Protocol

Perineural Electrical Dry Needling Migraine Treatment Study

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1.0 Study Summary

Study Short Title/ Number	PNED for migraine headaches
Study Title	A Randomized Controlled Crossover study to Determine the Effectiveness of Peri-Neural Electrical Dry Needling (PNED) vs. Standard Care for the Treatment of Patients With Migraine Headaches.
Study Design	Random controlled cross over trial
Primary Objective	Determine the validity and treatment effectiveness of PNED for patients with migraine headaches
Secondary Objective(s)	Determine the affects of PNED for migraine headaches for patients who are and are not on a CGRP antagonist drug
Research Intervention(s)/ Investigational Agent(s)	Perineural electrical dry needling.
Study Population	Individuals in the community with migraine headaches.
Sample Size	30 individuals
Study Duration for individual participants	A total of 5 weeks (2 weeks of treatment, 1 week wash out period, 2 weeks of treatment)
Study Specific Abbreviations/ Definitions	PNED (perineural electrical dry needling)

2.0 Purpose and Objectives

2.1 The purpose of this study is to improve care and outcomes for patients with migraine headaches. It will help to offer patients non-pharmacological management of their migraine headaches and/or offer an option for those looking to decrease their current dosage of medication.

2.2 PNED will result in a decrease of reported pain intensity and frequency of patients with migraines.

3.0 Background

From current understanding of migraine pathophysiology, we know that it involves excitability of the trigeminovascular system. Intercranial vasculature containing nociceptor innervation consists of unmyelinated (c-fibers) and thinly myelinated (a-delta fibers) axons which hold vasoactive neuropeptides including substance P and calcitonin gene related peptide (GGRP). When a migraine occurs, there is a cortical spreading depolarization, which on a molecular level involves a release of ATP, glutamate, potassium, hydrogen ions, glia or vascular cells, and CGRP and nitric oxide by activated perivascular nerves. These substances, including CGRP diffuse to come in contact with nociceptors causing neurogenic inflammation (vasodialation), thus propagating a headache.

relevant preliminary data.

3.1 Electrical perineural dry needling causes the release of substance-P and CGRG predominantly from non-neural structures, facilitating a negative feedback loop to neural and neuroactive components of the target tissue. This causes a lowering of the levels of CGRP which in turn decreases the inflammatory component thought to play a role in migraine headaches.

Other studies have looked into other electro-analgesic treatments of both transcutaneous and percutaneous methods. Both types providing promising results in regards to decreased headache pain. This study seeks to investigate a specific protocol of PNED and its effects on migraine headaches.

4.0 Study Endpoints

4.1 This study will conclude once all 30 patients have been treated for 5 weeks.

4.2 While there is no secondary safety outcome identified, a secondary outcome of the study will include an analysis of whether the purposed treatment protocol differed from those patients who are and who are not currently taking a CGRP antagonist drug.

5.0 Study Intervention/Investigational Agent

5.1 This study aims at investigating a treatment protocol. <u>The device used is not investigational and currently in use as a treatment in physical therapy.</u> It involves use of an ES-130 by ITO (Japan) using a DC 9V battery producing an asymmetrical biphasic waveform. The unit has 6 available leads with alligator clamps, connecting to monofilament dry needle shafts of 15 or 30 mm length, 0.25 mm diameter.

5.2 Drug/Device Handling: The above-mentioned device is available to all trained staff at this site for use in patient care

6.0 Procedures Involved

This Study will be a random controlled crossover consisting of a standard care arm and standard care plus perineural electrical dry needling. Each arm is defined below:

Standard care will consist of standard physical therapy care which may include the following: cervical or thoracic manipulation or mobilization, muscle stretching, muscle strengthening, *electrical trigger point dry needling (see section 15), soft tissue release and prescribed therapeutic exercises.

Perineural electrical dry needling will consist of standard care plus perineural electrical dry needling. The key difference will be that instead of trigger point electrical dry needling, perineural needling as described below will be done.

In regards to perineural electrical dry needling the following regions may be treated: frontalis muscle with needle placement either along the supraorbital or supratrochlear nerve pathway, semispinalis capitus muscle along the greater occipital nerve pathway, Sternocleidomastaoid muscle with placement along the lesser occipital nerve pathway. Patients will be placed in either a supine, prone or side-lying position based on needle placement and patient comfort. A monofilament needle of 15 or 30 mm length, 0.25 mm diameter will be placed utilizing the therapist's dominant hand following palpation of correct needle location. An IES unit will be used to conduct an electrical impulse. The unit used will be an ES-130 by ITO (Japan) using a DC 9V battery producing an asymmetrical biphasic waveform. The unit has 6 available leads with alligator clamps, connecting to needle shafts. Parameters of PNED will include intensity set at a strong yet comfortable setting according to patient feedback. Treatment duration will be 15 minutes. Treatment frequency will be set to Medium at level 8 (80 Hz). Parameters will be set to elicit a sensory response.

Following DN procedures patients will be given follow-up instructions to minimize any complications, including instruction to rest, hydrate and apply ice as needed if any muscle soreness occurs.

Study subjects will be randomized into a treatment arm of the study via random number generator decided prior to the study beginning in which numbers 1-30 will be randomly generated. All odd numbers will correlate to the investigational arm of the study, for example, the numbers 3,17,8, 19 would equate to patients placed in the investigational arm, investigational arm, standard care arm, investigational arm.

6.1 Describe:

- Any patient who is deemed to have any contraindications to dry needling will not receive this treatment. Patients will be treated by a certified dry needling practitioner using sterile, individually sheathed dry needles.
- Device used: Please refer to section 5.1. This unit is needed in order to perform PNED.
- The source records that will be used to collect data about subjects. Data collection sheet, neck disability index.

6.2 Data to be collected: VAS/pain rating, neck disability score, frequency of headaches.

7.0 Sharing of Results with Subjects

7.1 Describe whether results will be shared with subjects or others: Patients will be actively in treatment and aware of whether their migraine headaches have improved or not. Patients will be able to view their specific results if they choose.

8.0 Study Timelines

8.1 Describe:

- Each subject will be involved in the study for 5 weeks consisting of treatments of 2 days per week for 2 weeks, a washout phase, followed by crossing over to the opposite treatment arm of the study for 2 weeks. The duration anticipated to enroll all study subjects is unknown and reliant on both direct access patient care and referral from other providers. A wide possibility can include a period of 2-5 months.
- Assuming IRB approval and recruitment of participants starting in February 2020, a completion date for this study is set at November, 2020.

9.0 Inclusion and Exclusion Criteria

9.1 individuals will be screened for eligibility, based off of an initial interview and a review of their past medical history. As these participants will be patients, this initial interview will take place as part of a subjective H &P portion of their first evaluation.

9.2 ***Eligibility criteria:***

Men and women age 18 to 100 years old with acute or chronic manifestation of migraine headaches with pain rating of 30 mm or greater on a visual analog scale (VAS) or subjective rating of 3/10.

Exclusion Criteria:
Participants will be excluded if any of the following applies: History of epilepsy, currently pregnant, needle-phobia, unstable psychological status, compromised immune system, metallic allergy, haven't eaten within the past 3 hours, inability to lie in prone, supine or side-lying, pregnant or trying to become pregnant, inability to consent or understand English.

9.3 Vulnerable members will not be included in this study which includes the following: Adults unable to consent, individuals who are not yet adults, pregnant women, prisoners.

10.0 Local Number of Subjects

10.1 The total number of subjects to be accrued locally is 30.

11.0 Recruitment Methods

11.1 Study subjects will be accessed either via health care provider referral from physicians, physician assistants, nurse practitioners, dentists, optometrists, physical therapists or from patient to patient referrals. Potential Participants may also be contacted by flyers, information sheets, or over the phone. Most subjects will be identified from patients the PI will be treating or has treated in the past. The PI will present the study to possible subjects in person or possibly contact by phone. In addition, colleagues may refer possible subjects by presenting the study verbally or using the flyer and the PIs contact information. If they agree to be contacted, the PI may contact them to follow up.

The PI will determine general eligibility before presenting the full study to subjects. Most information will be known to the PI if he is treating the patient, or is available in the EMR. Some questions may be asked (see attached) but responses will not be recorded.

11.2 The source of patients will be patients at the clinical site

11.3 Potential subjects will be identified via clinician referral or based off of the initial evaluation/appointment as a physical therapy patient, if being seen via direct access and not referral.

11.4 Recruitment materials attached as part of the IRB application.

12.0 Withdrawal of Subjects

12.1 Subjects will be withdrawn from research without their consent if 1. It is deemed medically necessary and in the best interest of the patient and 2. If the subject is non-compliant with the study, including but not limited to: no showing to 3 or more appointments.

12.2 There is no procedure for termination. Participants will have the option to remain as patients and continue to receive treatment.

12.3 If a subject decides to withdraw from the research, all data collected concerning that subject will be promptly terminated.

13.0 Risks to Subjects

13.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

Risks may include the following: 1. Pain or discomfort, 2. Needle break, 3.Medulla oblongata puncture, 4. Vaso-vagal response "needle shock" or fainting, 5. Infection.

In regard to the risks mentioned above:

Pain associated with using the ES-130 device will be minimized with slowly

ramping the intensity of electric impulse to be within the patients comfort level while observing the patient's verbal and non-verbal response.

(moderate-low probability)

A needle break will be avoided by using high quality needles and not autoclaving reusable needles. The needles used are seirin brand needles which are sterilized and individually sheathed.
(low probability)

Medulla oblongata puncture will be avoided by utilizing proper techniques in the procedure of dry needling and proper sized needles per above. The primary investigator who is performing the treatments is certified by the Dry Needling Institute and has 5+ years experience with DN.
(low probability)

A vaso-vagal response will be minimized with patients placed in a prone side lying or supine position and not seated when dry needled. Signs of potential fainting following treatment will be observed: turning pale, weak pulse, feelings of being unwell, sweating, having a sense of giddiness, weakness, palpitations, nausea or vomiting will be monitored. Precautions will be made to avoid causing a fainting response by making sure the patient is not overly anxious, hungry (especially if diabetic) or fatigued prior to the procedure. If signs and symptoms appear, needles will be removed and the patient will lye supine with legs elevated.

(low probability)

Risk of infection will be reduced with the treatment provider utilizing proper hand washing prior to performing the procedure, wearing gloves and using an alcohol wipe to cleanse the treatment area.

(low probability)

*It should be known, again, that this treatment is currently in use in physical therapy and not experimental. This study is set to identify whether the protocol for treatment is valid and effective for patients with migraine headaches.

13.2 Aside from those mentioned above, no unforeseeable risks are identified.

13.3 Dry needling is contraindicated when pregnant. Subjects will not be included if they are pregnant or trying to become pregnant.

13.4 There will be no risks to anyone who is not a subject.

14.0 Potential Benefits to Subjects

14.1 This crossover study will allow all patients to receive the experimental treatment and potentially benefits from reduced migraine pain and reduced frequency and intensity of headaches. Based on the outcome observed from using the treatment protocol on current and past non study related patients there is a high probability of achieving a favorable result lasting anywhere from 1-6 months.

15.0 Data Analysis

Null hypothesis: There will be no difference between treatment groups in regard to pain and neck disability rating including frequency and intensity of headaches. Alpha will be set to 0.05

This will be a random controlled crossover study.

We will use two different study periods that will each begin with a baseline assessment to compare the two different treatments. Study subjects will have baseline assessments, then receive the treatment they were randomized to: (the standard treatment arm or standard treatment and perineural electrical dry needle treatment arm) and then be assessed at the end of the two week treatment period to see if there has been a change in neck disability index or pain rating. After a 1 week washout period the study subjects will again have a baseline assessment of their pain and neck disability index and then crossover into the other study treatment arm for two weeks of treatment and again will be assessed at the end of the treatment period to see if there has been a change in neck disability index or pain rating.

Primary Outcomes

We will use the Wilcoxon Sign-rank test to determine if perineural electrical dry needles significantly improve pain when compared to standard treatment. A paired t-test will be done to determine if there is a significant improvement in the disability index following perineural electrical dry needle treatment when compared to standard treatment.

Secondary Outcome

Because this is a small trial it is unlikely that we will be able to determine if migraine drugs significantly modify the effect perineural electrical dry needle treatment has on pain and the neck disability index. However we will look for any trends in interaction between perineural electrical dry needle treatment and migraine drugs using exploratory data analysis and box plot comparisons

Assuming we recruit 30 study subjects, using a one-sided P value (0.025), the study will have power over 0.80 to detect a 50 % difference among treatment groups effects on the neck disability index.

16.0 Data Management and Confidentiality

16.1 Each subject will have a corresponding data collection sheet which will be kept in a secure file cabinet. The P.I will have access to this document. As subjects will also be patients, data will also be made part of their chart using the EPIC documentation system.

16.2 Quality control of data will be done via the assistance of a data safety individual, Sara Kotchi, who will assist in the integrity and interpretation of the data via access to Carroll University's statistical analysis capabilities.

16.3 Describe how data or specimens will be handled study-wide:

- Data will include, whether the subject is currently taking a CGRP antagonist drug, frequency and intensity of headaches, neck disability index score and rating of pain.
- Data will be stored via paper collection sheet in a secure cabinet and via EPIC
- Data will be stored for the duration of the study.
- The P.I. and research associate will have access to study data. Please note that once the research associate has the data, she will be blinded to the data, there will be no "identifiers" associated with any person.
- The P.I. is responsible for data transmission.
- Paper copies of data will be transmitted via in-person transfer.

17.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

17.1 Describe:

Any adverse effect as part of this research will be documented in the patient's chart in EPIC. Any adverse effects will also be documented on the data collection sheets. The research associate will have access to the data collection sheets and will assist in monitoring for adverse effects. Both the P.I. and research associate will communicate any adverse effects of this research to the IRB.

- Safety data and untoward events will be reviewed once per month.
- Safety information will be collected during study visits/patient treatment encounter.
- The data will be collected 2 days per week for 4 weeks with attention to safety beginning after the initial treatment.
- The P.I and research associate will review the data.
- Data will be reviewed 1 time per month.
- There is no current statistical test for analyzing potential harm to subjects.
- Conditions that trigger an immediate suspension of the research will include any noted harmful or adverse event that is a result of performing this research.

18.0 Provisions to Protect the Privacy Interests of Subjects

18.1 Subjects in this study will be patients, thus privacy interests will be kept strictly to a patient-provider relationship.

18.2 Subjects will be "at ease" as he/she will be involved in this research as a patient. There will be no intrusiveness as subjects will be receiving treatment at a location, at a time and by a provider of their choosing.

18.3 As subjects will be patients, the P.I. will have access to patient records via EPIC for any relevant data pertaining to their care.

19.0 Economic Burden to Subjects

19.1 As patients, participants will be responsible for the cost of the treatment they receive in physical therapy.

20.0 Consent Process

20.1 Consent will be obtained. Please refer to the consent form attached.

- Consent will take place in a private treatment room.

- As patients, subjects will have the option to "think It over" and discuss further any questions concerning consent at their next scheduled appointment.
- Regarding ongoing consent, Patients will be asked each treatment visit regarding whether they have any questions or concerns regarding this study.
- Whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:
    - Consent will be obtained by the P.I.
    - The time devoted to a consent discussion may include, prior to a patient's scheduled appointment, during the scheduled appointment, after a scheduled appointment.
    - Steps that will be taken to minimize the possibility of coercion or undue influence, include a clear explanation of the voluntary nature of this study and the fact that the subject is able to receive the same care as the experimental group without being in the study.
    - Time will be taken to clearly explain this study allowing for subjects to ask any questions that they might have as to make sure they clearly understand the study.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

- No waiver or alteration of consent will be made. All patients will sign a consent form, attached to the IRB application.

20.0 Process to Document Consent in Writing

20.1 The consent form/template provided by the Ascension IRB will be used when obtaining consent.

20..2 The consent form is attached to the IRB application

21.0 Setting

1.2 Research will be conducted at a clinic located at 2500 West Layton Avenue, Milwaukee, WI. 53221 in the rehabilitation department in suite 160.

- Any patients who are receiving care, and or friends and family of patients in the clinic may be made known of this study.
- Research procedures will be provided in a private treatment room.
- No advisory board aside from the Ascension IRB will be involved in this study.

22.0 Resources Available

- Subjects will be current patients with recruitment depending on clinician and or self-referral.
- Time devoted to this research will include that of working as a provider, approved time (2 hours per week) as this research is part of the Ascension Rehabilitation Master Clinician program and my own personal time. It is estimated that 4-6 hours per week will be devoted to this research.
- The facility is an outpatient clinic.
- In the building of which this research will take place, there is primary physician services. The closest hospitals are St. Francis Hospital and Franklin Hospital.
- Prior to performing the actual research the P.I. and research associate will discuss the research procedures, duty and function.

23.0 References

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