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Hypothetical Link Between Osteopathic Suboccipital Decompression and Neuroimmunomodulation

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Abstract

Emerging evidence has begun to depict the molecular mechanisms by which inflammation is regulated via the vagus nerve. Specifically, inflammation can be controlled by neuroimmunologic circuitry, dependent upon vagal afferent and efferent fibers, operating in a reflexive continuum. This neuro-immune reflex, known as the inflammatory reflex arc, has some control on serum concentrations of numerous molecular mediators of inflammation such as C-reactive protein and interleukin-6. Importantly, both of these inflammatory proteins are elevated in acute ST-elevation myocardial infarction and are associated with worse cardiac sequelae. Suboccipital decompression by osteopathic manual treatment has been demonstrated to enhance vagal output to the heart, as measured by increased high frequency spectral power of heart rate variability, in a statistically significant manner further supported by a significant decrease in the low-/high frequency spectral power ratio among healthy adults compared to sham treatment and time control. Considering this association, we postulate that suboccipital decompression may stimulate the efferent branch of this vagal-mediated reflex, the cholinergic anti-inflammatory pathway, thereby suppressing C-reactive protein and interleukin-6 levels post-ST-elevation myocardial infarction. Furthermore, we provide a detailed clinical study that can determine the validity of our hypothesis.

Keywords: Neuroscience; Osteopathic manipulative medicine; Neurorehabilitation; Vagus; Inflammatory reflex arc; Inflammation; Cytokines

Introduction

Substantiation of osteopathic manual treatment (OMT) has been primarily associated with the physician's post-treatment observation as well as patient-reported outcomes such as improvements in pain scales, muscle tonicity, symmetry,

tenderness, or articular range of motion [1]. Nevertheless, the osteopathic community has long-recognized that OMT can be utilized to improve autonomic insufficiency [2]. The anatomical relationship of vagal efferents to the cervical musculature at the base of the occiput may impart some credibility to this hypothesis; however, there is little objective evidence in the osteopathic literature to confirm this postulation [3-5]. Although the literature establishing a relationship between OMT and changes in autonomic tone is sparse, a study recently demonstrated that suboccipital decompression improves vagal output to the heart, as measured by heart rate variability spectral power, in a statistically significant manner [3].

Suboccipital decompression is an OMT technique that targets the atlanto-occipital junction and overlying cervical musculature [3]. It is thought that this technique treats articular compression between the occiput and the atlas, which may impede the function of the vagus nerve [3]. The vagus nerve is in proximity to the cervical musculature in the suboccipital region of the neck; therefore, it is reasonable to deduce that native inflammation, muscle hypertonicity, muscle spasm, or edema may cause compression on the vagus nerve, thereby impeding vagal afferent and efferent activity [3]. Giles et al hypothesized that suboccipital decompression enhances vagal output to the heart as measured by indices of heart rate variability [3]. They demonstrated that suboccipital decompression enhances vagal output to the heart, as measured by increased high frequency spectral power of heart rate variability, in a statistically significant fashion further supported by a significant decrease in the low-/high frequency spectral power ratio among healthy adults compared to sham treatment and time control [3]. The OMT used specifically consisted of 5 minutes of kneading the cervical musculature (applying a perpendicular force to the long axis of the muscle) followed by 2-3 minutes of suboccipital decompression [3]. For sham treatment, fingers were placed as near as possible to the occipital condyles, with no tension applied, for 8 minutes [3]. In the time control, subjects had no physical contact for 15 minutes [3]. Heart rate variability was not observed prior to each intervention [3].

Acute ST-elevation myocardial infarction (STEMI) causes pathologic inflammation that may often lead to further cardiac complications such as pericarditis or Dressler's syndrome. Emerging evidence has begun to depict the molecular mechanisms by which inflammation is regulated via the nervous system [6-18]. Specifically, inflammation is controlled by neuroimmunologic circuitry, dependent on the vagus nerve, operating in a reflexive continuum. Known as the inflammatory reflex arc, this pathway exhibits an afferent and efferent arc: both of which derive from vagal nerve fibers [7-9]. The afferent arc is comprised of vagal receptors detecting specific ligands indicating injury [7-9]. An activated afferent arc will initiate the efferent arc, the cholinergic anti-inflammatory pathway, which regulates systemic inflammation [7-9]. This neuro-immune reflex has some control on serum concentrations of numerous molecular mediators of inflammation such as C-reactive protein (CRP) and interleukin-6 (IL-6) [7-14]. Importantly, both of these inflammatory proteins are elevated in acute STEMI and are associated with worse cardiac sequelae [19]. Considering that suboccipital decompression can significantly increase vagal output, we suggest potential neuroimmunomodulation of this reflex with suboccipital decompression. We postulate that suboccipital decompression may stimulate the efferent branch of this vagal-mediated reflex, the cholinergic anti-inflammatory pathway, thereby suppressing CRP and IL-6 levels post-STEMI linking suboccipital decompression to cholinergic anti-inflammatory pathway stimulation.

While measures of heart rate variability showed significant changes with OMT directed at the vagus nerve in healthy adults, previous research attempting to characterize changes in heart rate variability among particular cardiac illnesses have been unsuccessful [3]. Serum markers of inflammation may be the optimal way to assess changes in vagal activity among individuals with cardiac conditions [19]. Vagal output has been demonstrated to control the activity of the cholinergic anti-inflammatory pathway, which suppresses the release of cytokines including IL-6 and CRP [7-14]. Therefore, we reason that suboccipital decompression may increase vagal efferent activity, which will increase the activity of the cholinergic anti-inflammatory pathway thereby suppressing IL-6 and CRP levels, and, to at least some extent, suppress systemic inflammation.

The vagus nerve activates the cholinergic anti-inflammatory pathway via projection to the celiac ganglion, not the heart [6-18]. Although it would be ideal for previous OMT studies to indicate an association between suboccipital decompression and stimulation of vagal efferents projecting to the celiac ganglion, there are currently no such studies that demonstrate this relationship in the osteopathic literature. However, hand placement during suboccipital decompression, as near as possible to the occipital condyles, and proximity of vagal efferents traveling at the base of the occiput lends us to reason that all "unbranched" vagal efferents traveling here may be subject to stimulation. This includes vagal efferents projecting to the heart and, importantly, the celiac ganglion, among many other structures [3,7-14]. It is worth mentioning that vagal efferents branching in proximity to the occipital

condyles (e.g., pharyngeal branches to pharyngeal plexus, external laryngeal nerve, and the right recurrent laryngeal nerve) may not necessarily be subject to stimulation with suboccipital decompression [20].

Proposed Clinical Study

Hypothesis: We postulate that suboccipital decompression can stimulate vagal efferent fibers projecting to the celiac ganglion, which will stimulate the cholinergic anti-inflammatory pathway and suppress CRP and IL-6 levels in the patient's post-STEMI.

Treatment and control groups: This study will consist of 150 patients admitted to a hospital for acute STEMI with 50 patients randomly assigned to each group. The study will be 5 days in length for each patient. A single blind study will be performed. Patients will not be told the group that they have been placed in. Treatment and control groups will be similar to those utilized by Giles et al [3]. The OMT treatment group will consist of 5 minutes of kneading the cervical musculature followed by 3 minutes of suboccipital decompression [3]. The sham treatment group will consist of fingers placed as near as possible to the occipital condyles, with no tension applied, for 8 minutes [3]. The time control treatment group will consist of patients subject to no physical contact for 15 minutes [3]. Prior to treatment, all patients should lay comfortably supine. In order to avoid heterogeneity of OMT between osteopathic physicians, this study will consist of three physicians with one physician assigned to each group of patients.

Inclusion criteria: Acute STEMI manageable by medication with or without percutaneous coronary intervention.

Exclusion criteria: Acute STEMI requiring coronary artery bypass graft surgery, previous STEMI, vagotomy, splenectomy, splenic neurectomy, implanted or transcutaneous vagus nerve stimulator, and history of autoimmune disease, medial arcuate ligament syndrome, additional inflammatory pathology, smoking/illicit drug use or pregnancy.

Treatment protocol: Patients should receive the standard of care for treatment of STEMI throughout this study. The first 24 hours will consist of no OMT as serum IL-6 and CRP levels are still rising (peaking approximately 1 day post-STEMI) [19]. The first blood sample should be collected from patients at 24 hours post-STEMI (baseline) prior to performance of any OMT. Starting 24 hours post-STEMI, patients will receive an intervention (suboccipital decompression or sham or control conditions) 3 times per day, every 4 hours, for 4 days total. Blood samples will be taken subsequent to each treatment on days 1-4 of intervention (hospital days 2-5) A blood sample will also be taken 2-weeks post-STEMI as a follow-up time point.

Molecular diagnostics: ST-elevation myocardial infarctions significantly increase serum IL-6 and CRP levels [19]. Importantly, both of these cytokines have been shown to be regulated by the cholinergic anti-inflammatory pathway [7-14]. Serum IL-6 and CRP levels peak approximately on day 1 post-STEMI and can stay elevated for weeks [19]. In measuring the concentration of serum cytokines, it is important to note that

relative to the high threshold of activation for central receptors of vagus, peripheral activation can be achieved with lower cytokine concentrations [7-9]. This implies that molecular diagnostics utilized to measure serum IL-6 and CRP concentrations must exhibit a substantial degree of sensitivity. Therefore, we recommend use of a multiplex enzyme-linked immunosorbent assays to measure serum concentrations of CRP and IL-6 [21-25]. Furthermore, cytokines not regulated by the cholinergic anti-inflammatory pathway will serve as a negative control. Specifically, cytokines released by type 2 helper T cell, including IL-4, IL-5, and IL-13, will be used as the negative control(s) [26].

Conclusion

Here, we have suggested that suboccipital decompression may stimulate the efferent branch of the inflammatory reflex arc, the cholinergic anti-inflammatory pathway, thereby suppressing systemic inflammation. Demonstrating a relationship between suboccipital decompression and suppression of systemic inflammation, via stimulation of the cholinergic anti-inflammatory pathway, could provide a supplementary treatment option that may benefit patients suffering from acute and chronic inflammatory pathologies.

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