**Protocol and Statistical Analysis Plan**

**Study Title**: The Usefulness of Osteopathic Manipulative Medicine in the Management of Headaches with Post Concussion Syndrome

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**Protocol (last update on January 11, 2019)**

A concussion, or mild traumatic brain injury (i.e. mTBI) is a complex pathophysiologic process that is caused by traumatic biomechanical forces to the head [1]. There are an estimated 1.6–3.8 million sport-related concussions every year in the United States [2]. However, this likely underestimates the true incidence, as there are many mild traumatic brain injuries that go unreported or unrecognized [3]. The term concussion is synonymous with mild traumatic brain injury, however the term concussion may be used to describe instances where the individual experiences transient alteration in mental status, such as from a sports related head injury, whereas a mild TBI is used in the general medical context [4]. A mTBI is defined as an injury with Glasgow Coma Scale of 13–15 with loss of consciousness less than 30 min and post - traumatic amnesia less than 24 hrs. Overall, terms such as concussion, mild head injury, and mild TBI are often used interchangeably to describe the physical injury itself as well as its immediate and later symptomatic consequences [5].

Mild TBI results in a constellation of physical, cognitive, vision, emotional and sleep-related disturbances. Signs and symptoms are broad and include headache, dizziness, gait disturbance, nausea, vomiting, photophobia, trouble focusing, and fatigue. Symptoms may last from several minutes to days, weeks, months or even longer in some cases [6,7]. Headache is the most common physical complain after traumatic brain injury (i.e. TBI) and historically is more common in patients with mTBI, with incidence ranging from 30-90% [8]. Current treatment of those with mTBI has been physical and cognitive rest, as about 80-85% of patients with a concussion will recover to their neurological baseline within 1-2 weeks with this treatment [2]. Similarly, it is believed that most patients with Post Traumatic Headaches (PTH) recover within a few weeks. However, studies have shown 15-42% of patients reporting PTH at 3 months, and 36% at 6 months [8].

Patients who do not recover after three months after a mTBI are categorized as having post concussive syndrome (PCS), which affects approximately 15% of patients [6,7]. A longitudinal study assessing 285 patients with PCS found that 27% of the population studied eventually recovered and 67% of those who recovered did so within the first year [8]. In this study, no patient recovered who had PCS lasting 3 years or longer. Symptoms included persistent headaches and depression. Guidelines for management of PCS have not been completely established, and patients are generally recommended to continue physical and cognitive rest.

Osteopathic Manipulative Therapy (OMT) is a nonpharmacological, noninvasive form of manual medicine. Osteopathic practitioners use a wide variety of therapeutic manual techniques to improve physiological function and help restore homeostasis in the body. There is a structural assessment is to identify possible abnormalities of tissue texture. Areas of asymmetry and misalignment of bony landmarks are also evaluated, along with the quality of motion, balance, and organization. These asymmetries, also known as somatic dysfunctions, are then treated by a variety of manual treatments, administered by osteopaths [10].

There has been research showing the effectiveness of OMT in the treatment of various types of headaches. A recent systematic review assessed 6 studies with various

types of headaches including tension-type headaches, migraine headache, all which showed statistically significant changes in various outcome measures. Outcome measures included the Headache Impact Test (HIT-6) score, headache pain intensity / frequency, and HRQoL [10]. A randomized control trial studied 62 patients with tension-type headaches, and showed that manual therapy techniques to the suboccipital region offered a positive improvement in some aspects of the patient's quality of life [11]. Another systematic review assessing migraine type headaches showed a preliminary low level of evidence that OMT is effective in the management of headache [12]. Overall, studies concluded that more rigorous designs and methodology are needed to strengthen the evidence that OMT has benefit in headache management.

Less has been studied regarding OMT in the treatment of symptoms related to concussion and post traumatic headaches. In our review of the literature, three case reports were found of OMT in the treatment of concussion symptoms. One case assessed a 16 year old female who had a chief complaint of headaches, and had significant improvement of overall symptoms after treatment [13]. Another case report examined a 27 year old man with vestibular symptoms, who had symptomatic improvement after OMT [14]. A third case described OMT to a 50 year old female with mTBI, and showed improvements in HIT-6 scale [15].

In the review of literature, we did not find any studies specifically looking at headaches related to post concussive syndrome. However, as shown above, such headaches can persist for a significant amount of time and adversely affect patient's quality of life. With this study, we seek to study the effect of OMT on this population. The techniques that will be utilized in our study are described below:

1. Cervical muscle energy using postisometric relaxation - Muscle energy is a form of OMT that engages the patient to voluntarily use targeted muscles on request. After physical assessment of the patient's neck and paraspinals, the physician will place him/her into a precisely controlled position in a direction towards the tight or restricted soft tissue barrier. The physician will then instruct the patient to contract equally against the offered counterforce by the physician. This is an isometric contraction where the distance between the origin and insertion of the muscle remains the same. As the muscle contracts there will be a stretch of internal connective tissues. Golgi tendon organs will sense this change in tension and cause a reflex relaxation of the muscle fibers; similar to a negative feedback loop. This reflex relaxation of the muscle will then allow the physician to passively stretch the patient's previously tightened muscle into an improved range of motion in all planes of motion. This process will require isometric contraction
   for 3-5 seconds, then relax, and repeat for a total of 3 repetitions. Overall objective is to stretch tightened muscles of the neck and improve range of motion and pain tolerance.
2. Myofascial Release of cervical paraspinals - Myo (muscle) and fascia (fascial, connective tissue) release involves a similar approach to muscle energy, in that, the objective is to engage restrictive barriers. However, the treatment is more superficial directed toward fascial tissues that encompass and compartmentalize all structures of the body. Fascia is normally a flexible and pliable tissue, but under physical trauma or stress the fascia may become tight and restrictive. Steps of the myofascial release will include the physician palpating the patient's neck to identify

an area of restriction. Restrictive barrier will be identified as muscle tension, tenderness or decreased movement of tissue. Once identified, the physician will then move myofascial tissues toward a restrictive barrier, directly applying a traction along the long axis of the muscle being engaged. He will then add transverse forces (clockwise or counterclockwise) towards the restrictive barriers. The patient will be asked to provide slow deep breaths to enhance a relaxation and release of these tight tissues. The physician will then await a "release". This is a palpatory finding that requires a skilled practitioner to assess. It will consist of a feeling that the previously noted tight tissues release in pressure, or "melt away". This may take several attempts. The goal of this approach is to restore functional balance to all integrative tissues in the musculoskeletal system, improve range of motion, pain tolerance and improve lymphatic flow by removing myofascial restrictions.

3. Sub-occipital Release - Sub-occipital release is a more focused form of myofascial release that engages the sub-occipital muscles. This technique focuses on releasing the fascia surrounding the sub-occipital muscles that attach to the C1- C2 vertebrae of the neck. With the patient laying on their back, the physician will place his/her hands just below the occiput or base of the skull. The physician will then cradle the occiput and apply gentle finger pressure using only the fingertips up into the sub-occipital space. This gentle pressure will be continued until tissue starts to soften and release; approximately 30 seconds to one minute of pressure. As the tissue softens, the head will extend back and rest in the physicians palms. The goal of this technique will be to improve pain, stiffness and headaches. [16]

Potential participants, after signing an informed consent, will be identified based on the following criteria:

- Sustained a concussive injury at least 3 months ago
- The injury did not involve any diagnosed bleeding within the brain
- You did not lose consciousness for longer than 30 minutes
- You have no history of severe migraine headaches prior to the injury
- Were 18 years of age or older at the time of the injury
- Are currently receiving treatment as an outpatient with Dr. Christine Greiss
- You are not currently receiving IV infusions of medications from a headache specialist at the time of treatment
- You do not have a history of rheumatoid arthritis

The research protocol will be designed in the following way:

1. A goal of 15 patients are to be enrolled in the study as well as an equal number of 15 control subjects who will not participate in osteopathic treatments. The selected patients will be seen for a total of three visits of which the first two sessions will be treatment visits. All visits will be in 4 week intervals.
2. Patients selected to participate in the study will undergo a musculoskeletal examination of the cervical spine. Testing will be comprised of :

a. Range of motion testing involving cervical rotation, lateral side bending, flexion and extension.
b. Muscular palpation of the cervical paraspinals for hypertonicity of the muscles and/or tenderness.

3. The patient will then be placed supine on the examination table after which treatment will commence.
4. Treatment sessions will last for 5-10 minutes each and will be performed by one osteopathic physician. In the time allotted, three OMT techniques will be performed: cervical muscle energy, myofascial release of the cervical paraspinals and a suboccipital release. The three physicians will have met prior to treatment to standardize protocol.
5. Patients will be asked to complete the Headache Impact Test (HIT-6) at visit 1 and 2 between about 6 weeks. All patients will also quantify their pain using a pain scale before and after treatment.
6. Change scores between pain scales between treatments will be assessed, and improvements between HIT-6 scores will be analyzed for statistical significance.

**Recruitment and Informed Consent**

Participants will be recruited from individuals who are being evaluated by Dr. Christine Greiss for Post Concussive Symptoms.

Written informed consent will be obtained from all enrolled participants accordance with Institutional Review Board (IRB) policies. Potential participants will be informed that there is no penalty for refusal to participate. A quiet private space will be available for the consent process and there will be no time limits. Dr. Christine Greiss, the attending physician, as well as the residents participating in the study will be available to answer any questions or concerns that may arise.

Consent will be in a language that is easily understood by most individuals with at least a $6^{th}$ grade education and each participant/proxy/informant will have a checklist to follow to ensure they understand study procedures. All participants will be informed that the purpose of the study is to help the participants pain and headaches, and will be informed regarding the resident education component of the study.Time and effort commitments
required for study participation will be explained. Verbal feedback will be solicited from potential participants about their understanding of the study, its risks, and potential benefits prior to completion of the written informed consent form. Each potential study participant will be asked to state in his/her own words what the purpose of the study is, what he/she is expected to do, and what the risks and benefits are.

All potential participants (or designated family member/legal guardian) will be given a copy of the written consent form. Prior to signing the consent documents, all potential participants will be given the opportunity to review the consent document, discuss it with whomever they choose (including the study investigators), and take as much time as they need to consider the information that has been presented to them in order to make an informed decision.

**Potential Risks**

There are no anticipated physical or medical risks associated with participation in the study. There will be no high velocity or high impact techniques that would cause any harm. There may involve some temporary discomfort during the procedure and worsening of headache and neck pain. There is very little risk of any foreseeable psychological, social, legal, or financial risks or harms that might result from participating in this research study. There is very little risk of any orthopedic or musculoskeletal injuries that would result from the treatment.

**Protection Against Risks**

All treatment will be conducted by osteopathic physicians (Doctors of Osteopathy i.e. DO), and residents will be supervised under the attending physician Christine Greiss, DO.

Participants will be informed at the time of consent that they will be offered treatment by JFK Medical Center in the event of a medical emergency, although the costs of this treatment will not be included as part of the research. Participants will be informed that they can withdraw their consent to participate at any time during the study without any consequences to them and their access to medical services.

Confidential information will be protected by separating identifying material from data files and securing files in locked cabinets and/or password protected encrypted electronic files. JFK-JRI has internal security measures to further protect digital data, including identifying medical and clinical data, as per HIPAA requirements. Participants (or proxies) will be informed that identifying records may be inspected by the sponsoring agency or by the IRB and, therefore, absolute confidentiality cannot be assured.

**Importance of the Knowledge to be Gained**

We anticipate that the information gathered will make a significant contribution to the knowledge and understanding of the treatment of headaches with OMT. We hope that the treatment will improve symptomatology. We hope to provide an educational component to the other Physical Medicine and Rehabilitation residents in the program as well to increase the awareness and use of OMT in clinical practice.

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**Statistical Plan (last update on July 15, 2017)**

JMP version 14.1 (SAS Institute Inc) was used for statistical analysis. Descriptive statistics (mean, median, SD) and graphical (box plots, bar charts) methods were used. For the treatment group, a paired Wilcoxon signed rank test was performed to assess the change in VAS data from pretreatment to posttreatment. With 10 patients, we had 89% power to detect a change of 2 in the VAS scores from pretreatment to posttreatment, assuming a 2-sided significance level of 5% and a standard deviation of 2 (effect size =1). The Wilcoxon rank sum test for continuous (eg, age) and discrete (eg. variables (eg, change in HIT-6 scores, time from injury to visit [months]) and the Pearson x2 test for categorical variables (eg, mechanism of injury, history of prior MTBI) were performed for comparison of the treatment and control groups. With 20 patients (10 per group), we had 80% power to detect a difference in the means of 10 between the groups in HIT-6, assuming a standard deviation of 8, and a 2-sided significance level of 5%. Two-sided P value <.05 was considered statistically significant.