frequently identified as correct than chance alone ($p<0.05$) suggesting that subjects were not blinded to treatment group. Correct responses in the inactive placebo group were not significantly different from either the new transient placebo or the active TENS groups ($p>0.05$). Correct responses were identified less frequently in the new transient placebo compared to the active treatment ($p<0.05$).

Treatment Effects

There were no significant changes in PPT, HPT, or pain intensities to tonic heat or pressure after the new transient placebo TENS or inactive placebo TENS treatments were applied (Figures 2-3 a & b and 2-4 a, b, c, & d). There were also no significant differences in effect between the two placebo groups.

In the group receiving active TENS, changes in PPT were not significant overall (Figure 2-3b). However, when considering those receiving higher pulse amplitudes (17-25mA; N = 17), there was a significant increase in PPT (17.5% ± 5.0%) compared to those receiving lower pulse amplitudes (< 17mA; N = 13) ($F_{1, 29} = 9.8$, $p = 0.004$) and increases in PPT were significantly correlated with increases in pulse amplitude (Pearson's correlation, $r = 0.3$, $p = 0.05$). In the new transient placebo group, PPT increased only 3.5% ± 4.4% (Figure 2-5 a & b) and increases in PPT were not significantly correlated with increases in pulse amplitudes ($r = -0.03$, $P = 0.44$).

Similarly, changes in pain intensities to tonic pressure were not significantly different overall in the group receiving active TENS. However, those receiving higher pulse amplitudes (17-25mA; N = 17) had significantly lower pain intensities to tonic pressure compared to those receiving lower pulse amplitudes (<17mA; N= 13) ($F_{1,29} = 5.3$, $p = 0.028$). A reduction in pressure temporal summation was observed for the group receiving active TENS with mean baseline pain rating increases of 20.5 ± 7.3 mm and post-treatment pain rating increases of only 2.4 $\pm$ 3.9 mm. Whereas, in the transient placebo TENS group, no change in temporal summation occurred: baseline increase of 14

± 0.6 mm and post-treatment increase of 21 ± 0.6 mm. A significant negative correlation was observed between change in pressure temporal summation and pulse amplitude for the active TENS group ($r = -0.42$, $p = 0.02$) but not for the transient placebo group ($r = 0.03$, $p = 0.88$) (Figure 2-5 c & d).

Changes in HPTs and pain intensities to tonic heat were not significantly different after active TENS treatment. Comparing high and low TENS amplitudes in this group did not result in significant differences.

Discussion

Adequacy of Blinding

The new transient placebo completely blinded the allocation investigators to treatment while these investigators were always aware when they were applying the inactive placebo. This finding supports our hypothesis that the transient placebo results in significantly higher investigator blinding than the inactive placebo TENS. The high level of investigator blinding with the new transient sham device was due to the presence of muscle contraction each time this device was applied, similar to what they saw when applying the active treatment. This resulted in the investigator thinking they were applying an active unit. There was no muscle contraction when the inactive placebo was applied making it obvious that a placebo unit was being used.

The new transient placebo TENS could also be applied using the same script and parameters as the active TENS treatment, whereas a separate script and parameters were needed for application of the inactive placebo (see Table 2-2). This approach has obvious cost and protocol advantages for prospective randomized clinical trials by allowing the same investigator to both apply the treatment and assess outcomes. It also eliminates investigator expectation bias. Investigators, having been exposed to research goals and hypotheses, can inadvertently influence respondents to produce outcomes consistent with those expectations [36,188]. During application of an inactive placebo TENS, the

investigator, knowing a placebo treatment is being applied, may inadvertently approach this application differently and in a manner subtly suggesting lack of effect which may influence the subject's expectations and responses. This influence on outcome results is particularly possible when measuring subjective outcomes like pain.

Subject blinding for the new transient placebo TENS was not significantly different than subject blinding for the inactive placebo TENS (which occurred in frequencies consistent with prior studies [51]). Thus, our hypothesis that subject blinding would significantly improve with the new transient sham device was not supported. However, it is possible that the 40% of correct responses occurred by chance and subjects were totally blinded to treatment when using the new transient sham device. If subjects did not know what treatment they received and had to guess, they would have a 50% chance of guessing the correct treatment. In this case, 40% of subjects guessed correctly.

It is also possible that these subjects felt the stimulation ramp off suggesting to them that they are receiving a placebo treatment. Since use of a high amplitude is associated with improved outcomes [18,35], intensity goal was set to a strong but comfortable level. It is necessary to approach a transient placebo in this same manner to maintain investigator blinding and eliminate the effects of expectation bias. Another approach may be to use the transient placebo in a sub-sensory manner so subjects feel the stimulation initially but not once it is set to the sub-sensory level or when ramping off. The disadvantage of this approach is eliminating investigator blinding and requiring a separate investigator to measure outcomes. This approach is costly and presents challenges of providing multiple individuals to apply treatment and assess outcomes in a randomized clinical investigation.

An important but not surprising finding is that both subjects and investigators correctly identified active treatment with the majority of applications (87% and 93%, respectively) and correctly identified active treatment significantly more often than placebo treatment when the transient sham device was used. These results are consistent

with prior research [51] and demonstrate a lack of blinding for both subjects and investigators to active treatment when using physical modalities such as TENS. This lack of blinding can lead to an expectation bias that may overestimate treatment effect in groups receiving active TENS. The constant stimulation may influence subject responses to outcome measures because it confirms to them that active treatment is being delivered. Investigators may inadvertently influence respondents due to their expectation that active treatment should produce better outcomes. These findings highlight the importance of assessing the degree of blinding when evaluating the efficacy of physical modalities such as TENS. It is important to keep this effect in mind when interpreting results to avoid overestimating the effects of treatment.

Treatment effects

Subjects treated with the transient placebo had no significant physiologic effects from the short duration of treatment they received. PPT, HPT, and pain intensities to tonic heat and pressure were unchanged after treatment with the new transient placebo TENS. Therefore, this new sham device performed as an adequate placebo, mimicking the treatment without producing treatment effects.

Subjects treated with active TENS had the greatest increases in PPT and tonic pressure pain intensities compared to inactive and transient placebos, though these changes were only significant with higher pulse amplitudes. These data corroborate previous studies displaying an effect of TENS on PPT in humans and animals[39,41,71,114,164] and an intensity effect of TENS treatment[2,18,34,35,184]. Further, there was a reduction in pain intensities to tonic pressure with active TENS at higher pulse amplitudes when compared to placebo TENS. These data suggest a central mechanism, as wind-up of dorsal horn neurons is thought to be the underlying mechanism for temporal summation. This central effect of TENS further validates animal

studies showing reduction in sensitization and nociceptive activity of dorsal horn neurons and activation of central inhibitory pathways by TENS[65,82,109,165].

Surprisingly, there was no significant difference in HPTs during active TENS, contrary to our initial hypothesis. This is in agreement with prior studies who similarly showed no differences in HPT with high-frequency TENS [55,174] but in contrast with other studies showing an effect in healthy subjects [21,29,44,185]. Differences in experimental design may account for these findings. For example, positive effects for high-frequency TENS were observed if electrodes were placed over the radial or median nerves or over acupoints with the heat pain stimuli applied over the skin area of the stimulated nerve [21,44,174]. Electrode placement in the current study was over the extensor muscle of the posterior forearm with heat pain stimuli applied over the muscle body. Other possible differences include: use of high frequency TENS versus a modulated frequency which has resulted in higher HPT elevations [174], use of a 16 X16 mm stimulator instead of a larger stimulator which has shown positive effects on HPT [21,131,174], and conducting measurements only during TENS stimulation rather than continuing to measure HPT after TENS application which has demonstrated a positive effect on HPT[21,44].

These results provide evidence for the use of a new transient sham TENS device, although several study limitations should be addressed in future studies. We used a young healthy cohort, thus these findings may vary with older individuals or patients with specific diseases/illnesses. The subject blinding effects to the active treatment may even improve in clinical cohorts, although the subject blinding to the placebo was similar to chance and thus may remain similar. With two placebo devices and an increased number of placebo groups there could have been an increased chance that the subject chose the placebo treatment. However this is unlikely since the subject guess the active TENS device more accurately than chance. It is likely that the strong intensity of stimulation used in this study, which is necessary to produce an analgesic effect, made it difficult to

blind the subject to the active unit. Investigator blinding is not likely to be strongly influenced by study population, thus the improved investigator blinding with the transient device would be expected to be a robust finding.

Our study involved a relatively small, although adequately powered, sample size. Larger studies may be able to detect even smaller differences between the sham devices than reported here. While we assessed for blinding, we did not assess for expectation of treatment effect. Expectation of treatment effect can clearly influence outcome [16,70]. Lastly, variations in pain sensitivity observed here may not translate to other quantitative pain assessments (e.g. cold presser task) or pain ratings resulting from clinical or experimental pain conditions. Future studies may help to clarify these issues.

Conclusions

These data support the use of a new transient placebo TENS in future double-blind, randomized, clinical trials of TENS. It provides cost and protocol advantages while eliminating expectation bias.

This study was supported by NIH R03 NR010405, Congdon Faculty Development fund, and the Carver College of Medicine at the University of Iowa. We wish to thank Shannon Lehman for assistance with recruitment and scheduling, and Matthew J. Granquist for his assistance with data collection.

Treatment Group – random assignment	Inactive Placebo (n = 14)	Transient Placebo (n = 25)	Active TENS (n = 30)
Gender			
Male	7 (50%)	14 (56%)	15 (50%)
Female	7 (50%)	11 (44%)	15 (50%)
Age (Mean ± SD)	29.92 ± 3.08	28.16 ± 1.48	25.10 ± 1.35

Table 2-1: Subject demographic information with no significant difference between groups on gender, age, or BMI (Body Mass Index).

Active and Transient Placebo TENS Script: *
"The goal of this study is to test the effect of a high intensity TENS treatment. I am going to increase the intensity level until you feel a strong but comfortable sensation. If the stimulus becomes uncomfortable, I will turn the intensity down from that point." Press channel up arrow to increase the intensity to the point the subject indicates it is a strong but comfortable sensation. If muscle contraction occurs, reduce amplitude 10% from point of muscle contraction (protocol 1) or if muscle contraction causes movement of the wrist or fingers turn amplitude down (protocol 2).
Placebo TENS Script: +
"The goal of this study is to test the effect of a low intensity TENS treatment. I am going to set the intensity at a level that you may or may not feel." Set intensity level to "25". "Do you feel anything?" If subject responds "no" state "That is alright. The stimulus will still get to your nerve fibers even if you don't feel it." If the subject answers "yes" state, "Good. If the feeling goes away, that is alright because the stimulus will still get to your nerve fibers even if you don't feel it."

* Same script used for active and transient placebo TENS application.

+ Separate script used for inactive placebo TENS application.

Table 2-2: TENS protocol scripts.

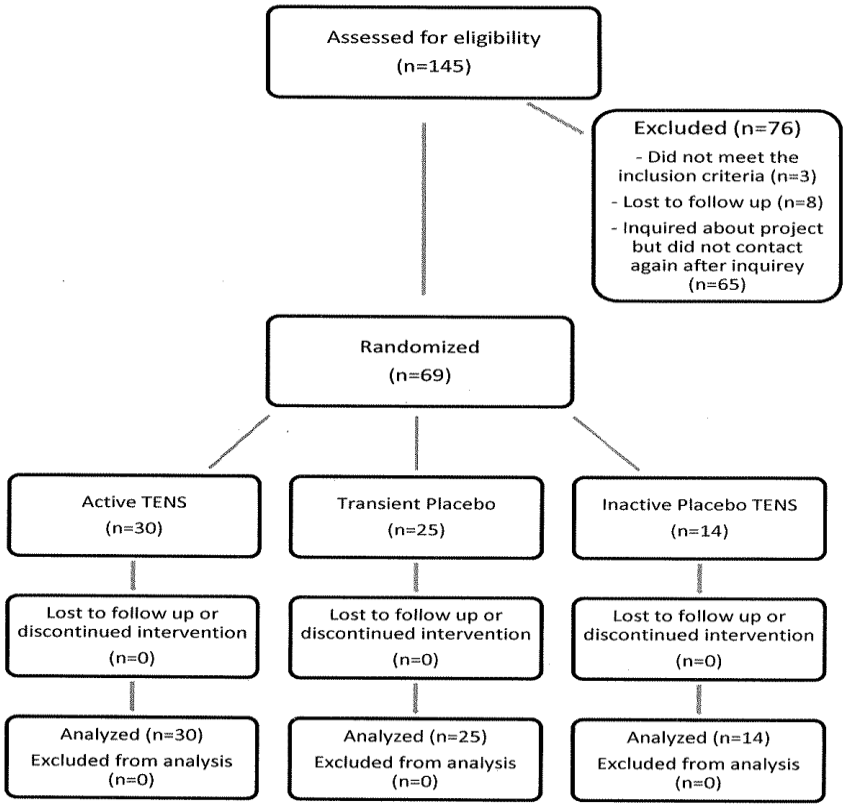


Figure 2-1: Consort trail flow-chart.

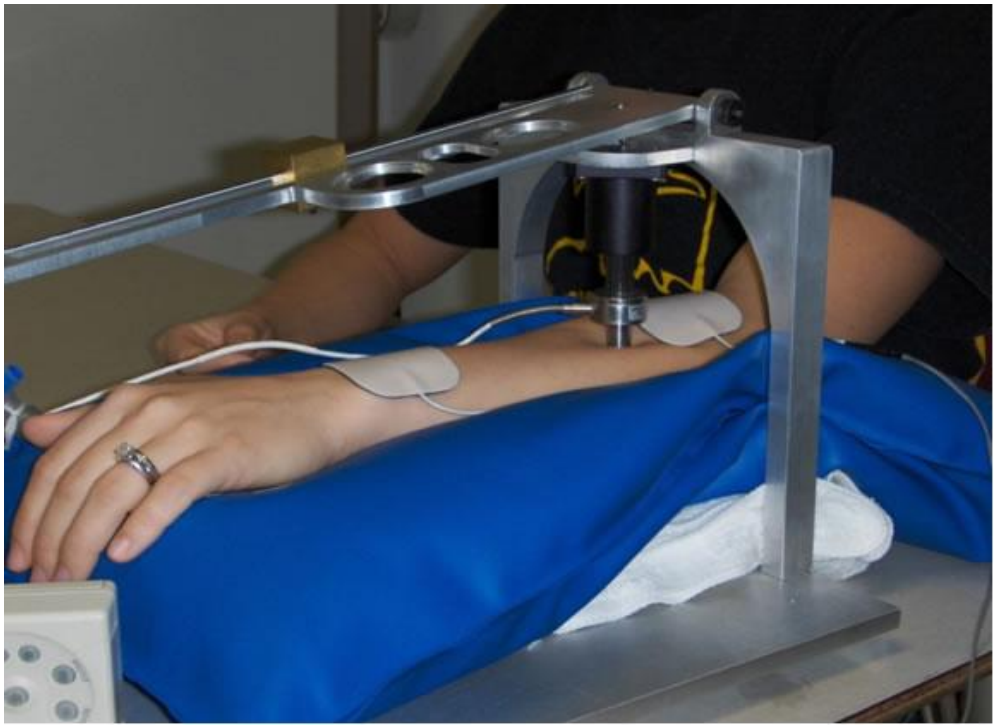
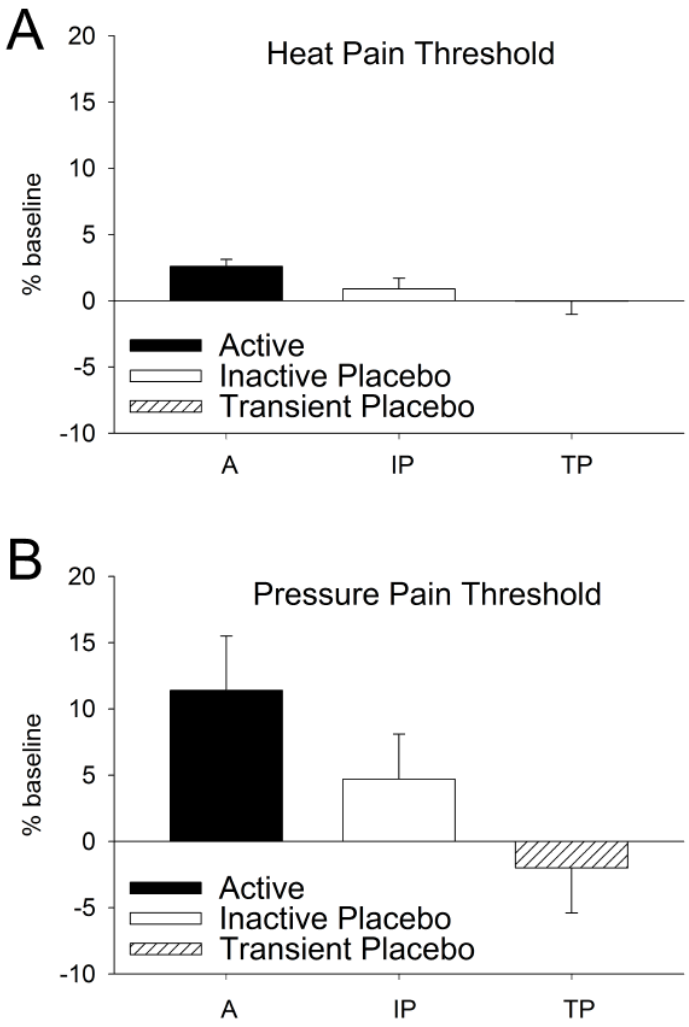
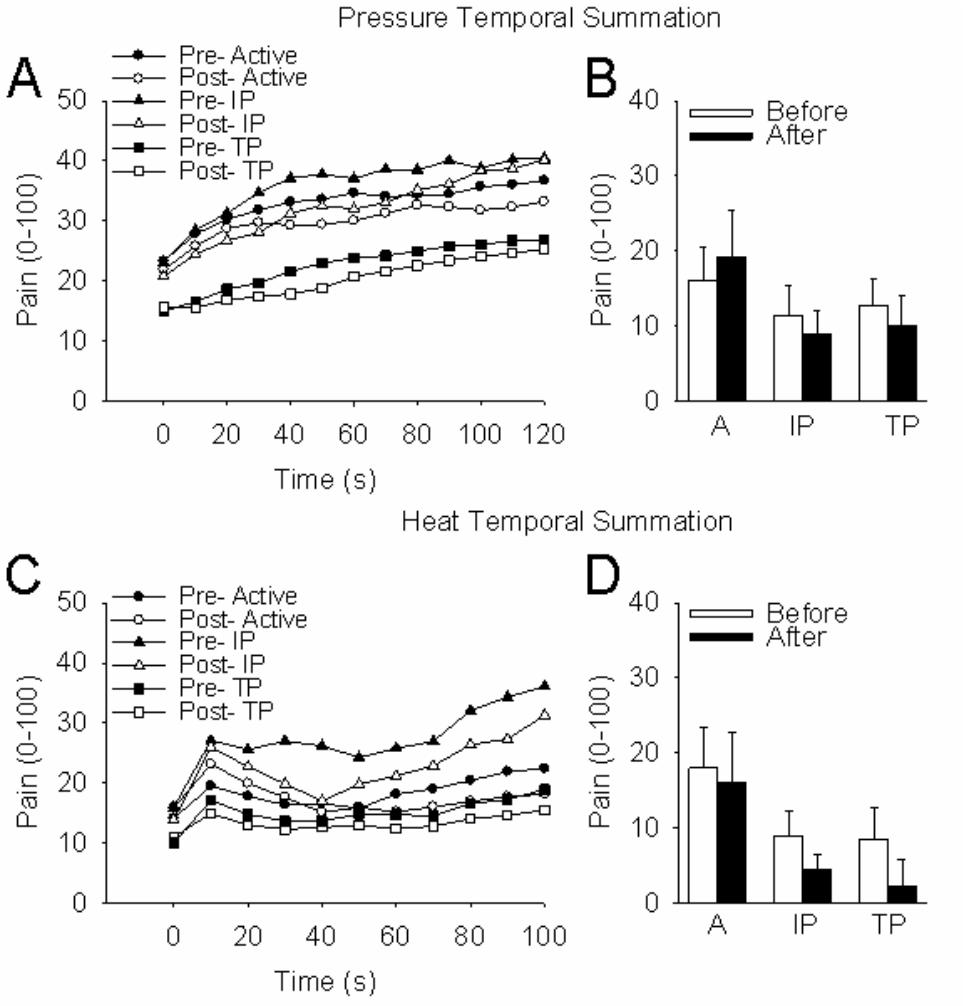


Figure 2-2: Pressure temporal summation measurement during TENS application Pressure device includes a pressure transducer and a lever with a movable weight to grade the force delivered. The pressure stimulus is delivered through a 1 cm^2 probe over the extensor muscle mass.



A=Active TENS; IP=Inactive Placebo TENS; TP=Transient Placebo TENS.

Figure 2-3: Percent change from baseline to after treatment for: A) heat pain thresholds; and B) pressure pain thresholds for each group.



A=Active TENS; IP=Inactive Placebo TENS; TP=Transient Placebo TENS.

Figure 2-4: Temporal summation to pressure and heat stimuli. A) Pressure pain intensity scores pre and post treatment for each group from 0-120 seconds; B) Average pressure pain intensity scores pre and post treatment for each group; C) Heat pain intensity scores pre and post treatment for each group from 0-100 seconds; D) Average heat pain intensity scores pre and post treatment for each group.

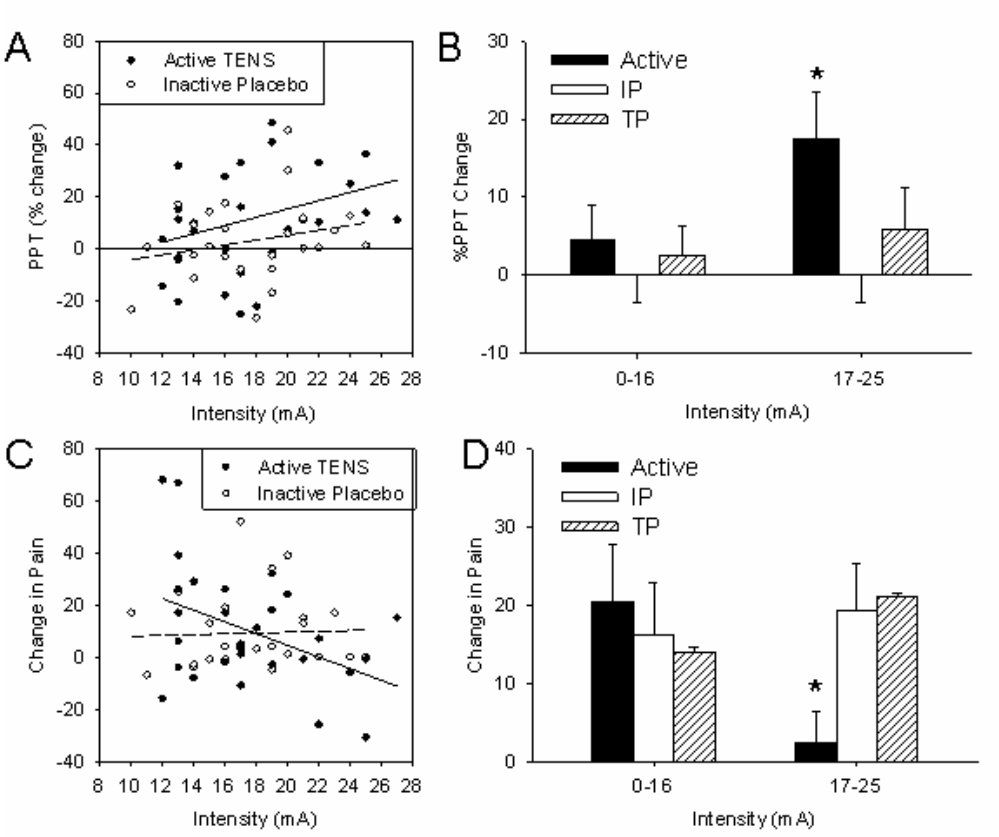
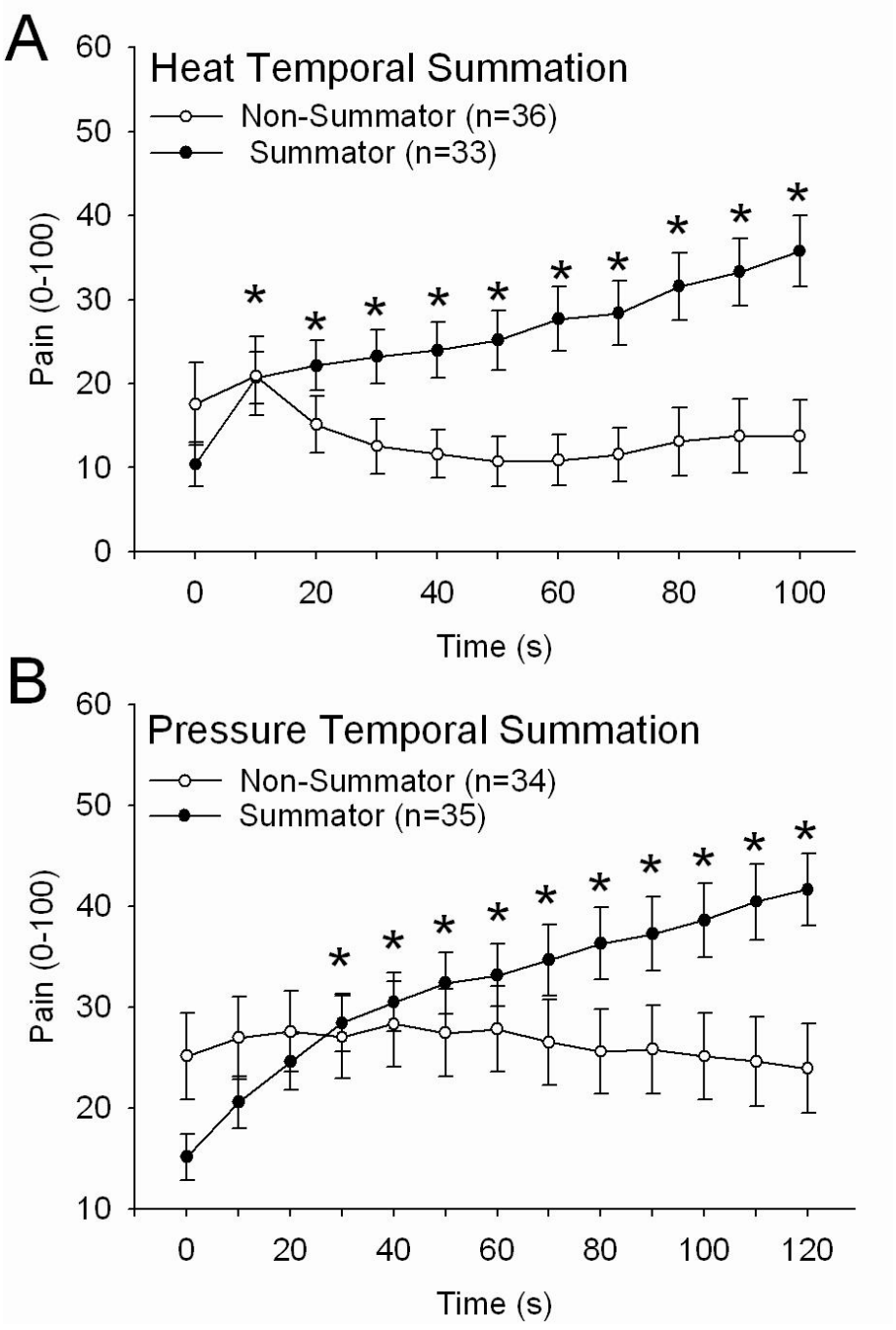


Figure 2-5: A) Scatter plot and correlation between percent change in Pressure Pain Threshold (PPT) and TENS pulse amplitudes; B) percent change in PPT for low (0-16mA) and high (17-25mA) TENS pulse amplitudes; C) scatter plot and correlation between change in average pain intensity during temporal summation and TENS pulse amplitudes. Those receiving higher TENS pulse amplitudes in the active TENS group (17-25mA; N = 17), had a significant increase in PPT compared to those receiving lower pulse amplitudes (< 17mA; N = 13) ($F_{1, 29} = 9.8$, $p = 0.004$); D) change in average pain intensity scores during pressure temporal summation and low (0-16mA) and high (17-25mA) TENS pulse amplitudes.



* scores significantly higher than baseline (0 seconds) which confirms temporal summation.

Figure 2-6: Pain intensity scores for subjects who experienced temporal summation and subjects who did not experience temporal summation to: A) heat stimuli; and B) pressure stimuli.

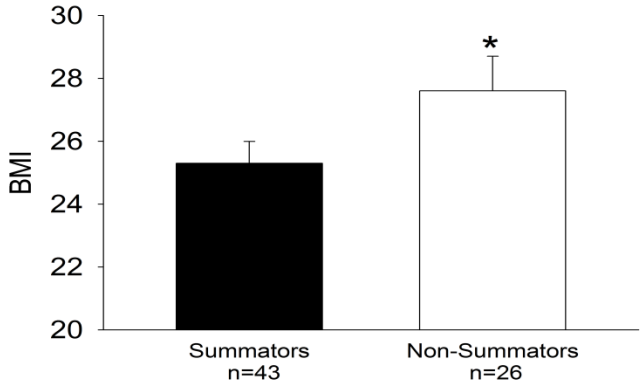


Figure 2-7: Average BMI (Body Mass Index) of subjects who experienced temporal summation to either heat or pressure stimuli. Subjects who temporally summated had a significantly lower BMI than subjects who did not summate to either heat or pressure stimuli (p=0.007, t-test)

CHAPTER III

EFFECTS OF TENS ON PAIN, PAIN SENSITIVITY AND FUNCTION IN PATIENTS WITH OSTEOARTHRITIS: A RANDOMIZED CONTROLLED TRIAL[d]

Abstract

Background and Objective: Transcutaneous Electrical Nerve Stimulation (TENS) is commonly used for treatment of pain; however the effects on a variety of pain and function measures is unclear. The purpose of the current study was to determine the effect of high (HF) and low (LF) frequency TENS, on a variety of outcome measures: resting pain, movement-evoked pain, and pain sensitivity in subjects with osteoarthritis of the knee.

Subjects: 75 subjects with knee osteoarthritis (31-94 years, M=29, F=46) were assessed.

Methods: Subjects were randomly assigned to receive HF-TENS (100 Hz) (n=25), LF-TENS (4 Hz) (n=25) or Placebo (P) TENS (n=25) [pulse duration=100 μsec; intensity=10% below motor threshold]. The following measures were assessed before and after a single TENS treatment: cutaneous mechanical pain threshold (CMPT), pressure pain threshold (PPT), heat pain threshold (HPT), heat temporal summation (HTS), Timed Up and Go (TUG) test, and pain intensity at rest and during the TUG test. A linear mixed

[d] Published as: Vance CG, Rakel BA, Blodgett NP, DeSantana JM, Amendola A, Zimmerman MB, Walsh DM, Sluka KA. Effects of Transcutaneous Electrical Nerve Stimulation on Pain, Pain Sensitivity, and Function in People with Knee Osteoarthritis: A Randomized Controlled Trial. Phys Ther. 2012; 92(7):898-910.

model ANOVA compared differences before and after TENS, and between groups (HF, LF, and P).

Results: When compared to P-TENS, HF-TENS and LF-TENS increased PPT at the knee; HF-TENS also increased PPT over the anterior tibialis muscle. There was no effect on CMPT, HPT, or HTS. HF-, LF- and P-TENS significantly reduced the pain at rest and during the TUG test.

Conclusion: When compared to P-TENS, HF- and LF-TENS reduced pressure pain sensitivity le in knee OA subjects -P-TENS had no significant effect on PPT. Cutaneous pain measures were unaffected by TENS. Subjective pain ratings at rest and during movement were similarly reduced by active and placebo TENS suggesting a strong placebo component to the effect of TENS.

Introduction

Transcutaneous Electrical Nerve Stimulation (TENS) is an inexpensive, non-invasive intervention used to treat a wide variety of painful conditions. Previous studies show TENS increases pressure and heat pain thresholds in healthy subjects [32,34,35,44,174,185], and reduces mechanical and heat hyperalgesia in arthritic animals [74,141]. However, a recent systematic review showed that TENS was not effective for knee OA pain [156] and is in direct contrast to a prior systematic review that concluded TENS was effective for knee OA pain [130] and a meta-analysis that showed a significant reduction in pain with TENS in knee OA [19]. Several limitations in the included trials may explain the lack of TENS effect; including small sample size, poor methodological quality, and inadequate randomization and blinding methods.

A key factor that may explain the lack of TENS effect is that prior studies routinely examine resting pain as their main outcome [156]. However, TENS produces a

greater effect on movement pain, an evoked stimuli, and subsequently results in improved function [145]. Evoked stimuli are used to measure pain-like behaviors in animal studies and commonly examine responses at the site of injury, i.e. primary hyperalgesia, and outside the site of injury, i.e. secondary hyperalgesia. Primary and secondary hyperalgesia are surrogate measures for sensitization of the peripheral (site of injury) and central nervous system (outside site of injury), respectively. It is possible that the effectiveness of TENS varies by outcome.

Dosing is also critical to TENS effectiveness [18,122,144,145]. Animal studies show both high frequency (HF, >50 Hz) and low frequency (LF < 10 Hz) TENS, delivered at an intensity of 90% motor threshold (strong-sensory intensity), reduce pain sensitivity in arthritic animals [71,82,87,164,165]. Several studies of HF-TENS in healthy human subjects show that greater intensities, generally described as strong but comfortable, result in greater pain reduction [32,35,39,41,122,144]. Similarly, studies of post-operative pain show that adequate intensities are necessary to produce analgesia and that low intensities are ineffective [18,145]. It is unclear if the frequencies and intensities used in animal studies will have similar effects in human subjects.

The purpose of the current study was: 1) to determine the efficacy of high and low frequency TENS for knee OA pain, and 2) to determine which outcome measures (pain at rest, movement pain, pain sensitivity, and function) are most likely to be affected by low and high frequency TENS in human subjects with pain to inform the design of future studies. We compared the effect of TENS, applied with parameters used in our prior animal studies[46,71,87,111,164,166,167,178], to a new placebo TENS on a variety of outcomes including resting and movement pain, pain sensitivity measures, and function in OA. We hypothesized that both HF-TENS and LF-TENS would reduce pain during movement, but not pain at rest, decrease pain sensitivity, and increase function.

Methods

Design Overview

The current study was a double-blind randomized clinical trial that included 75 subjects with knee osteoarthritis randomly allocated to one of three groups (HF-TENS, LF-TENS, and P-TENS). Outcome measurements were taken before and during a single TENS treatment.

Setting and Participants

Following approval by the Human Subjects Institutional Review Board, subjects were recruited through flyers and active screening by experimenters in the Orthopedic and Sports Medicine Department of a large Midwestern tertiary care center. The inclusion criteria were: diagnosis of medial compartment knee osteoarthritis (radiographically and symptomatically diagnosed by an orthopedic surgeon), 18 to 95 years of age, able to ambulate to mail box and back, stable medication schedule for three weeks prior to testing, and pain > 3/10 during weight bearing (verbal rating scale). Lateral compartment knee OA was excluded in order to standardize the test sites for pain sensitivity measures. Pain rating less than 3/10 was needed to derive a clinically meaningful change due to the intervention. Initial screening was performed by the recruiter, or a phone screen was conducted by the project coordinator to determine inclusion. Exclusion criteria included: uncontrolled diabetes mellitus or hypertension, dementia or cognitive impairment, neurologic disorder, permanent lower extremity sensory loss, prior TENS use, knee surgery in last six months, or knee injection in last four weeks. In order to avoid interaction with medications, subjects were given instructions not to take any analgesic medication four hours prior to the test session. A complete list of current medications was obtained at the first visit. On the first visit we

also assessed for bilateral sharp dull recognition at the L_3-S_2 dermatomes and proprioception of the great toe to rule out loss of sensation (exclusion criteria). All testing was conducted in one of two dedicated research spaces at the University of Iowa.

Figure 3-1 provides the consort diagram for the current randomized controlled trial. As illustrated, 311 patients were assessed for eligibility and 87 subjects declined to participate. We were unable to make contact with 31 subjects, and 116 were excluded. Seventy-five of the remaining 77 subjects were allocated to a treatment group and completed the testing. Two subjects were excluded in the secondary screening process due to reduced sensation.

Randomization

The SNOSE allocation concealment protocol using permuted blocks of 3 and 6 was used to randomize subjects to group [52]. Allocation envelopes were kept in a separate location from testing and were not available to the data collection examiner. The foil lined envelopes were signed, dated and opened by the allocation examiner immediately prior to TENS application and after the data collection examiner left the room.

Transcutaneous electrical nerve stimulation

A commercially available TENS unit (Rehabilicare Maxima, DJO, Inc, USA) was used to deliver TENS. The unit uses an asymmetrical biphasic waveform, pulse duration was set at 100μsec, and intensity was 10% below motor threshold. We chose to modulate frequency and keep all other parameters the same to test if there is a frequency-dependent effect on outcomes. The same parameters were previously used in pre-clinical animal and human studies of TENS from our laboratory[46,48,111,122,144,164,166,167,178].The P-TENS unit (DJO, Inc.) was identical in appearance and applied identically to active TENS using 100Hz, 100 μsec pulse duration, intensity 10% below motor threshold. The

new transient placebo delivered a current for the first 30s then ramped down to zero over 15s. The transient placebo is valid and has no effect on pain measures in healthy controls [144]. Neither the TENS allocator nor the data collection examiner could differentiate between the active and placebo TENS, and importantly, all subjects received the same set of instructions. Blinding was assessed at the end of TENS treatment prior to subjects leaving the clinic. Subjects were asked if they thought they received active or placebo TENS.

TENS was applied using four self-adhesive 2"x 2" electrodes (DJO, Inc, USA) to bracket the OA knee and apply paraesthesia encompassing the painful knee. Two electrodes were placed above the knee and two below. The current was delivered across the joint through two channels. One channel was connected to an electrode above the knee medially and below the knee laterally; the second channel was connected to an electrode above the knee laterally and below the knee medially. The specific electrode sites were determined by the allocation examiner using points of least impedance [15]. Points were located by having the subject and examiner each hold a gelled electrode in their hand. The examiner completed the circuit by placing a water dipped finger on the subject's skin and increasing intensity to the experimenter's sensory threshold. The examiner then glided her finger over the area to locate the points of least impedance (i.e. points where increased sensation occurred for the examiner). The points were always located within the frontal plane and within 25-75mm of mid patella. The points were cleaned with water and the electrodes were applied.

TENS units were turned on for 20 min prior to testing to reach peak effect and turned off when testing was completed with a total application time of 40-50 min (i.e. 20-30 min after reaching peak effect). The greatest effects of TENS occur when the unit is on. All of our measures were done in the same order so that quantitative sensory testing was done immediately after 20 min and TUG/Function testing was performed last. Thus

we are comparing effectiveness between subjects with the same length of TENS treatment.

Outcome measures

Subjective Pain Intensity: Subjects were asked to rate their pain on a horizontal 100mm Visual Analog Scale (VAS). The anchors utilized were “no pain” and “worst imaginable pain”. The VAS is valid and reliable when compared to other pain rating scales (r=0.71 – 0.78, ICC=0.71 to 0.99) [81,190]. Pain was assessed at rest, during the timed up and go test (TUG) and heat temporal summation (HTS).

Pain Sensitivity: Pain sensitivity was measured using quantitative sensory tests outlined below. Three sites were marked 1cm apart at the medial joint line, bilaterally. Another three sites were marked 2.5cm apart on the anterior tibialis muscle bilaterally, with the top site marked 7.5cm below the inferior boarder of the patella. All pain sensitivity measures were taken at all six sites except for heat pain thresholds and HTS (see below) which were taken over the middle point of the knee and anterior tibialis muscle, due to the larger size of the thermode stimulator probe. All sites were assessed bilaterally.

Cutaneous Mechanical Pain Threshold (CMPT): CMPT was assessed with a set of 20 von Frey filaments (North Coast Medical, Gilroy, CA) applied to the test sites in ascending order (0.008-300g). The tip of the filament was applied perpendicular to the site and pressed until bending occurred. One trial per filament was done. CMPT shows excellent test-retest reliability (r=0.97)[190].

Pressure Pain Threshold (PPT): (PPT) was assessed with a handheld pressure algometer (Somedic AB, Farsta, Sweden) applied at 40kPa/s (1cm2 circular tip). Subjects

were instructed to press the hand-held response switch when the sensation first became painful. Subjects were familiarized with the procedure by performing a practice test on the forearm. PPT demonstrates excellent test-retest reliability (r=0.7- 0.94) and is a valid measure for deep tissue hyperalgesia based on prior studies showing decreases in chronic pain compared to healthy controls[171].

Heat pain threshold (HPT): Heat pain thresholds were assessed with the TSA II NeuroSensory Analyzer (Medoc Ltd, Ramat Yishai, Israel) using a 5cm2 probe. The probe was placed at the middle of the three marks at each site. Initial temperature was set at 37oC, and increased 1°C/s to a maximum of 52^{o}C. Subjects indicated when they first felt pain (1/10) by pushing a button which terminated the stimulus.

Heat Temporal Summation (HTS): HTS was measured using the same TSAII NeuroSensory Analyzer described above. A tonic heat stimulus of 45.5oC was applied for 20s. After building to 45.5oC in the first 5s, subjects rated pain every 5s for 15s. A difference between the first pain rating at 5s and pain rating at 15s was used for analysis. Thermal measurements show good test re-test reliability (ICC 0.77) in subjects with knee OA [190].

Timed Up and Go (TUG): The TUG is a standardized test where subjects arise from a chair with no arm rest, ambulate 9.8 feet as quickly as possible, turn, ambulate back, turn and return to sitting in the chair [135]. Subjects were timed in a standardized fashion from the moment the upper back left the chair until return to full sitting position with back in contact with the chair. We previously used the TUG in subjects with OA and show a reduction in TUG time demonstrating the sensitivity of the TUG to a single joint mobilization treatment [123] .The TUG test has good reliability (ICC.92 -.99) in elderly

populations [135][76,173] and demonstrates good construct validity with significant correlations with gait speed (r=.61 -.75), Berg balance scale (r=.81), and step length (r=.77)[76,173]

Test Protocol

A timeline of procedures is shown in Figure 3-2. Testing was performed with the same equipment by the same examiner. At the testing session, informed consent was obtained followed by sensory screening. If the sensory exam was normal, testing began. First subjects completed the demographic questionnaire, and height and weight were recorded. Resting pain was measured and then pain sensitivity measurements were performed. The order of these measurements remained consistent for all subjects: CMPT was followed by PPT, HPT, and HTS. The testing order for each of the four areas and three test sites was randomized to prevent an ordering effect of testing. Subjects then completed the TUG and rated the maximum pain during this test.

Once testing was completed, the data collection examiner left the room and the allocation examiner allocated TENS. The allocation examiner stayed with the subject for 20 min at which time the data collection examiner reentered and repeated the testing as described above. The same blinded examiner performed all pre and post-TENS outcome measurement. Once the second testing session was completed, the TENS allocator returned to remove TENS and assess subject blinding.

Statistical analyses

Sample size calculations were made using preliminary PPT data to compare HF-TENS and LF-TENS against P-TENS. Pain thresholds are commonly used in animal and healthy human studies [35,141,144,164,178].The study sample size of n=25 subjects per group was determined based on an expected PPT difference of 100 kPa and a standard deviation of 110 with a 0.05 significance level and 0.80 power. For the other outcome

measures, the detectable difference was at least 10 mm (out of 100 mm) on the VAS (SD=0.9) and 1.4s on the TUG (SD=1.5s). Therefore, the sample size is powered to detect clinically significant differences in all variables given that pain ratings and impairments are minimal in early OA [172].

Mean and SEM were calculated for all variables before and after TENS and for the difference score before and after TENS within individual groups. In addition, 95% confidence intervals were calculated for primary outcome measures and are included in the tables. Linear mixed model analysis for repeated measures was used to compare mean changes between the treatment groups (HF, LF, P) in our outcome measure for the site (knee, anterior tibialis), side (affected, contralateral), and time (pre vs. post) (within subjects effects). The model included baseline values and BMI as co-variates (see results), as BMI differed between groups (Table 3-1). To test for specific comparisons of interest, test of mean contrasts based on the fitted method was performed. To account for the multiple tests performed related to a specific hypothesis, p-values were adjusted using Bonferonni's method. The Kruskal-Wallis test was used to detect differences in non-parametric data.

Role of the Funding Source

The current study was supported by the National Institutes of Health, R03-NR010405, Marsha and Ralph Congdon Faculty Development Fellowship in Acute Care for the Chronically Ill, and University of Iowa Carver College of Medicine.

Results

Table 3-1 provides the demographic information for all treatment groups as well as the baseline values for each measure. There were no significant differences between groups on demographic characteristics with exception of BMI ($p = 0.027$). BMI was, therefore, controlled for in the analyses. All baseline measures were similar between groups with the exception of HPT ($p = 0.02$). Baseline measures were also controlled for in the analyses. Eleven (15%) subjects were taking opioid medication for pain control, and 54 (72%) were taking non-opioid medication. There were no significant differences between groups in the number of subjects taking analgesic medication (Table 3-1).

TENS Amplitude and Blinding

The pulse amplitude required to achieve the desired TENS treatment intensity was similar between groups (i.e. mean amplitude was 27.4±1.7mA for HF, 24.1±1.8mA for LF, and 24.5±1.6mA for P). Of those subjects receiving P-TENS, 57% correctly identified the treatment as placebo while 43% felt they received the active treatment. Subjects in the active TENS group correctly identified their treatment as active 92% of the time.

Pain Sensitivity

HF-TENS increased PPT at the affected knee ($p=0.002$) and anterior tibialis muscle on the affected leg ($p=0.0001$) when compared to pre-TENS values (Table 3-2) (Figure 3-3). LF-TENS significantly increased PPTs at the ipsilateral knee site only ($p=0.05$). P-TENS did not significantly change the PPT (Figure 3-3). Pairwise comparison of the treatment group showed a significant difference in mean change in PPT between HF-TENS and P-TENS ($p=0.026$); there was no significant difference between LF-TENS and P-TENS, or between LF-TENS and HF-TENS.

Baseline CMPT, HPT, and HTS values for each group prior to TENS are presented in Table 3-1. HPT, CMPT, and HTS were unchanged after all treatments and there were no significant differences between groups (Table 3-2).

Pain at Rest

Pain at rest decreased significantly in all three groups (HF, $p = 0.001$; LF, $p = 0.01$; P, $p = 0.0001$). However, there was no significant difference between groups (Figure 3-4**,** Table 3-2).

Function (TUG) and pain during function

Pain during the TUG test decreased significantly in all three groups (HF $p=.001$; LF $p=.03$; P $p=.001$); however there was no significant difference between groups (Figure 3-5, Table 3-2). The time to perform the TUG test did not change significantly in any of the groups and there was no significant difference between groups (Table 3-3).

Discussion

The current study showed an increase in PPTs at the knee joint with HF- and LF-TENS and anterior tibialis muscle with HF-TENS compared to P-TENS; P-TENS had no significant effect on PPTs. However, subjective pain at rest and during the TUG decreased equally with all three treatments. No differences were observed for CMPT, HPT, HTS or function. These data show that TENS is effective for deep pain sensitivity induced by OA. It further shows that a single treatment of TENS has minimal effects over placebo on pain and function.

HF and LF-TENS reduces deep tissue pain sensitivity

The current study shows HF-TENS and LF-TENS increases PPTs at the site of injury, which we interpret as a reduction in primary hyperalgesia. Changes in primary hyperalgesia measures suggest changes in nociceptor sensitivity [50] and parallel changes we previously observed in animal studies [178]. We also show that HF-TENS increases

PPTs over the anterior tibialis muscle, an area outside the site of injury, which we interpret as a reduction in secondary hyperalgesia. Changes in secondary hyperalgesia measures suggest changes in central neuron excitability[50]and parallel changes we previously observed in animal studies[87] The increases in PPT are similar to studies in healthy controls showing increases in PPTs during active TENS[32,34,35,44,122,144,174,185] and in arthritic animal models that examine hyperalgesia immediately after TENS using the same parameters [82,164,167]. TENS reduces excitability of nociceptive neurons in the central nervous system in arthritic animals [109] and higher intensities have greater reductions in excitability [64]. Thus, changes in PPT by TENS are likely mediated by reduced central neuron excitability. The current study is the first to show effects of TENS on hyperalgesia in OA, and may be a useful measure of neuron excitability. PPTs correlate with movement pain (Sluka, Rakel, et al, unpublished observations), both of which are evoked pain stimuli. Further, palpation tenderness is an essential part of the physical examination of patients; PPT measures may offer the clinician an improved objective measure of tenderness.

The lack of changes in CMPT, HPT or HTS may be because these measures are cutaneous stimuli, and they are not sensitized by knee OA. Previous studies in OA showed enhanced temporal summation to pressure that is greater in those with greater pain [9] .However, a recent study showed enhanced HTS in subjects with OA [100]. Alternatively, TENS could have minimal effects on cutaneous heat pain but be more effective for deep tissue pain. In support of this notion, we show no change in HPTs in healthy human subjects with TENS [106] but significant reductions in PPTs and temporal summation to mechanical stimulation of muscle [144]. Together these data support the idea that TENS is more effective in reducing deep tissue hyperalgesia.

Effects of TENS on pain and function

We previously showed that active TENS reduces movement-evoked postoperative pain when compared to placebo [144]. Surprisingly, the current study showed equivalent

reductions in pain during the TUG test for both active and placebo TENS, but no change in function. The lack of difference between active and placebo TENS could be because the TUG minimally increased pain above resting pain (<10mm/100mm) suggesting the TUG test was not painful enough in our sample to evaluate movement pain. In contrast to the current study involving a single visit, 2 weeks of active TENS, reduced TUG times in people with symptomatic knee OA compared to placebo [95]. Previously, we show decreases in TUG time in OA after a single joint mobilization [123] showing the capacity of a single treatment to modify TUG times. It is possible that the difference between studies with successful improvements in TUG and our study are related to the severity of functional limitations. For instance, in prior OA studies which had a positive effect on TUG, times were 20-24s [95,96,123] while times in the current study were 12-14s, close to normal($\leq$10s) [135]. Therefore for less severe symptomatic OA the TUG may not be an appropriate measure to examine movement pain and function. Future studies should use a function test that produces greater pain such as stair climbing.

We previously showed no significant effect of TENS on resting pain (VAS) when compared to placebo after abdominal surgery [49]. In the current study, both placebo and active TENS reduced resting pain ratings by 10-18/100mm. These changes are minimal and not clinically important when people have pain ratings below 50/100mm on the VAS [172]; pain ratings in our subjects averaged between 24 and 28mm. Thus, the effects on resting pain may depend on the pain intensity.

Prior work shows that high doses of caffeine can reduce analgesia produced by TENS [116]. Our study did not control for caffeine and thus caffeine may have influenced our results. However, our prior studies in healthy subjects did not control caffeine and show positive effects of TENS over placebo [41,107,122,144], and we show effects on PPT in the current study. Opioid intake could also influence results and subjects that are tolerant to opioids show reduced LF-TENS, but not HF-TENS effects [101,166]. However, the majority of our subjects (85%) were not taking opioid analgesics, and the

number of subjects taking opioid analgesics was similar between groups. Additionally, subjects did not take analgesic medication for 4h prior to testing to eliminate the effect of analgesia on test results.

Intensity is critical for TENS effectiveness

Prior studies in subjects with OA included in the 2009 Cochrane review[156] support the need for high intensity TENS. Intensities in the included studies varied widely [156]. HF-TENS was given at a strong, but comfortable intensity in seven trials [4,25,30,31,72,95,96], sensory threshold or below in 5 trials [3,11,63,80,192], noxious level in one trial [45], and unreported in two trials [139,168]. LF-TENS was applied at a motor intensity in three studies [58,126,191] and strong sensory stimulation in one [95]. Trials that reported effective TENS generally used higher intensity than those that reported no effect. The current study applied TENS at 90% of motor threshold, a strong sensory intensity. It is possible that higher intensities of TENS would be more effective in reducing pain since we show in recent studies that higher intensities result in greater reductions [18,41,122,132,144,145]. In fact, the intensity of stimulation is positively correlated with the change in PPT produced by TENS [122,144]. Another variable which could have influenced our results is the fact that we did not continuously adjust the stimulation over time, as is common in clinical practice. Titrating TENS intensity upward during treatment increases hypoalgesia in healthy controls [132].

Finally, LF-TENS may not have been as effective because we used a lower pulse duration and intensity than is commonly used clinically, i.e. motor intensity [58,95,126,191]. The total current applied with HF-TENS is greater than that with LF-TENS when given at the same intensity and pulse duration. While LF-TENS is traditionally delivered at motor intensities, prior work by us show strong sensory intensity LF-TENS produces equivalent effects to strong sensory HF-TENS [164,178] ·We also show opioid–mediated analgesia at sensory intensities with both LF-TENS and

HF-TENS [82,165]. Thus, the current study focuses on the effect of frequency delivered at a strong sensory intensity for both HF-TENS and LF-TENS.

Blinding of active and placebo TENS

The current study was the first to validate and test the new transient placebo TENS in a patient population. We were able to adequately blind the subjects receiving P-TENS (57% correctly identifying the placebo) which was not significantly different than chance (50:50) If blinding was ineffective, it would be expected that this percentage correct would be closer to 100% as we obtained for the active TENS unit. The new placebo unit can completely blind the experimenter applying TENS, and we previously show complete inability of the examiner to correctly identify active or placebo TENS [41,122,144]. Adequate blinding is important because prior TENS studies use separate instructions for active and placebo TENS which can influence patient expectations and have profound effect on treatment outcome [16,27,67,103,104]. For example, seminal work by Levine and Gordon [103] shows a significant analgesia with a placebo drug when given in a completely blinded manner; the placebo had equivalent analgesia to that of low-dose morphine. On the other hand, negative or neutral instructions result in less reduction in pain after spinal manipulation when compared to positive instructions [16]. By giving the same instructions, we were able to show that active TENS in OA patients produced similar pain reduction to P-TENS, suggesting TENS has a strong placebo effect on OA pain. It is possible that the initial placebo effect that occurs with a single treatment is reduced with repetitive TENS. In support, 10 days of electroacupuncture, or 2 weeks of TENS, in subjects with knee OA show significant improvements in pain and function [7,95] . Further, Marchand and colleagues showed a cumulative effect of active TENS but not placebo TENS, given twice per week, in patients with chronic low back pain [115]. Thus, future studies should examine effects of repetitive active TENS when compared to

the transient placebo TENS where the experimenter applying TENS can also be blinded to group.

In the current study subjects were able to correctly identify active TENS 92% of the time. Previously we showed similar responses to the active TENS in healthy controls [144]. Despite subjects knowing they received active TENS there was no difference between active and placebo TENS on subjective pain rating. Blinding of an electrical modality such as TENS has always been difficult and few studies report blinding to active TENS.

Conclusion and Clinical Implications

In summary, the current randomized clinical trial examines the effect of a single treatment of HF- and LF-TENS knee OA pain and function. Utilization of various outcome measures, different frequencies, and an improved placebo provide insight for management of knee OA pain with TENS. We piloted a series of outcome measures designed to parallel and validate animal models of TENS and to test effects of TENS in a true double-blinded manner. We show that both HF and LF TENS reduces primary and hyperalgesia and HF TENS only reduces secondary hyperalgesia in people with OA using PPTs as an objective measure of pain sensitivity. Quantitative sensory testing using cutaneous mechanical and heat pain measures were not affected by HF, LF, or P-TENS, suggesting that TENS has no effect on cutaneous hyperalgesia. Alternatively, it is possible that people with OA did not have cutaneous mechanical and heat hyperalgesia. All treatments had a similar but minimal effect on subjective pain measures suggesting a placebo component to the effect of TENS. None of the treatments had an effect on TUG times. The TUG test may not be an appropriate functional outcome measure in patients with early symptomatic OA of the knee as increases in pain and decreases in function were minimal. Future studies, should expand outcome measures used in TENS studies to include not only pain at rest, as commonly assessed, but also pain during physical function tasks and deep tissue hyperalgesia measures. The effects of repetitive treatments

and of higher intensities should be tested in people with painful conditions to further elucidate the most effective use for TENS.

Shannon Lehman, is to be commended for her role as TENS effectiveness coordinator, and TENS units and supplies donated by EMPI, Inc.

Variable	HF-TENS	LF-TENS	P-TENS	P-value
Demographics mean ± SEM				
Age	57 ± 11.8	55 ± 14.4	57 ± 10.9	.756
Male	11 (44%)	9 (36%)	9 (36%)	.492
Female	14 (56%)	16 (64%)	16 (64%)	.492
BMI	33.6 ± 7.7	36.2 ± 6.0	39.2 ±7.0*	.027*
Pain on screening(0-10)	5.6 ± 1.9	5.5 ± 1.7	5.6 ± 2.3	.95
Knee Pain Duration (mo)	108.8 ± 113	121.6 ± 141.2	83.5 ± 86.4	.743
Analgesic medication use Non-opioid Opioid	18 (72%) 17 (68%) 4 (16%)	20 (80%) 20 (80%) 4 (16%)	18 (72%) 17 (68%) 3 (12%)	.757 .556 .900
Outcome measures - baseline (Ipsilateral) mean ± SEM 95% CI				
Pain at rest (10 mm scale)	1.77 ± .50 .74 – 2.80	2.95 ± .53 1.86 – 4.05	2.12 ± .51 1.08 – 3.17	.251
Pain during TUG (10 mm scale)	2.42 ± .44 1.52 – 3.33	2.83 ± .46 1.88 – 3.79	2.75 ± .44 1.]\84 – 3.65	.792
TUG time (sec)	12.1 ± .81 10.4 – 13.8	14.7 ± 1.66 11.3 – 18.2	13.4 ± 1.0 11.2 – 15.5	.315
CMPT (g)	1394 ± 111 1165 – 1623	1105 ± 131 835 – 1376	1023 ± 150 713 – 1333	.119
PPT (kPa) (Knee)	315.7 ± 27.0 259.9 – 371.4	247.8 ± 20.2 206.1 – 289.6	259.5 ± 20.6 217.0 – 302.0	.087
PPT (kPa) (Anterior Tibialis)	349.5 ± 37.9 271.4 – 427.7	319.0 ± 30.9 255.2 – 382.7	319.4 ± 30.1 257.2 – 381.5	.757
HPT (°C) (Knee)	45.5 ± .45 44.5 – 46.4	43.2 ± .71* 41.7 – 44.6	44.5 ± .52 43.5 – 45.6	.020*
HPT (°C) (Anterior Tibialis)	46.3 ± .52 45.2 – 47.4	45.4 ± .67 44.0 – 46.8	45.5 ± .57 45.3 – 45.7	.66
HTS (5 sec)(100 mm scale)	24.7 ± 4.7 14 -34.4	37.3 ± 5.1 26.8 – 48	27.6 ± 4.4 18.6 – 36.7	.15
HTS (10 sec) (100 mm scale)	28.8 ± 5.5 17.5 – 40.1	35.6 ± 5.3 24.7 – 46.5	31.1 ± 4.7 21.6 – 40.8	.64
HTS (15 sec) (100 mm scale)	30.6 ± 6.0 18.3 – 42.9	37.4 ± 5.6 25.9 – 49.0	28.3 ± 4.3 19.3 – 37.2	.46

* significantly different from other groups.

Table 3-1. Demographic characteristics (mean ± SEM) and outcome measures before TENS (mean ± SEM, 95% CI) of study participants.

Variable	**HF-TENS**	**LF-TENS**	**P-TENS**
Measure X ± SEM 95% C**I**			
PPT Knee (kPa)	65.81 ± 17.05* 30.6 – 101.0	51.50 ± 20.65* 8.9 – 94.1	22.6 ± 13.66 **(-)**5.6 – 50.8
PPT Anterior Tibialis(kPa)	82.14 ± 18.90* 43.1 – 121.1	44.20 ± 15.50 12.2 – 76.2	20.67 ± 16.27 **(-)**12.9 – 54.2
TUG time (sec)	.47 ± .29 **(-).**13 – 1.06	**(-).**72 ± .46 **(-).**23 – 1.66	.52 ± .36 **(-).**22 – 1.23
Rest Pain (0-100mm)	10.32 ± 4.00 2.05 – 18.59	16.14 ± 5.23 5.34 – 26.94	16.84 ± 4.81 6.09 – 26.78
TUG Pain (0-100mm)	9.44 ± 2.56 4.15 – 14.73	8.70 ± 3.93 .58 – 16.82	14.18 ± 3.55 6.86 – 21.50
CMPT (g) Knee	153 ± 95 (-)18 – 324	259 ± 83 87- 431	19 ± 83 (-)152 – 191
CMPT (g) (Anterior Tibialis)	271 ± 101 68 – 479	144 ± 66 7.8 – 280	(-)24 ± 87 (-)204 – 156
HPT (°C) (Knee)	.06 ± .36 (-).68 - .8	1.3 ± .55 .18 – 2.4	(-).2 ± .28 (-).78 - .38
HPT (°C) (Anterior Tibialis)	.5 ± .34 (-).2 – 1.2	.09 ± .36 (-).65 – .83	.08 ± .46 (-).87 – 1.0
HTS (100 mm scale) (Knee)	(-)1.3 ± 1.6 (-)4.5 – 1.9	.3 ± .36 (-)2.3 – 2.9	(-)3.9 ± 2.3 (-)8.7 – .89
HTS (100 mm scale) (Anterior Tibialis)	(-)1.1 ± 1.9 (-)4.8 – 2.6	(-).8 ± 1.0 (-)2.9 – 1.3	.08 ± 1.2 (-)2.4 – 2.6

***** significantly different from placebo

Table 3-2. Primary and secondary measures expressed as difference scores (mean ± SEM, 95% CI).

Group	Baseline	During-TENS	Difference
Placebo TENS	13.4 + 1.0 s	12.9 + 0.98 s	0.52 + 0.36 s
Low Frequency TENS	14.7 + 1.6 s	14.0 + 1.4 s	0.72 + 0.46 s
High Frequency TENS	12.1 + 0.8 s	11.6 + 0.83 s	0.47 + 0.29 s

Table 3-3. TUG walking times (mean $\pm$ SEM) before and during TENS demonstrating no difference between groups with TENS.

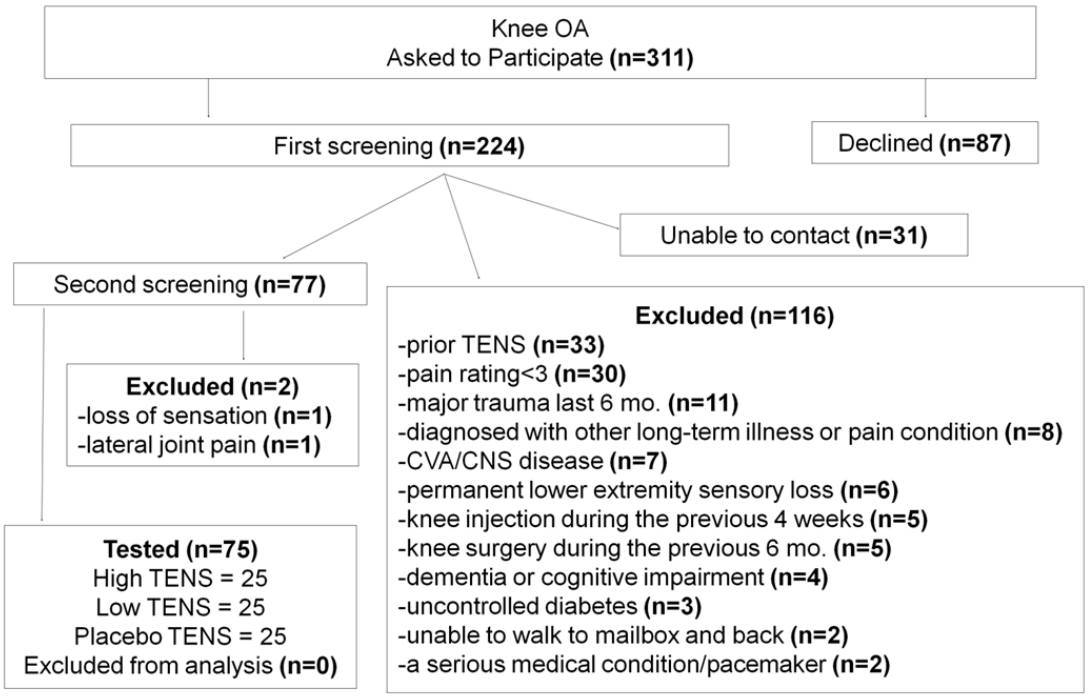


Figure 3-1. Consort diagram which indicates the majority of subjects were excluded from the initial screening due to prior TENS use or minimal pain.

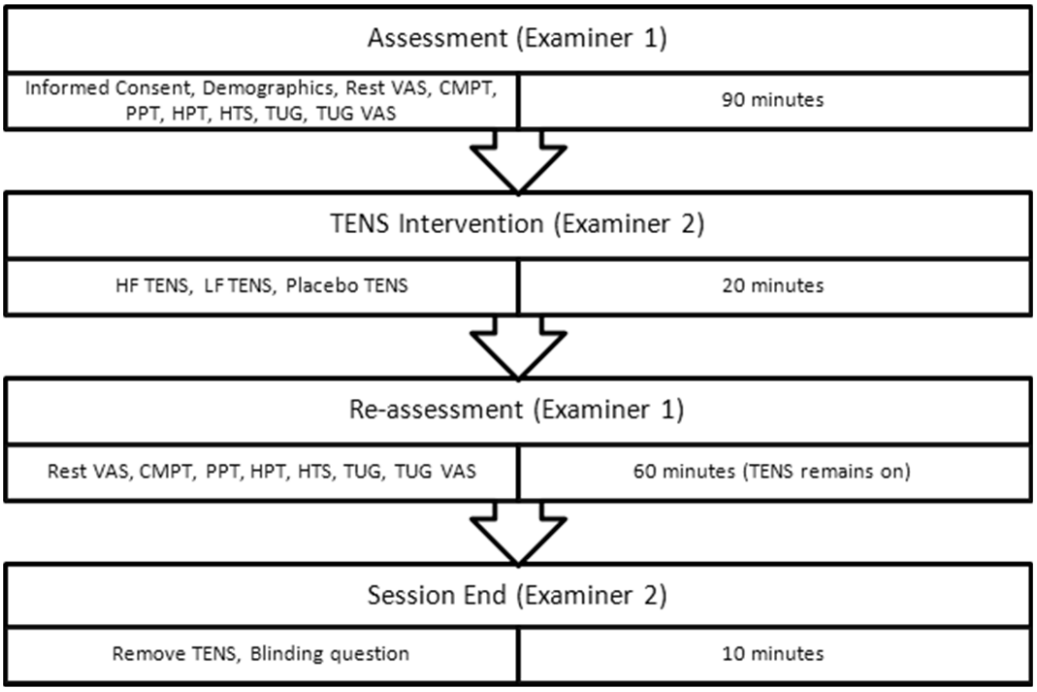
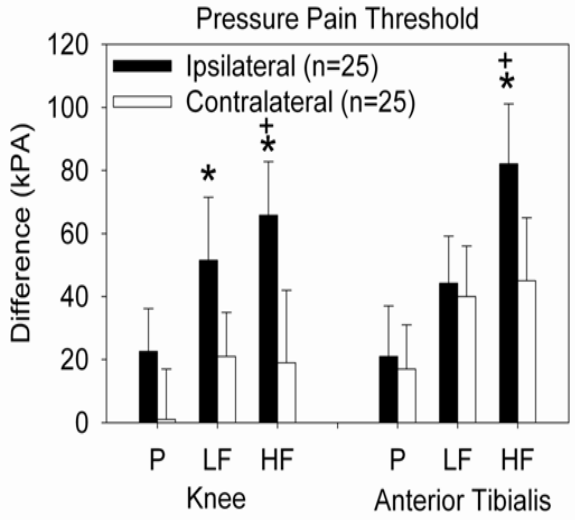
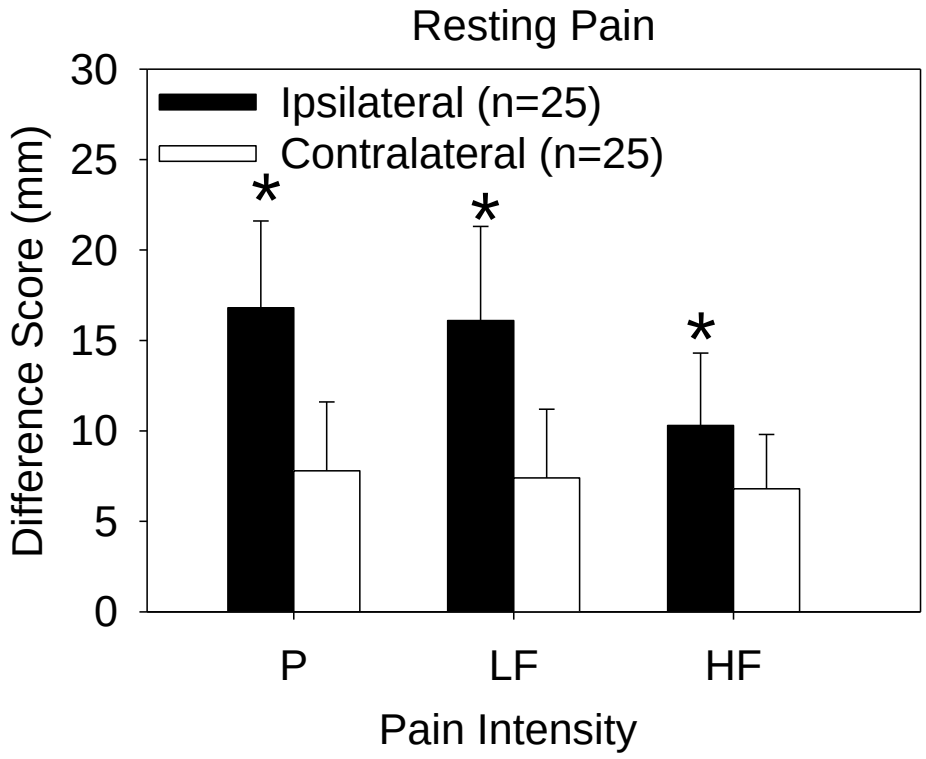


Figure 3-2. Time line for the 3 hour test session.



* significantly different from baseline
+ significantly different from placebo.

Figure 3-3. Differences in PPT after TENS when compared to before TENS are shown in bar graphs for both the knee and for the anterior tibialis muscle both ipsilaterally (black bars) and contralaterally (white bars). P=Placebo TENS; LF=Low Frequency TENS; HF=High Frequency TENS. Data are expressed as the mean +/- S.E.M

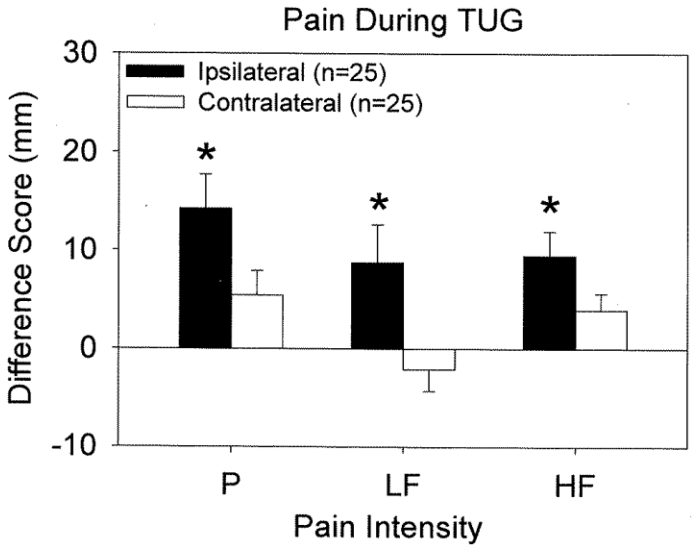


* significantly different from baseline.

Figure 3-4. Resting pain difference scores for the ipsilateral (black bars) and the contralateral (white bars) knee for intensity are shown in the bar graph. Significant decreases were observed ipsilaterally for all 3 groups – placebo, low frequency, and high frequency. P=Placebo TENS; LF=Low Frequency TENS; HF=High Frequency TENS. Data are expressed as the mean +/- S.E.M.

Difference Score (mm)

-



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CHAPTER IV

THE EFFECTIVENESS OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION ELECTRODE SITE SELECTION TO PRODUCE HYPOALGESIA

Abstract

Transcutaneous Electrical Nerve Stimulation (TENS) is a non-pharmacological intervention used to manage acute and chronic pain. TENS effectiveness is greater when the appropriate parameters for application are used. Few studies addressing the parameter of electrode site selection are available to clinicians. This repeated measures randomized trial examines skin impedance differences between TENS electrode sites selected as "optimal" (OSS) and those considered "sham" (SSS) in the forearm of healthy volunteers. In addition, the analgesic effectiveness of TENS over OSS and SSS was evaluated by change in Pressure pain thresholds (PPT). Initially, ten subjects were recruited to determine the relationship between electrode site and skin impedance. Impedance measured significantly higher at sites classified as SSS (17.69 ± 1.24 Ω) as compared to OSS (13.53 ± .57 Ω) ($p=.007$). A second study examined twenty four (12 male, 12 female) subjects that were recruited and randomly allocated to one of three treatments -OSS TENS, SSS TENS and Placebo (P) TENS. Subjects completed three visits within a ten day period with a minimum of 24 hours between visits. Skin impedance was measured with an impedance meter and with a TENS unit. PPT was measured at baseline, 15 and 30 minutes following each TENS treatment. TENS was applied with pulse duration of 100 μs and pulse frequency of 100 Hz for 30 minutes.

Treatment amplitude was “strong and non-painful” and increased to patient tolerance every 5 minutes. P-TENS was identical to the active treatment with the exception of an automatic gradual ramp down to “off” in 45 seconds. Patients rated treatment comfort at the conclusion of each TENS treatment. Impedance measurements were significantly higher over SSS with both the impedance meter ($p = .001$) and the TENS unit ($p = 0.012$). PPT change was significantly greater than P-TENS for both OSS-TENS ($p = 0.024$) and SSS-TENS ($p = 0.025$). However, there was no difference between the two active TENS treatments ($p = 0.81$) Subject comfort was similar between active TENS treatments ($p = 0.20$), and significantly different between active TENS and P-TENS ($p = 0.001$). Amplitude for sensory threshold was similar between all visits ($p = 0.35$) while maximum treatment amplitude was significantly higher for active TENS as compared to P-TENS ($p = 0.0001$). Mean treatment amplitude between OSS-TENS (19.2 ± 1.0 mA) and SSS-TENS ($21.2 \pm .7$ mA) was not significantly different ($p = 0.35$). The PPT examiner was blinded to electrode site 100% of the time and blinded to TENS treatment 95% of the time.

Perspective

Skin impedance is lower at sites characterized as optimal using the described technique of electrode site selection. When TENS is applied at adequate intensities, skin impedance is not a factor in attainment of hypoalgesia of the forearm in healthy subjects. Further investigation should include testing in patients presenting with painful conditions. When using electrotherapy for pain management clinicians should be encouraged to choose sites that are well tolerated by patients to allow for strong non-painful contractions which may include motor contractions.

Introduction

TENS is a non-invasive intervention used in the practice of physical therapy to modulate pain. However, there is conflicting literature on the effectiveness of TENS. Eight Cochrane reviews of TENS and painful conditions from 2008 to 2012 end with a determination of "inconclusive", "insufficient" or "conflicting evidence" [53,78,84,90,124,128,130,156,181]. One factor that may contribute to this conflict is the use of appropriate parameters of application. Negative findings in TENS reviews may be explained by low fidelity with bias in treatment outcome measures and suboptimal dosing [77]. TENS involves application of a low voltage alternating current to stimulate large diameter afferent nerve fibers. The clinician chooses the pulse frequency, pulse duration, pulse amplitude, electrode site application and treatment duration. Previous work by us and others shows that treatment parameters are important in producing analgesia by TENS. Specifically, stimulation intensity [2,34,35,38,132,144] and pulse frequency [82,101,102,163-165,183], are important parameters that require consideration to achieve analgesia with TENS. On the other hand, little data exists on electrode placement sites for TENS. Textbooks describe multiple methods of electrode placement and include segmental, peripheral, or contralateral site placement. Mannheimer stressed that not all pain conditions will be best treated by using the same electrode selection method [113]. One method that has been described in textbooks and used clinically is the use of "sites of least resistance" for application of TENS. Using this technique, the therapist detects points of decreased impedance - these points are associated with peripheral nerve anatomy and acupuncture points [15,73,125,136]. For the purpose of this manuscript this procedure will be referred to as optimal site selection (OSS). Many clinicians use

acupuncture theory and OSS in their methodology of site location for TENS electrodes. With most physical therapists receive little training in the classical location techniques, using the OSS method is readily accepted as a logical method to enhance proper site location. To date, no literature exists to determine the effectiveness of this clinical practice. OSS provides a novel way to find electrode sites for treatment and may lead clinicians to feel they are refining their practice in a positive manner. They may be inclined to believe OSS is more objective but in reality "expert opinion" is the highest level of evidence available for this commonly used technique.

Speculation has existed for decades regarding the existence of distinct electrical properties associated with acupuncture points and meridians [6].These acupoints have lower resistance and may be similar to the OSS sites described above. The inherent problems with the majority of this body of work relates to validity and reproducibility of the devices used to locate and test the points [40,186]. Further, failure to control for subject hydration, TENS frequency, and electrode type, size and location are some of the numerous difficulties associated with obtaining consistent electrical readings from the skin [5,6].

Clinically, application of TENS at these acupoints (low resistance sites) reduces pain and may be more effective than when applied over non-acupoint sites [33]. In healthy controls, TENS over acupoint sites significantly increased heat pain thresholds [28,185] and electroacupuncture significantly increases pressure pain thresholds [12,94,157]. TENS applied at acupuncture points decreased pain following laparoscopic surgery [108], chronic prostatitis/pelvic pain syndrome [99], primary dysmenorrhea [110], and total hip arthroplasty [93] when compared to sham TENS. More importantly,

TENS at acupoint sites reduced opioid intake, nausea and dizziness when compared to TENS at non-acupoint sites in post-operative hysterectomy patients [33]. Although these studies show evidence that TENS over acupoints is effective, it is not clear how these sites are selected. Acupoints are thought to be sites with lower skin impedance [79,133,153] and thus using the method of OSS may be an ideal method for finding acupoint sites.

The purpose of this study was to 1) determine if OSS sites have lower impedance than sham selection sites (SSS) using an optimal site selection technique in healthy subjects, and 2) determine if TENS over OSS was more effective than TENS over SSS by examining changes in pressure pain thresholds (PPT) in healthy subjects.

Methods

Design Overview

The current study was a crossover design double-blind randomized clinical trial that included 24 healthy normal subjects randomly allocated to one of three groups (TENS with OSS, TENS with SSS, or Placebo (P)-TENS with OSS). Subjects completed three visits receiving a different allocation each visit. Outcome measurements were taken before and during a single TENS treatment. Prior to commencing the experiment above, 10 healthy normal subjects were evaluated to determine the relationship between the electrode site selection technique and skin impedance.

Setting and Participants

Following attainment of approval the University of Iowa Human Subjects Committee, 10 healthy subjects (5 male, 5 female) were recruited to determine the relationship between skin impedance and the electrode site selection technique. An

additional 24 healthy subjects (12 female, 12 male) were recruited to examine the effects of TENS at different electrode sites (SSS vs. OSS). The age criterion for both experiments ranged from 18-60 and subjects were acquired through responses to a mass emailing. A screen was performed to assess eligibility. Inclusion criteria were no current pain condition, willingness to avoid physical exercise 4 hours prior to testing, and urine specific gravity (USG) in the range of 1.000-1.200. Exclusion criteria included recent trauma or loss of sensation in right upper extremity, currently taking pain medication, current acute or chronic pain, pregnancy, cardiac pacemaker, stroke, myocardial infarction, or other serious pathology for both experiments. Prior TENS treatment was an additional exclusion for the TENS trial. Following informed consent, demographic information and a urine specimen were collected. Bilateral sensory testing for sharp dull discrimination of the C6-T1 dermatomes was performed and all testing was performed between the hours of 9:00 AM and 5:00 PM. Room temperature and humidity were recorded. See Table 1 for subject demographics.

Figure 1 provides the consort diagram for the current randomized controlled trial. As illustrated, 42 subjects were assessed for eligibility and 34 subjects were eligible to participate. Four subjects were screened and scheduled but failed to report. They did not reschedule nor return follow up calls. Four subjects were excluded due to prior TENS treatment and four subjects were unable to attend during the test times. One subject was excluded in the secondary screening process due to reduced sensation. All of the remaining 29 subjects were allocated to a treatment order and completed the testing. Five subjects were excluded from the analysis due to a change in the test protocol. Ten subjects were recruited for the skin impedance testing and all ten completed testing.

Hydration status: Urine specific gravity

In order to ensure proper hydration status subjects provided a 3-5mL clean catch urine sample. Urine specific gravity (USG) was determined with test strips (Teco Diagnostics, Anaheim, CA). Subjects who tested in the normal USG_{range} of 1.000-1.020 were allowed to proceed to further testing [23,138,177]. After failing to meet the USG requirement on visit two, one subject chose to return for testing and proceeded to complete the rest of the trial. All other subjects met the inclusion criteria for USG for all visits.

Patient preparation

Following measurements of height and weight, subjects were seated with the right forearm in the pronated position with palm resting flat on a table. The dorsal surface of the forearm and hand as well as the palmar surface of the hand were cleansed with a wet wipe and the test protocol was reviewed as the arm was allowed to air dry.

Optimal site selection technique and skin impedance

In the first experiment, a flexible plastic grid with eight 5 x 5 cm sections, identical to the size of the TENS electrodes used in the second experiment, was secured with paper tape to the dorsal aspect of the arm of the ten subjects recruited for this portion of the study. The corners of each of the eight squares were marked on the arm through pre-punched holes in the grid so as to define eight distinct areas for assessment. Two additional marks were made, one at the base of the first and second metacarpal bones in the thenar eminence (optimal site) and the other at the lateral aspect of the hand bisecting the 5^{th} metacarpal (sham site). An electrode impedance meter (Checktrode

1089e, UFI, Morro Bay, CA) was used to measure the impedance. A 30 Hz sine wave current of <10 µA was passed through the each of the eight sites when paired with the optimal site or the sham site-this gave a measure of impedance in Ohms (Ω). Measurements taken at 10 and 15 seconds by the first examiner were taken from the optimal site first on odd numbered subjects followed with measurements for each area and the sham site second. The inverse order was performed for even numbered subjects. All electrodes were then removed and discarded and a second examiner used the OSS technique to assess of each of the eight areas and identify them as either optimal or sham sites.

The technique for site selection proceeded as follows: With TENS parameters set at 50 Hz, 100 µs, continuous mode and electrode gel covering the surface of each 2 x 2 inch carbon electrode, the examiner held one gelled electrode in the palm of her right hand with the subject doing the same with the other electrode. The examiner moistened the tip of her right index finger and made contact over the dorsum of the hand on the test side. The level of pressure was maintained such that the pad of the index finger is in contact with the subject's skin without blanching of the examiners nail hyponychium. TENS amplitude was increased until sensory tingling was felt in the pad of the index finger. The examiner glided her finger over the optimal site and determined the lowest intensity which differentiated this point from the area surrounding it. Several trials were repeated to verify the difference in electrical sensation in the fingertip when on the optimal point as compared to when specifically not over the point. The finger was remoistened by the examiner as needed to maintain good contact. With the intensity level constant, the examiner assessed each of the eight areas marked on the subjects arm.

Examiner 1 recorded the responses of "0" or "1" as indicated by Examiner 2 where "0" indicated a definite electrical sensation in the fingertip and "1" indicated little to no electrical sensation perceived by the examiner. After each area was assessed, the TENS unit was turned off, the subjects hand and arm were cleaned and compensation forms were completed.

Electrode site selection

Four electrode sites (2 sets of 2) were located and marked for all 24 subjects participating in the TENS experiment according to the protocols for OSS and SSS, as described below. The same TENS unit was used to locate points for all subjects who were assessed in the seated position with upper extremity resting on the table (see figure 2- photo of electrodes on an arm). The order of site selection remained constant for all subjects and occurred as listed below.

Optimal Site Selection (OSS)

With TENS parameters set at 50 Hz, 100 µs, continuous mode and electrode gel covering the surface of each 2 x 2 inch carbon electrode, the examiner held one gelled electrode in the palm of her right hand with the subject doing the same with the other electrode. The examiner moistened the tip of her right index finger and made contact over the dorsum of the hand on the test side. The level of pressure was maintained such that the pad of the index finger is in contact with the subject's skin without blanching of the examiners nail hyponychium. TENS amplitude was increased until sensory tingling was felt in the pad of the index finger. The examiner glided her finger over the skin to locate a point near the base of the first and second metacarpal in the thenar eminence; and a second point in the proximal forearm extensor mass. These points represented areas

where the most electrical sensation was felt by the examiner compared to the area surrounding them. The intensity level was recorded in mA. Several trials were repeated to verify the difference in electrical sensation in the fingertip when on the optimal points as compared to when specifically not over the point. The finger was remoistened by the examiner as needed to maintain good contact. When the sites were verified three times, each one was marked with a permanent marker. Two self-adhesive 2" x 2" electrodes marked "A" were placed with lead wires extending proximal at the hand site and extending distally from the forearm site. The center of the electrode was placed over the mark. The cathode (black pin) was placed proximally and the anode (red pin) distally for uniform application across subjects.

Sham Site Selection (SSS)

The procedure to locate the sham sites (SSS) was identical to that of OOS outlined above; however, these sites were marked over the lateral boarder of the 5^{th} metacarpal and 1-2 inches adjacent to the extensor mass optimal site. These sites were specifically selected making certain they corresponded with sites where the examiner felt little to no electrical sensation even as intensity and level of pressure remained the same. These two sites were marked with a marker in identical fashion as outlined above, and electrodes bearing the letter "B" were placed over these sites. An effort to duplicate the inter electrode distance was executed within subject anatomy.

Skin impedance and voltage at optimal and sham electrode sites

The electrode impedance meter (Checktrode 1089e, UFI, Morro Bay, CA) was used to measure the impedance through the two optimal site electrodes and between the

two sham site electrodes. Measurements were taken at 10 seconds. For odd numbered subjects the A (optimal) sites were measured first and for even numbered subjects the B (sham) sites were measured first. The digital display representing impedance was recorded and values were averaged for data analysis.

The electrodes remained in place and the instrumentation was changed to measure voltage with an AC current source. The Rehabilicare Maxima TENS unit (DJO Global, Vista, CA) with pulse duration of 100 μs and pulse frequency of 100 Hz was placed in series with the patient circuit and an oscilloscope (Hitachi V-1565, Hitachi Denshi, Ltd., Japan) and placed in parallel with the two points of measure. Voltage waveform was derived from the peak to peak values at 3, 6, 9, and 12 mA. For odd numbered subjects OSS (A sites) were measured first followed by SSS (B sites). The inverse occurred for even numbered subjects. Impedance was calculated using current (I) values from prior TENS calibration Impedance (Z) = voltage (V)/Current (I). The scores for each of the four intensities (3, 6,9,12 mA) were analyzed using repeated measures ANOVA and were also averaged and analyzed for overall differences. All testing was performed with the subject in the seated position utilizing the same pre calibrated TENS unit dedicated to this portion of the experiment. Following all testing, electrodes remained in place and the subject was prepared for TENS treatment by the second examiner.

Randomization

The SNOSE allocation concealment protocol using permuted blocks of 6 was used to randomize subjects to treatment order for the TENS trial [52]. The allocation envelopes served to dictate the order in which the three treatments were allocated. Allocation envelopes were sealed with a signature and were not available to the data

collection examiner. The foil lined envelopes were signed, dated and opened by the allocation examiner immediately prior to TENS application out of view of the data collection examiner. Allocation envelopes were kept with TENS allocation data sheets maintained by the allocation examiner.

Outcome Measures

Pressure Pain Threshold

A handheld digital pressure algometer (Somedic AB, Farsta, Sweden) was used to assess pressure pain threshold – this was the primary outcome. The algometer has a visual screen which displays the rate of pressure increase and the total pressure applied in kilopascals (kPa). Pressure was applied perpendicular to the skin at 50 kPa/s using the 1 cm^2 circular probe. The rate of increase was monitored by the examiner and kept at a level per instructions accompanying the algometer. Three PPT recording sites were marked with an indelible marker 8, 9 and 10 cm below the lateral elbow flexion fold over the extensor mass (Figure 2). A standardized PPT script was read to each subject. The subjects were given a hand held switch to press indicating when the pressure applied would be described as pain (distinct from pressure or discomfort) [60]. At this time a digital reading was recorded a second examiner. Participants were given two or three practice demonstrations of the PPT procedure on their non-test side middle deltoid to ensure they understood the concept of PPT recording. Subjects were instructed to consider a scale of 0 to 10 where"0 is no pain and 10" is worst pain imaginable" and to press the button when they considered the sensation to be a 1 out of 10. The importance of replicating their method of assessment for each trial was stressed.

With the subject in the seated position, three measurements were taken at each of the recording sites at each time point and an average of the three trials was used in data analyses. PPT readings were recorded in ordinal fashion for subjects with odd allocation numbers and in reverse ordinal fashion for even numbers subjects. PPT was recorded at baseline, 15, and 30 minutes. TENS intervention was not interrupted for PPT testing. The algometer was calibrated on a monthly basis. PPT change scores were calculated by subtraction of baseline values from the 15 and 30 minute measurements. The difference score and area under the curve was used in statistical analyses.

Subject perceived comfort

A 10 cm visual analog scale (VAS) was used to assess subject comfort of the TENS application. The VAS scale was presented to subjects after 30 minutes of treatment. Subjects were advised to rate their level of comfort during the TENS application by marking a single vertical line on the 10 cm VAS with anchors of "most comfortable" and "most uncomfortable". A metal metric ruler was used to measure from the left end of the scale to the leading edge of the mark to be used for data entry for each time-frame. Scores ranged from 0-10 with lower numbers representing more treatment comfort, and higher numbers indicating the treatment was more uncomfortable.

TENS application

TENS was administered with the Rehabilicare Maxima TENS unit with dedicated manufacturer lead wires by a trained examiner that was not involved in data collection. EMPI 5000 electrodes (DJO Global Vista, CA) were used for all subjects. The units were calibrated prior to onset of data collection using an oscilloscope to measure the peak to peak voltage across a 1 kΩ resistor. The active unit delivered an asymmetrical square

waveform with pulse duration of 100 μs and pulse frequency of 100 Hz. The placebo unit was identical in settings and appearance to the active unit; the difference being that it was active only during the intensity adjustment period and slowly ramped down to "off" in 45 seconds.

Subjects remained seated with their right arm resting comfortably in the pronated position with palm down. A standardized script was read to the subjects and intensity was increased to sensory threshold and then to maximally tolerated intensity. For the active TENS interventions the intensity was adjusted every five minutes as determined by the subjects' answers to the following questions: (1) Are you doing alright? and (2) May I turn it up? For subjects receiving the placebo treatment, the intensity was advanced to a comfortable sensory level and every five minutes subjects were asked "Are you doing alright?" No other prompts were given with regard to stimulus intensity. Any subject questions regarding lack of sensation were addressed with reminders that different TENS treatments can vary in sensation from imperceptible to moderate muscle twitching.

Both pair of electrodes were connected to lead wires attached to the unit. After only turning on the channel attached to the appropriate sites per the allocation protocol, the unit was placed in a concealment pouch in order to blind the outcome assessor with regard to electrode site.

Stimulus amplitude was recorded in mA every five minutes and the maximal value was used in data analysis. TENS was applied for 30 minutes. Following the final PPT assessment electrodes were removed and subjects reminded of their next test session. On visit three, compensation forms were completed by each subject.

Blinding

The PPT examiner was blinded to treatment group by the use of an independent TENS application investigator, the allocation concealment protocol, and the pouch concealing the TENS unit. In addition, because all four electrodes were placed at each visit with lead wires leading to the concealed TENS unit, the examiner was blinded to which electrode pair received the active stimulation. If muscular contractions were present, TENS intensity was decreased by the TENS examiner just prior to the return of PPT examiner. In addition, to blind the examiner from knowledge of PPT values, the TENS examiner recorded the PPT values for each test session. Baseline values and subsequent values recorded at the 15 and 30 minute time frames were kept out of view from both examiners. The subject was blinded to treatment group by virtue of the transient placebo unit, and the fact that all four electrode sites were marked on each subject with no specific information given to subjects with regard to the difference between the sites. The TENS application investigators were not blinded to treatment group, however they did not participate in electrode site selection, electrode impedance data collection, and did not be execute PPT testing. To assess blinding the PPT investigator was independently asked the following questions at the conclusion of the TENS application: (1) Do you feel the TENS application was active, placebo, or I don't know? (2) Do you feel the sites were optimal, sham, or I don't know?

Experimental overview

<u>Optimal site selection technique and skin impedance</u>

1. Consent, Hydration screen, Demographics
2. Skin preparation and site demarcation

3. Impedance measurement

4. Optimal site selection assessment

Optimal site selection and TENS

1. Consent, Hydration screen, Demographics

2. Skin preparation, site demarcation and electrode application

3. Impedance measurement

4. Voltage measurement

5. PPT baseline

6. TENS

7. PPT at 15 min

8. VAS comfort and PPT at 30 min

9. Reminder of next visit (visit 1, 2)

10. Subject blinding (visit 3).

Data Analysis

The study was a crossover design with random assignment to OSS-TENS, SSS-TENS or P-TENS, with every subject receiving each of the three treatments. Sample size calculations were made using a mean difference of 11.97 and a standard deviation of 12.63 obtained from data collection involving two active TENS treatments [32]. With significance level of $P < .05$ and power of 80%, sample size was 24 per treatment. Descriptive statistics were calculated for each variable to evaluate for normal distribution. Normality was evaluated using the Kolmogorov-Smirnov test. Repeated measures ANOVA was performed on demographics, baseline PPT, impedance measures, change in PPT, and area under the curve between treatments. Repeated measures ANOVA were

also performed on intensity, and perceived comfort. Follow up paired t tests were performed to test significant differences between visits. To account for the multiple tests performed related to a specific hypothesis, p-values were adjusted using Bonferonni's method. Statistical significance was considered at $p < 0.05$.

Results

Demographics and baseline measures

Table 4-1 provides the demographic information and impedance measures for the 10 subjects included in the electrode selection technique and forearm impedance analysis. Demographic information and baseline PPT measures for the 24 subjects included in the analysis of TENS and optimal site selection are presented in Table 4-2. There were no significant differences across time for demographic characteristics. All subjects met the inclusion criteria for USG prior to each test session. Treatment times ranged from 33.9-35.3 minutes.

Impedance is greater at sham site when compared to optimal sites

In the initial experiment with 10 subjects, impedance measured $13.53 \pm .57\ \Omega$ for areas on the forearm classified as optimal sites for TENS electrode placement (OSS). Areas classified as non-optimal (sham, SSS) had a mean impedance of $17.69 \pm 1.24\ \Omega$ and were significantly higher than those from the optimal sites ($p = .007$).

Impedance remains constant at sites and is higher in SSS than OSS

For the 24 subjects included in the TENS analysis, impedance measures for the OSS and SSS sites were measured at each site over the 3 visits. There was no significant difference in impedance across time. Mean impedance was 13.55 ± .36 Ω for OSS and 14.99 ± .38 Ω for SSS electrode placement sites. SSS were significantly higher than OSS ($F_{1, 23} = 59.30$, p =. 0001) (see Figure 4-2.A).

Impedance measures through the TENS unit at 3, 6, 9, and 12 mA settings were assessed at each visit and pooled across visits. There was a significant difference between calculated impedance for OSS and SSS ($F_{1, 23} = 10.36$, p = .004) (Figure 4-2.B).

Pressure pain threshold

When compared to pre-TENS values, PPT at the forearm were significantly increased with OSS-TENS (p =0.002), SSS-TENS (p =.0001), and P-TENS (p =.007) (Figure 4-2.C). The area under the curve shows a significant difference in PPT between OSS-TENS and P-TENS (p =0.024) and between SSS-TENS and P-TENS (p =0.025). There was no significant difference between the two active treatments (p =.81) (Figure 4-2.D).

Perceived Comfort

The data for perceived comfort at 30 minutes showed no significant differences within each treatment. When subjects received P-TENS, the comfort was rated as .41 ± .11. For the two active TENS treatments OSS was rated as 2.5 ± .34 and SSS was rated as 2.1 ± .42. There were no significant differences between the active TENS

treatments (p =.20). P-TENS comfort scores were significantly lower than active TENS (p =.0001).

TENS Amplitude

The pulse amplitude required to achieve the desired (highest tolerable) TENS treatment intensity was similar between the two active TENS treatments (i.e. mean amplitude was 19.2 ± 1.0 mA for OSS-TENS, and 21.2 ± .7 mA for SSS-TENS). Mean amplitude for P-TENS was 15.2 ±.4 mA and was significantly lower than the two active TENS treatments (p < .0001). The time course for mean TENS amplitude every 5 minutes during the 30 minute treatment is presented in Figure 4-3. Sensory threshold was 6.6 ± .48 for OSS-TENS, 6.7 ± .29 for SSS-TENS and 7.0 ± .39 for P-TENS and was not different between treatments (p =.35). When subjects received OSS-TENS 12/24 (50%) chose treatment amplitudes that achieved motor contraction. When subjects received SSS-TENS 8/24 (30%) chose amplitudes placing them in the range for motor contractions during TENS.

Experimental Blinding

The PPT examiner was blinded to differences between OSS and SSS application 100% of the time. The examiner was also blinded to whether the subjects received placebo or active TENS 95% of the time.

Discussion

The current study showed skin impedance was significantly lower between OSS when compared to SSS by two independent methods. Despite this difference in skin impedance, there was no difference between the analgesia produced by OSS-TENS or SSS-TENS – both produced significant and equivalence increases in PPTs when

compared to placebo TENS. Thus, TENS delivered over OSS was not more effective than TENS delivered over SSS suggesting that skin impedance is not a factor in TENS effectiveness.

Impedance

When mapping the forearm into eight areas, in the first experiment, we were able to determine there was a difference in impedance between those sites classified as optimal versus sham by the examiner. This information established the fact that the examiner perceptions were predicative of differences in electrode site selection. This relationship held true for the 24 subjects included in the TENS analysis using the impedance meter at individual sites, as well measuring impedance through the TENS unit at four stimulation intensities. This experiment did not address the potential cause for the difference in impedance between sites. Our urine specific gravity screen was included to avoid differences in hydration status as previous studies indicate hydration affects impedance [61,85,133,153]. Several theories suggest that lower impedance at points on the skin could be due to proximity to peripheral nerve branches, electrode polarization, stratum corneum impedance, presence of sweat glands, and choice of contact medium [6,117,118].

The TENS impedance data was collected at four sub-motor intensities. The data show impedance increasing over 3-9 mA with a decrease for both electrode site pairs occurring at 12 mA. This could be related to the resistive properties of the skin and the rationale for using strong intensities during TENS treatments to obtain hypoalgesia. Previously, we show that activation of deep tissue afferents is required to produce analgesia [141] and thus adequate amplitude is required to produce analgesia. Thus, skin

impedance may play a minimal role when TENS is given at adequate intensities to produce hypoalgesia. Interestingly, while there was no difference in hypoalgesia between OSS-TENS and SSS-TENS, there was a difference in the number of subjects where amplitudes produced motor contractions - 50% of the time over OSS and 30% of the time over SSS. This could imply the OSS sites were closer to the motor endplate or nerve fibers allowing earlier depolarization of A-alpha fibers. Further, comfort was rated as similar between OSS-TENS and SSS-TENS indicating the presence of motor contractions did not appear to influence perceived comfort. Thus, differences in impedance are observed between OSS-TENS and SSS-TENS may lead to a higher likelihood of producing a motor contraction but does not play a role in effectiveness or comfort.

Skin impedance plays no role in TENS effectiveness

The increases in PPT are similar to studies in healthy controls showing increases in PPTs during active TENS [32,34,35,44,144,145,174,185]; however, the current study did not show differences in effectiveness of TENS between OSS and SSS when given at maximal tolerable intensities. This may be because skin impedance has a limited role at the intensities used. It is possible that less skin impedance is encountered when using TENS over optimal sites at lower intensities than when applied over sham areas. This carries importance only when patients or clients cannot tolerate strong, non-painful stimulation intensities. However, sensory threshold was not significantly different between OSS and SSS indicating that even at lower intensities skin impedance plays a minimal role.

Maximal treatment intensity was lower for the placebo treatment when compared to the two active TENS treatments. For both the active and placebo treatments intensity was increased to “maximal tolerable”. However, as the active treatment protocol included also increasing intensity every 5 minutes, this data suggest that when subjects received the active TENS they allowed the examiner to increase intensity during the 30 minute treatment.

When examining stimulation intensity in relation to outcome measures for reduction of pain in the experiments included in prior Cochrane reviews [156] and more recent experiments [41,122,132] there is strong support for application of high intensity TENS. In fact, the intensity of stimulation is positively correlated with the change in PPT produced by TENS [41,143,144]. Intensities utilized in prior studies varied widely, however trials that reported effective TENS generally used higher intensity than those that reported no effect [18,41,122,132,143,144]. The current study applied TENS at amplitudes maximally tolerated by the subject with requests to increase amplitude every 5 minutes during active TENS. Titrating TENS intensity upward during treatment increases hypoalgesia in healthy controls [132,137] .

Blinding of active and placebo TENS

The PPT examiner was blinded to electrode site 100% of the time. This was accomplished by preparation of all four sites including the attachment of lead wires to the unit and the unit being secured in a pouch only attended to by the TENS allocator. Because all four electrodes and lead wires were place on each visit and the use of the concealment pouch for the TENS; the outcome examiner was unable to discern which pair of electrodes was active during each treatment resulting in 100% blinding to

electrode site. The PPT examiner was blinded to TENS treatment 95% of the time by virtue of the randomization protocol, having the TENS examiner instruct subjects not to discuss their treatment with the PPT examiner, and reducing the amplitude to sub motor prior to PPT assessment. The placebo unit utilized has been previously shown complete inability of the examiner to correctly identify active or placebo TENS (see Chapter 2)[41,122,144]. Adequate blinding is important to remove bias in interpretation from the subject and the examiner. Prior TENS studies use separate instructions to the subject for active and placebo TENS which can influence patient expectations and have profound effect on treatment outcome [16,67,103,104,115]. By giving the same instructions, we were able to show that active TENS in healthy normal subjects increased hypoalgesia compared to P-TENS. Because each subject received all three treatments it is possible their perception was biased with repetitive treatments, however randomization to treatment order was utilized to decrease this effect.

In the current study subjects were not informed that one of the three TENS treatments was a placebo. Instead, subjects were told we were testing three different types of TENS. We then asked subjects to rate their comfort during the TENS at the conclusion of treatment session.

Conclusion and Clinical Implications

In summary, the current randomized trial examines skin impedance differences between sites deemed “optimal” and those categorized as “sham” and examines the effect of electrode site selection when using TENS on the upper limb of healthy normal adults. Although significant differences in impedance were found between the electrode sites, when TENS is applied at an adequate intensity skin impedance is not a factor in TENS

effectiveness. Further investigation of this parameter should include patients who presents with painful conditions to determine if electrode site selection is a critical factor when using TENS to reduce hyperalgesia. Regardless, clinicians should focus on choosing sites that are well tolerated by patients to allow for strong, nonpainful levels of stimulation which may include motor contractions.

We thank Arliss Dudley-Cash, Nicole Englehardt Jennifer Lee, Kristin Hood and Shannon Lehman who served as TENS allocators; Glenn Williams and Jason Wu for technical support; and donation of TENS units and electrodes by EMPI, Inc.

Variable	N = 10
Age (yr)	23.3± 4.4
Sex	5 M, 5 F
BMI	23.3 ± 3.4
USG ( )	1.01 ±.004
Room Temperature (F)	73.1 ±2.2
Room humidity (%)	48.8 ± 1.8
Impedance optimal sites (Ω)	13.53 ± .57*
Impedance sham sites (Ω)	17.69 ± 1.24

* p=0.007 significantly less than sham sites.

Table 4-1. Experiment 1 demographics and impedance measures for comparison of sham and optimal sites expressed as mean ± S.E.M.

Variable	**Visit 1**	**Visit 2**	**Visit 3**	**P-value**
Demographics /baseline mean ± SEM	M =12 F=12	M =12 F=12	M =12 F=12	
Age	31.75 ± 2.19	31.75 ± 2.19	31.75 ± 2.19	N/A
BMI	25.07 ± 1.09	25.09 ± 1.08	25.04 ± 1.09	.66
Room temp (F)	71.45 ± .39	71.94 ± .36	72.04 ± .4	.16
Room humidity (%)	51.25 ±.31	50.9 ± .31	51.04 ± .32	.57
USG	1.008 ± .001	1.010 ± .002	1.008 ± .001	.79

Table 4-2. Demographics and baseline measures for Experiment 2 comparing the effects of TENS on optimal and sham sites expressed as mean $\pm$ S.E.M. .

Outcome measures - baseline mean ± SEM *95% CI*	**OSS TENS**	**SSS TENS**	**P TENS**	**P value**
PPT (kPa)	191.3 ±15.7 *158.8 – 223.7*	202.4 ± 19.8 *161.4 – 243.4*	212.7 ± 25.1 *160.8 -264.6*	.22
OSS Impedance	13.2 ± .60 *12.25 – 14.71*	13.4 ± .55 *12.43 – 14.92*	13.1 ± .53 *12.08 – 14.92*	.77
SSS Impedance	14.95 ± .71 *13.6 – 16.06*	14.30 ± .56 *13.47 – 15.99*	14.38 ± .54 *13.72 – 17.04*	.12
mA sensory threshold	6.6 ± .48 *5.60 – 7.57*	6.7 ± .29 *6.07 – 7.26*	7 ± .39 *6.2 – 7.8*	.35
mA maximum	19.2 ± 1.03 *17.07 – 21.34*	21.2 ±.68 *19.41 – 22.60*	15.1 ± .68* *13.76 – 16.57*	.0001
Comfort (10cm VAS) (30 min)	2.68 ± .38 *1.89 – 3.47*	2.04 ± .40 *1.20 – 2.87*	.42 ± .10* *.20 – .63*	.0001

* significantly different from OSS TENS and SSS TENS.

Table 4-3. Primary outcomes measures prior to application of TENS expressed as mean ± S.E.M. and 95% confidence intervals.

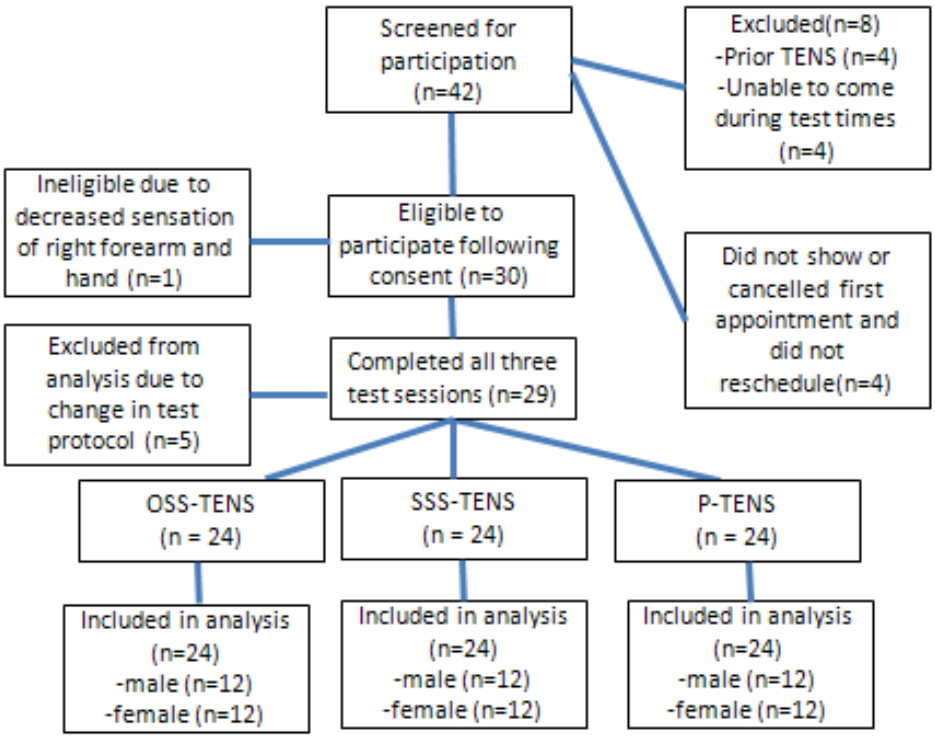
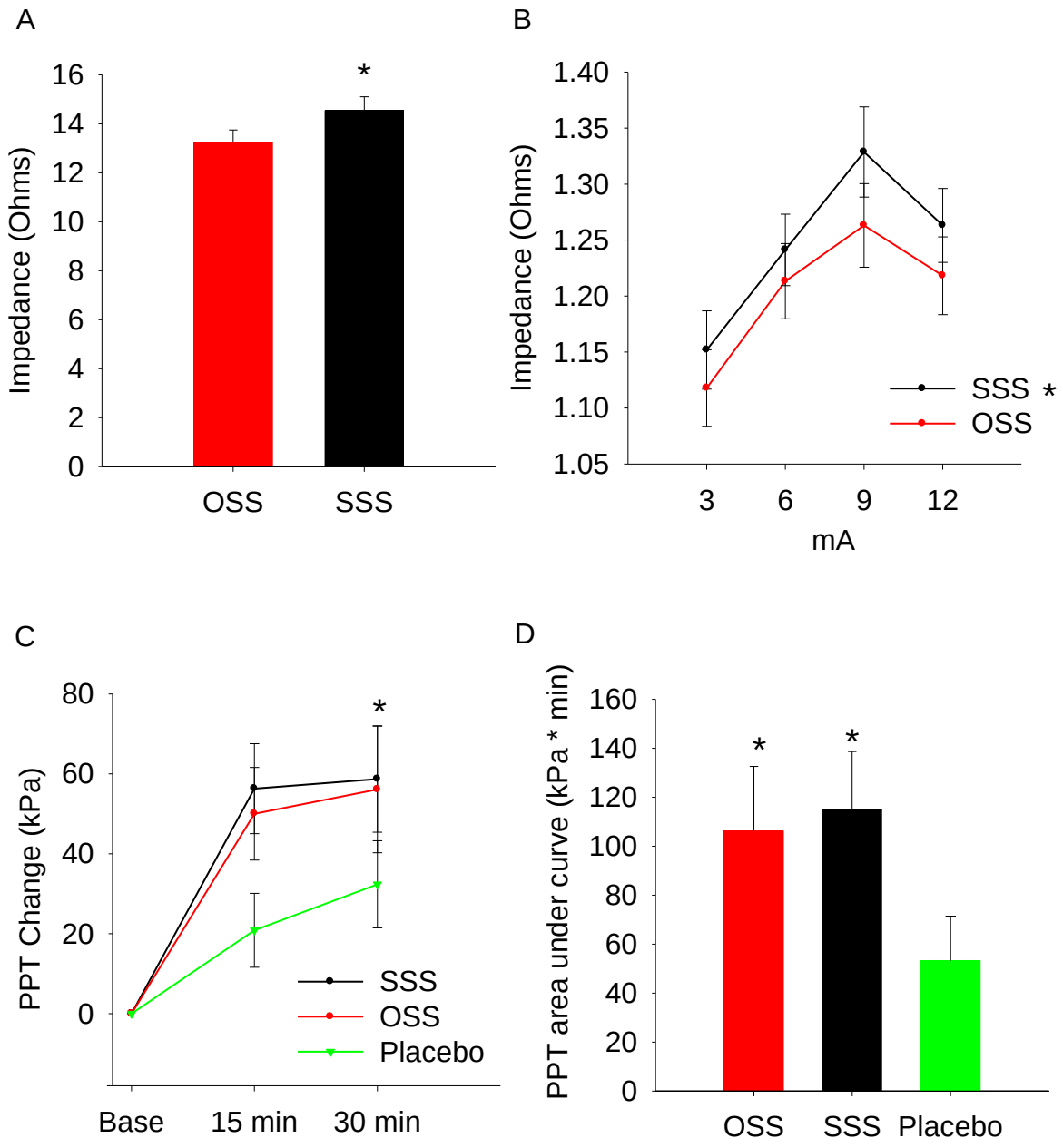
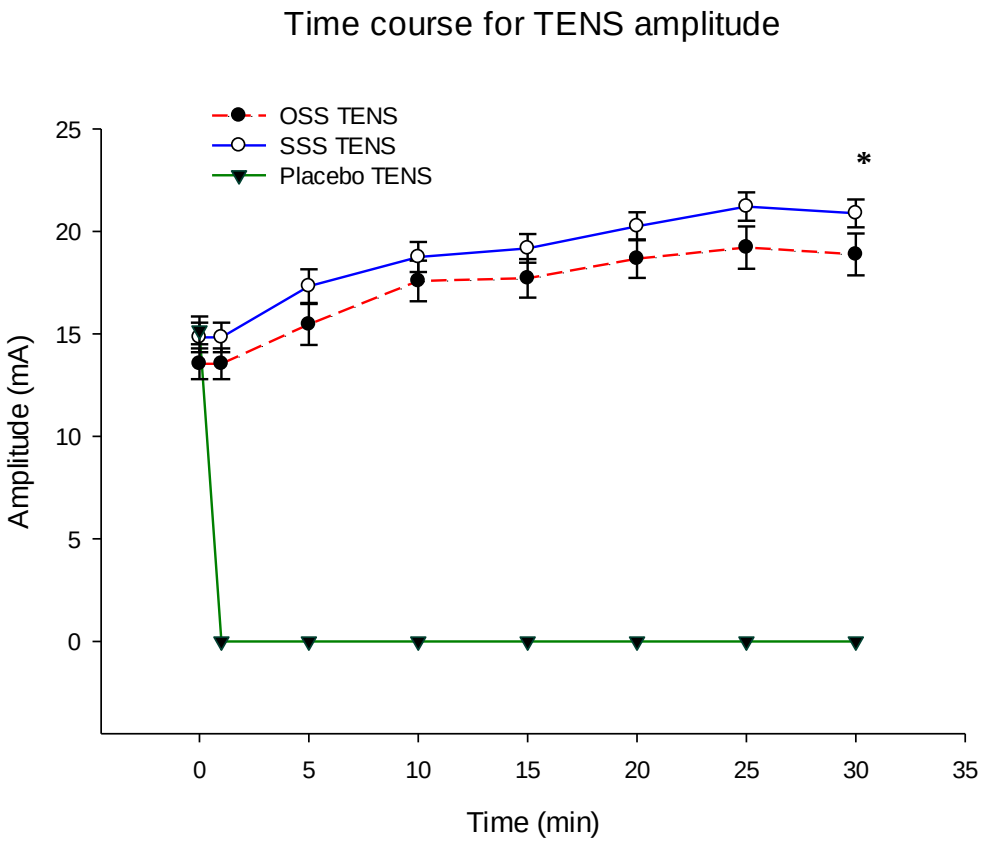


Figure 4-1. Consort diagram for the TENS experiment in this cross-over design.



* p < 0.05

Figure 4-2. A. Average impedance (Ω) using an impedance meter with sham sites significantly higher than optimal sites.* B. Impedance (Ω) measures using the TENS unit at 4 amplitudes with sham sites significantly higher that optimal sites.* C. Change in PPT at 15 and 30 minutes. OSS-TENS and SSS-TENS show significantly greater change in PPT when compared to P-TENS (placebo), yet not significantly different from each other.* D. PPT area under the curve from 15 and 30 minute time points with both active treatments significantly different from placebo and not different from one another.*



* p = .0001

Figure 4-3. Time course for TENS amplitude. OSS-TENS and SSS-TENS significantly greater than P-TENS

CHAPTER V

DISCUSSION AND CONCLUSION

Review of Experimental Hypotheses

The first reported TENS treatments represent an important milestone on a long pathway exploring the concept of pain and pain management. The report includes partial details of the treatments of eight patients with chronic pain. Four had upper extremity pain, three had lower extremity pain and one presented with facial pain. Two of the eight treatments used surface electrodes and the remainder of the treatments were accomplished with implanted electrodes. When reported, treatment times were between 2-10 minutes of stimulation with post stimulation follow up of various timeframes. All treatments were conducted with pulse frequency of 100 Hz and pulse duration of 100 μsec at a sensory level described as buzzing and tingling; and all cases reported temporary relief of the chronic intractable pain experienced by the patient [180]. Wall and Sweet felt their findings were of interest for the advancement of pain theory, but reported the therapeutic benefit of their discovery as "equivocal", stating that two patients who were stimulated multiple times per day reported a decreased effect on their pain after several months. The findings from Wall and Sweet's seminal paper were not only of interest for the advancement of pain theory, but supported the use a new non-invasive treatment for chronic pain.

Many important ideas arise in the analysis of their report now 45 years later. First is the obvious lack of a control or placebo group. Second, is the undefined outcome measure, and third is the failure to report all the treatment parameters necessary to

reproduce the treatments. Also of interest is their observation of tolerance in several patients after multiple days of treatment, their inclusion of different types of pain as classified by today's standards, and implanted electrode use in the greater number of experimental treatments. Subsequent TENS experiments stemming from this work continued with many of the same shortcomings. As established in the main body of this document, even when a placebo group is included, it remains difficult to blind both subjects and examiners. Most reports include some type of pain assessment taken while the patient was at rest and stimulation parameters are variable and incompletely reported.

This series of experiments accomplishes the goals of improving the TENS placebo, testing established parameters from basic science experiments in a patient population, testing multiple outcome measures to direct future investigation, and for the first time examined the effect of electrode site selection in TENS analgesia. These experiments were the first to establish a placebo that can 100% blind the person applying the TENS itself and the first to test this placebo in a patient population. These studies were also the first to show that although there are differences in impedance between optimal and sham sites, that this difference had no effect in the amount of analgesia produced by TENS.

Chapter 2, Hypothesis 1.

The stated hypothesis for Experiment 1 -" the new transient placebo TENS will result in significantly higher subject and investigator blinding than the traditional placebo TENS therapy; and the transient placebo TENS will not significantly increase PPT as expected for the active TENS therapy" is accepted for blinding of the examiners and shows adequate for blinding of the subjects. The transient TENS completely blinds the

allocation examiner to treatment. In addition, the transient placebo treatment did not produce significant increases in PPT, HPT, and pain intensities to tonic heat and pressure compared to active TENS indicating the unit mimicked the active treatment without producing treatment effects. Subjects were blinded 40% of the time which is not different from chance (50:50). In Experiment 2 knee OA subjects were similarly blinded to the transient placebo 43% of the time. It is possible that subject blinding may have been impacted by the protocol for setting intensity. In Experiment 1, subjects were allowed to select stimulation intensities well into "strong sensory" and the motor range. In Experiment 2 all subjects were treated at an intensity of motor minus 10%, a strong sensory intensity. Subjects may have been aware of the unit ramping to "off", However, blinding was similar between these two experiments despite differences in the protocol for intensity. As Experiment 3 was a cross over design, the bias due to the ramping off of the intensity was hypothesized to be stronger than when given in separate subject. Therefore, the protocol in Experiment 3 was structured so that the allocation examiner advanced the treatment intensity for all treatments to a comfortable sensory level. When active TENS was applied, the intensity was increased as tolerated every 5 minutes. When the placebo treatment ramped to "off", it should be less noticeable to subjects. In Experiment 3 subjects were not told they would be receiving placebo TENS as one of the three interventions. They were advised that each visit they would receive a different TENS treatment.

The word "placebo" was originally described as medicine given more to please patients than to treat them [43]. The idea of the placebo effect includes aspects of patient and examiner expectation, natural disease course, the desire to obtain relief from a

painful condition, the level of mystique and technology of an intervention and conditioning over several treatments [10].

The placebo effect in pain management is described as a reduction in pain not attributed to a specific therapeutic intervention [162]. In several studies subjects receive equivocal benefits when they are treated with placebo or active TENS [129,147]. Importantly, the placebo effect of pain reduction is modulated by specific neural mechanisms [159,179,193]. Placebo effects for pain relief are reversed by the opioid antagonist naloxone suggesting descending opioid pathways are activated [105]. The placebo activates an opioidergic network involving the pre-frontal and anterior cingular cortex, accumbens nucleui and per-acqueductal gray as identified using PET imaging [179,193].

The difficulty in providing an adequate placebo for experimental investigation of any physical intervention presents as a significant challenge. The factor of using a high technology device with relative mystique (most people are naive to electrical stimulation to the body for therapeutic purposes) predisposes TENS to this component of placebo effect and is difficult to eliminate [10]. Prior TENS investigations made use of an identical device that did not deliver current. Blinding the investigator was impossible because of the difference in instructions which examiners delivered to subjects because there was no electrical sensation, and thus there is a chance they will approach the treatment differently creating expectation bias. Clearly, it will always be most difficult to blind the subject to an intervention such as TENS. Placebo effects for all types of treatments including surgery, medication and physical modalities vary greatly between individuals and may be higher than the often cited 30% effect [176]. An improvement in

the placebo intervention is critical to ascertain the true effects of TENS treatments on painful conditions.

This experiment provides information of great magnitude for future experiments where electrical stimulation is used to test effectiveness. The high level of investigator blinding with the new transient sham device allows TENS to be applied using the same script and parameters as the active TENS treatment and eliminates expectation bias. In addition, there may be protocol advantages for prospective randomized clinical trials by allowing the same investigator to both apply the treatment and assess outcomes. In all prior TENS experiments using the traditional inactive placebo TENS, the investigator, knowing a placebo treatment is being applied, may have inadvertently approach this application differently and in a manner subtly suggesting lack of effect which may influence the subject's expectations and responses. This influence on outcome results is particularly possible when measuring subjective outcomes like pain. Thus, Experiment 1 was able to develop and validate an improved placebo unit, termed transient placebo, that allow future clinical trials to do double-blind investigations for both the subject and the experimenter.

When active TENS treatments are applied subjects are able to correctly identify the intervention as active. This lack of blinding is consistent with prior research and can lead to an expectation bias that may overestimate treatment effect when subjects receive active TENS. The constant stimulation may influence subject responses to outcome measures because it confirms to them that active treatment is being delivered. These findings highlight the importance of assessing the degree of blinding when evaluating the efficacy of physical modalities such as TENS.

Experiment 1 also showed an intensity dependent change in PPT where increases were observed only with higher stimulation intensities. This intensity effect has been observed in healthy controls [12,35,35,122,132] and in post-operative patients [18,145]. When reviewing the 31 trials included in the meta-analysis for postoperative pain and TENS, analgesic consumption was reduced by 35% with active TENS compared to placebo TENS in 11 trials conducted with intensities described as "strong sub-noxious" but not in those with inadequate intensities [18].

The placebo effect for subjects is minimized in basic science investigations and over the last 25 years many reports have offered insight regarding the mechanisms of TENS analgesia [71,82,87,164-167,178]. These important findings require translational experiments to be conducted in humans. Experiment 2 was designed specifically to test the effect of frequency from prior studies in our basic science laboratory, to evaluate the transient placebo in a patient population, and to test a variety of outcome measures.

Chapter 3, Hypothesis 2

The stated hypothesis for Experiment 2-"HF-TENS and LF-TENS will reduce pain during movement, but not pain at rest, increase pain thresholds, and increase function in subjects with knee OA" is partially supported.

PPTs were significantly increased at the knee with both HF-TENS and LF-TENS, which we interpret as a reduction in primary hyperalgesia, and at the anterior tibialis muscle with HF-TENS which we interpret as a reduction in secondary hyperalgesia. Experiment 2 is the first study to show effects of TENS on hyperalgesia in OA, and may be a useful measure of neuron excitability. Changes in primary hyperalgesia measures suggest changes in nociceptor sensitivity paralleling changes we previously observed in

animal studies [178]. In addition, HF-TENS increases PPTs over the anterior tibialis muscle, an area outside the site of injury, which we interpret as a reduction in secondary hyperalgesia suggesting changes in central neuron excitability [50]. This finding also parallels changes we previously observed in animal studies [87]. Previous studies show that TENS increases PPTs in people with myofascial pain, and decreases allodynia (pain to an innocuous stimuli) and increases PPT in people with neuropathic pain [24,66,146,152]. These data suggest that TENS is useful for evoked painful stimuli such as hyperalgesia, allodynia and potentially movement pain. Prior studies have also shown a reduction in evoked movement pain in people with postoperative pain and fibromyalgia [42,145]. Clinically, palpation tenderness is an essential part of the physical examination of patients; PPT measures may offer the clinician an improved objective measure of tenderness.

The effect of frequency has been documented in healthy subjects [32,35,174] and clinical trials in specific clinical populations [13,18,24,33,42,47,49,66,93,99,108,115,145]. In general both HF-TENS and LF-TENS show similar effects. HF-TENS reduces analgesic consumption, pain intensity and McGill pain ratings in postoperative pain [18,47,93,145]. Similarly, LF-TENS reduces analgesic consumption, pain intensities and McGill pain questionnaire ratings in post-operative pain [18]. One study directly comparing LF-TENS and HF-TENS showed similar analgesia in people with post-operative pain [49]. Another study delivered simultaneous 2 Hz and 100 HZ TENS and showed decreased analgesic consumption and side effects but no change in VAS scores following total hip arthroplasty [93]. Both HF-TENS and LF-TENS equivocally reduced pain intensity in patients with chronic pain

conditions including low back pain [115], chronic prostatitis [99], chronic pelvic pain syndrome [158], neuropathic pain following spinal cord injury [24], fibromyalgia [42], and latent upper trapezius trigger points [66]. In summary, both LF-TENS and HF-TENS are effective for several outcome measures: analgesic consumption and side effects, pain intensity and unpleasantness, and multidimensional pain ratings.

Clinical TENS experiments often examine a single outcome - resting pain- as the main outcome. Recent work suggests TENS is less effective on resting pain but significantly reduces movement pain [42,145]. It would be expected that if pain during movement is decreased, function would increase. The portion of the hypothesis regarding movement pain and function was not accepted. All groups including placebo improved pain ratings and TUG times following a single TENS treatment and were not significantly different from each other. A prior study of TENS and knee OA pain shows a positive effect on TUG times [96]. Times were reported as 20-24s; while times in Experiment 2 were 12-14s, close to normal ($\leq$10s). Therefore, for less severe symptomatic OA the TUG may not be an appropriate measure to examine movement pain and function. Also, it may have been that our subjects did not present with high enough baseline pain. Nevertheless, this finding has assisted in protocol development for other experiments in our laboratory, some, currently ongoing. The six minute walk test, Iowa Gait Speed Test, functional reach, repeated sit-to-stand, and functional jaw opening have been utilized to examine the efficacy of our TENS interventions [42,97,98,142].

The other pain sensitivity outcome measures, CMPT, HPT or HTS, did not produce significantly different results when comparing the active and placebo TENS groups. The lack of changes in CMPT, HPT or HTS by TENS may be because these

measures are cutaneous stimuli, and they may not be sensitized by knee OA. Prior studies in our laboratory similarly show no effect of TENS on heat pain thresholds with concurrent increases in PPT in healthy controls [106]. Importantly, thermal outcomes may have been different if our subjects had presented with higher baseline VAS pain scores [9], or it may be that TENS is less effective in for heat pain. Alternatively, TENS may not affect cutaneous pain sensitivity to heat when the pathology occurs in deep tissue such as the knee joint.

We were able to adequately blind the subjects with the transient placebo (43% of subjects did not correctly identify the placebo treatment) and we previously show complete inability of the TENS allocator to correctly identify active or placebo TENS (Chapter 2). Experiment 2 was designed so the TENS allocator and outcome examiner were blinded by the protocol. The TENS units were coded (A, B, C) and the applicator (blinded to the code) picked the unit as determined by the allocation concealment envelope. All treatments (HF, LF, P) were applied at motor minus 10%, and the outcome examiner had no interaction with the TENS application. Thus, this was the first double-blind study on TENS of patients with a pain condition. Lastly, it should be noted that conversational interaction between examiners and subjects may lead to an inadvertent un-blinding of the examiner [51] , and future studies may want to consider evaluating blinding of the experimenters.

Chapter 4, Hypothesis 3

The hypothesis of “Skin impedance will be significantly lower at OSS sites as compared to SSS sites“ is supported by two independent methods measuring skin impedance at sites located by the examiner and classified as OSS compared to those

classified as sham sites. Importantly, the sites were measured on three different days on each subject. Attempts to measure skin impedance at acupuncture and sham sites have produced conflicting results and speculation has existed for decades regarding the existence of distinct electrical properties associated with acupuncture points. Acupoints can be characterized by either higher or lower resistance [89], and 63% of the 631 sites evaluated by experimenters were not significantly different from the skin in the surrounding area. Authors conclude that resistance measurements may not be ideal for point location for therapeutic purposes. This point is relevant in review of the results associated with the second hypothesis of Experiment 3

Chapter 4, Hypothesis 4

" PPT will be significantly increased when using electrode stimulation sites determined by the OSS method to deliver HF TENS as compared to HF TENS delivered over SSS and both will be greater than placebo TENS."

The most critical portion of the hypothesis is rejected considering there was no significant difference between PPT change scores when using OSS and SSS HF-TENS. Not surprisingly, both active TENS groups demonstrated significantly greater PPT changes when compared to placebo TENS. This finding is in concurrence with other experiments examining PPT changes in healthy human subjects following TENS treatment [32,34,35,39,41,122,182,183]. Each of these studies may have presented with a different methodology of determining electrode site application, yet the outcome measures are similar and reflect our findings as well. This experiment utilized stimulus intensities to subject tolerance and there was no significant difference in intensity when comparing the OSS and SSS treatments. In summary, these findings suggest that when

TENS is applied at an adequate intensity skin impedance is not a factor in TENS effectiveness.

Clinical Significance and Conclusion

The primary purpose of the three independent yet related experiments described above was to improve the clinical application of TENS for the management of pain. Clinical outcomes have the potential of demonstrating attainment of goals when proper dosing of an intervention is accomplished. TENS is one of many interventions utilized in the practice of physical therapy where parameters have not been established for optimizing outcomes. Specifically, clinicians need to understand the best options for pulse frequency, pulse intensity, electrode site, and duration for specific pain presentations in order to deliver the appropriate dose of TENS. Importantly, TENS is recognized as an intervention option for patients with demonstrated central sensitization [127] and in multimodal management for ambulatory surgery patients [56].

For patients considered to be opioid tolerant HF-TENS would be recommended in order to activate δ-opioid receptors as LF-TENS is less effective in this patient population. HF-TENS at 100 Hz was utilized in the original 1967 Wall and Sweet experiments [180], in numerous basic science and clinical experiments, and in the three experiments outlined above. Clinicians should have confidence in selecting 100 Hz when HF-TENS is desired. The frequency range for LF-TENS is typically considered 1-10 HZ. The frequency of 4 Hz used in Experiment 2 has also been used in many experiments. Typically this is referred to as “acupuncture-like TENS” [73,125,136,149,150]. In the past, this low frequency setting was routinely applied at high intensities and motor contractions were an expectation of correct treatment and necessary to activate opioid

receptors. Seminal work by Sluka and colleagues demonstrate that regardless of intensity (i.e. sensory or motor), LF-TENS is mediated by activation of μ-opioid receptors [164,165,167,178]. Further, repeated application of TENS at the same frequency and intensity, i.e. dose, produces analgesic tolerance [26,107]. Thus, combining HF-TENS and LF-TENS in a single session could alleviate analgesic tolerance to TENS [48].

When considering TENS dosing it is very clear that electrical stimulation delivered at higher intensities is critical to positive outcomes in reduction of pain and hyperalgesia. In Experiment 1, PPT changes were only significant in subjects who tolerated treatment amplitudes greater than 17 mA. In Experiment 2 we specifically chose to treat at motor minus 10%, strong sensory intensity, replicating parameters from our basic science experiments. It is possible that a greater effect could have been observed had we used either protocol for intensity in Experiments 1 or 3, (intensity set as maximally tolerated by the subject). In addition, in Experiment 3 we asked patients if they were comfortable and if we could increase the intensity every 5 minutes to avoid habituation. Previous work similarly shows greater analgesia with greater intensities [12,35,122]. This has been the standard protocol of subsequent clinical TENS experiments in our group and shows greater analgesia than not increasing intensity [42,106,107,132]. Clinicians should be confident in choosing the intensity dose for patients as maximally tolerated. They should also include instructions for patients to increase the pulse intensity to the highest level tolerable every five minutes for the duration of the treatment. The phenomenon of habituation has been suggested to describe this need to titrate intensity upward [45,132]. However, clinicians should also expect

some patients may have a degree of hesitancy regarding electrical currents delivered to the body, particularly when TENS is a novel experience for the patient.

The most under investigated parameter in TENS for pain management is that of electrode site selection. The one thing most authors agree upon is that there is not one superior method by which clinicians should place electrodes [73,125,136,150], and not all pain conditions will be best treated by using the same electrode selection method [113,121]. OSS is a technique that clinicians utilize to locate points on the skin with supposed lower impedance. If impedance is lower, conductivity into the deep tissues will be improved. We demonstrate the importance of stimulating deep tissue afferents to reduce hyperalgesia [141].

Even in the presence of significant differences in skin impedance at sham and optimal electrode sites, when TENS is delivered at adequate intensities there was no difference in the level of hypoalgesia attained when testing on the forearm of healthy subjects. For patient care, this further supports the idea of strong, tolerable intensity as the proper dose. Future experiments may find differing conclusions with regard to skin impedance, electrode site and analgesia with TENS when testing in patients with painful conditions.

Although clinicians will never apply placebo TENS for patient management, several important concepts should be considered with regard to the placebo effect. First, clinicians should be aware that the placebo effect should not be considered a negative or confounding consequence of *any* intervention. It is real as evidenced by activation of endogenous opioid pathways and should be used to enhance treatment efficacy [105,179,193]. The neutral and particularly negative presentation of any intervention

should always be avoided; and the honest, positive method of informed consent should be practiced each time any intervention is to be used in patient care [16].

TENS is a non-invasive treatment for pain which can be utilized alone or as an adjunct to pharmacological interventions. Under normal circumstances pain is protective and critical to survival. However, there are numerous instances where pain presents as a limiting factor in recovery from illness or injury. First documented by Wall and Sweet in 1967, TENS is a relative newcomer to the vast array of treatments employed to address the oldest medical condition known to mankind. Support for TENS parameters of frequency and intensity have been examined in partial fulfillment of the goal to improve the clinical application of TENS along with examination of multiple outcome measures in a translational experiment involving patients with a common pain condition. The experiment to address method of electrode site also improves clinical care by determining OSS does not offer significantly greater hypoalgesia in healthy subjects and suggests clinicians should choose sites where TENS will be well tolerated by the subject to allow for strong, non-painful levels of stimulation which may include motor contractions. Future experiments should address the parameter of duration and frequency of treatments, further examine the phenomenon of tolerance to TENS application and proper dosing to minimize its effect, and potentially evaluate electrode site selection in patients with a painful condition.

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