Effect of Autonomic Nervous System Recovery from Sympathetic Challenge Using Osteopathic Cranial Manipulative Medicine – A Pilot Study

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ORIGINAL CONTRIBUTION

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Disclosures: none reported.

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Introduction

Throughout the history of osteopathic manipulative medicine physicians have used specific treatments to affect human physiology. In early osteopathic literature, there are references that specific forms of osteopathic cranial manipulative medicine can affect the autonomic nervous system (ANS) to benefit the patient.[1] Osteopathic practitioners of the time based their observations on the clinical response of the patient, including improved digestive function, decreased heart rate and blood pressure, and an overall sense of wellbeing. The goal of this research project is to begin to understand how osteopathic manipulative techniques, such as the cccipital-atlantal (OA) decompression and compression of the fourth ventricle (CV-4), can interface with human physiologic processes in response to a sympathetic nervous system challenge.

Definitive understanding of how these techniques interface with human physiology can ultimately guide osteopathic physicians in choosing treatments in their clinical practices.

Osteopathic research has not examined these specific techniques with regards to the physiologic response to a sympathetic nervous system stimulus such as pain. Through research in this area, osteopathic medicine will benefit with a deeper understanding of which techniques, if any, can benefit and help modulate the autonomic nervous system. The current understanding and technology for monitoring human neurophysiology allows us to challenge the assumption that osteopathic cranial manipulative medicine can affect the ANS.[2]

Background

Physiologic effect of a sympathetic challenge has commonly been referred to as a "fight or flight" response, with the parasympathetic nervous system being commonly termed the "feed and breed" response. Sympathetic response includes rapid heart rate, dilation of vasculature, improved airflow in the lungs, and rise in blood sugar as well as a slowing of digestion. The parasympathetic response slows the heart rate, decreases airflow demands on the lungs, and improves digestion. Anatomically, the sympathetic nervous system is composed of pathways that originate in neurons in cell bodies located from the first thoracic to the second lumbar vertebra. In contrast, the parasympathetic nervous system is composed of pathways that originate in neurons in cell bodies originating in the head region, including midbrain and medulla, and sacral portions of the spinal cord. Acetylcholine is the predominant neurotransmitter for parasympathetic postganglionic nerve endings where norepinephrine is the predominant neurotransmitter for the sympathetic postganglionic nerve endings.[3]

This study used two osteopathic manipulative techniques, which focus on the junction of the neck and head. Techniques such as the occipital-atlantal (OA) decompression technique and the compression of the fourth ventricle (CV-4)[4,5] have been felt to stimulate the parasympathetic response due to the proximity to the neurons in this region.[1] Specifically, these techniques are felt to affect cranial nerve X, the vagus nerve, due the close proximity to the area being treated. Robert G. Thorpe, DO, FAAO, states that if we resolve the "segmental dysfunction…so will the homeostatic mechanisms resolve the sympathetic hyperactivity."[6] The techniques referenced fall in the category of "osteopathy in the cranial field," a system of manipulation first developed by William Garner Sutherland, DO.

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While he analyzed the sutures of a disarticulated skull, he surmised that these sutures were made for motion, and he developed a system of treatment based on the motion of these bones. This form of treatment involves the structure and function of the cranial bones, and their inherent motion as integral to the health of the patient.[7]

The OA decompression technique is also believed to have beneficial effects on the parasympathetic nervous system due to close proximity of cranial nerve X during treatment. In addition, cranial nerve X, the vagus nerve, passes thru the foramen magnum and affects the autonomic control of heart rate and digestion. The OA decompression is felt to assist with the parasympathetic control of the heart.[7] Both sympathetic and parasympathetic systems assist in temperature regulation. Low temperature exposure stimulates autonomic nervous system response thru receptors in the skin in order to regulate body temperature. The body responds through thermoreceptors in the skin by vasoconstriction, increasing heart rate and blood pressure.[8] In addition, heart rate variability is an indicator of autonomic function in human subjects. During this project, low temperature is being used to simulate a sympathetic challenge.

Heart rate variability reflects the ability of the heart to adapt to situations in everyday life with an autonomic response. If there is high variability, the heart is adapting to a pathologic condition or insult. In low variability, the autonomic nervous system has become dominant and this indicator can be predictive of disease risk stratification. A 2013 study found heart rate variability improvement with specific osteopathic techniques. This study, which challenged physiologic response with OA decompression and cervical soft tissue techniques, demonstrated improved heart rate variability acutely.[9]

Measurement in changes of autonomic function can be helpful in determining if therapy is efficacious.[10,31] In this study, the PI utilized heart rate variability to determine recovery from a sympathetic challenge from low to high variability thru the use of frequency domain analysis and time domain analysis.

Time domain analysis and frequency domain analysis are widely used in fields such as electronics, acoustics, and telecommunications. Frequency domain analysis is used in conditions where processes such as filtering, amplifying, and mixing are required, while time domain analysis gives the behavior of the signal over time. This allows predictions and regression models for the signal.[11]

Novel devices now exist to monitor the heart rate variability. One such device is the emWave2, developed by the HeartMath Institute. The emWave device is a biofeedback tool that utilizes the cardiovascular system, specifically the heart rate variability (HRV) to assess the physiology of the individual. The emWave device uses spectral (color coded) data to represent the contributions of the ANS and neuroendocrine system. These hand-held devices, applied via ear lobe sensor in this case, monitor an individual's neurophysiology thru intrinsic cardiovascular feedback loops that are stimulated by efferent sympathetic activity and hormonal factors such as the renin-angiotensin system. Low frequency HRV reflects the baroreflex system and sympathetic input, which is involved in short-term blood pressure (BP) regulation, and high frequency HRV reflects parasympathetic input. The device monitors sympathetic input and gives feedback as to the amount of low frequency HRV through a spectral system. Though normally used as a biofeedback or coherence training tool, for the purposes of this study we are using the device solely for assessing heart rate variability.[2,12]

Anatomical and physiologic considerations of the OA decompression and CV-4 technique

An understanding of the anatomy of the brain and spinal cord is essential to the understanding of the effectiveness of the occipital-atlantal (OA) decompression and compression of the fourth ventricle (CV-4) techniques. The fourth ventricle of the brain has the pons located below it, the cerebellum above it and is walled by the lateral peduncles. The technique is thought to have a balancing effect on the fluids of the body and to relax secondary somatic dysfunction in the spine. The proximity of the parasympathetic nervous system to this region has been cited as the reason for the techniques beneficial effects on this system.[1,13]

The OA decompression technique: This technique is performed by the physician placing her finger pads at a 90-degree angle between the junction of the neck and the head near the sub-occipital triangle, and allowing the musculature and soft tissues to respond through relaxation using continuous palpatory feedback, usually no more than 60 to 90 seconds.

The CV-4 technique: This technique performed on the cranial base by the operator having the thenar eminences approximating one another and abutted against the boney portion of the cranial base medial to the mastoid portion of the temporal bone in a supine patient. The operator then monitors the patient for a subtle inherent sine wave like motion called the cranial rhythmic impulse, described in the previous paragraph. The physician then exaggerates the "extension" portion of this cycle, which is felt as slight motion caudad in a supine patient, while discouraging the "flexion" portion of the cycle. This is accomplished through slight appropriate traction through the thenar eminences at the appropriate time in the CRI cycle until neither flexion nor extension is palpated in the

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subject. This is called the "still point." The still point is held until inherent cranial rhythmic motion is reestablished.

In addition to the proximity to the autonomic fibers, the hydraulic effect of this technique seems to affect the arcuate nucleus that has fibers projecting to the periaqueductal grey (PAG) matter. The PAG surrounds the fourth ventricle. These cells may respond to the CV-4 technique by activating neuroreceptors prevalent in the PAG tissue that cause the release of endocannabinoids (opiod like substances). This then sends pain-inhibiting signals to the dorsal horn. PAG tissue is important in down regulating pain signal.[14,15,16] In animal models the hypothalamus and arcuate nuclear region are found to have beta, alpha and gamma endorphin peptides, which have been found to be immunoreactive and play an important role in the control of pain. Cranial rhythmic impulse (CRI) is a sine wave like motion occurring at a variable rate of 6-12 cycles per minute measured during osteopathic cranial manipulative treatment. In cranial flexion, if the operator is sitting at the head of the patient they experience slight motion cephalad, while extension is felt as slight motion caudad in a supine patient. The process of accentuating cranial extension while inhibiting flexion seems to affect the hypothalamus and arcuate nuclear region of the brain, causing them to release these neuropeptides producing a pain inhibiting effect.[16]

In addition to structural effects of osteopathic cranial manipulative treatment, there seems to be beneficial effects on the endocrine response to painful stimuli. Stimulation of hypothalamic-pituitary-adrenal (HPA) axis is a normal physiologic response to pain and inflammation. The HPA axis is one of the peripheral arms of the stress system and its main function is to maintain homeostasis of the basal system and stress related hormone system. The adreno-medullary system also plays a role in this homeostasis. Though these systems are not a part of the sympathetic nervous system, they are often simultaneously active. Robert G. Thorpe DO, FAAO, discusses a "hypothalamic-pituitary-endocrine-autonomic-ganglionic nervous system that does not think for itself" and is often responsible for a "mass sympathetic discharge" effect. He observed the "beneficial effects of the 4th ventricle cranial technique on the hypothalamic axis" in his December 1973 *Osteopathic Annals* article.[6]

The central components of this system are located in the hypothalamus and the brain stem. The system is activated by many blood born signals, including cytokines, produced by immune-mediated inflammatory reactions, such as tumor necrosis factor alpha, interleukin-1, and interleukin-6.[17]

Osteopathic manipulation has been shown to increase endocannabinoids such as anandamide by over 168%, and N-palmitoylethanolamide 1.6 times over pre-treatment levels.[18] The endocannabinoid system was discovered indirectly in 1801 after the endorphin system and promotes homeostasis and healing. It is theorized that this system helps the individual to "relax, eat, sleep, forget and protect."[18]

Endocannabinoids affect the autonomic outflow through both peripheral and central nervous system by elevating parasympathetic activity. They also are shown to provide antihypertensive effect and have been found to have a protective role in myocardial infarction.[19,20]

The phenomenon of "entrainment" has been shown to occur with use of the CV-4 technique by a practitioner. This phenomenon has been seen in pendulum clocks, where all the pendulums will swing in synchrony with the heaviest pendulum. It has been seen as well when the CV-4 technique is used where the cranial rhythmic impulse (CRI) of the practitioner syncs with the CRI of the patient. This process may serve to slow the sympathetic hyper-stimulation of the patient as the practitioner can help modulate the patients CRI.[14] In contrast, if the physician is experiencing stress and not the patient, the entrainment phenomenon may not be as beneficial.

Thermal regulation is an important aspect of this study and is also involved in regulating arterial pressure. Human biology revolves around a 24-hour circadian clock that optimizes temperature for the economy of biologic needs. These rhythms affect the baroreflex via feedback loops in the endocrine, sympathetic and parasympathetic nervous systems.[21] The arterial baroreflex has two important functions. First, the arterial baroreflex is a negative feedback loop that regulates arterial pressure around a preset value called a set or operating point. Second, the arterial baroreflex also sets the systemic arterial pressure when the operating point is reset. That is, modulating the response of baro sensitive neurons in the central nervous system (CNS) sets the operating point of systemic arterial pressure.[22]

Heart rate variability (HRV) is a measure of beat-to-beat variability in heart rate that is mediated by the autonomic nervous system. HRV is mediated through preganglionic sympathetic and parasympathetic neurons innervating the heart via the stellate ganglia and the vagus nerve respectively.[23,33]

Parasympathetic influence on HRV is primarily mediated via the vagus nerve and is primarily responsible for the rapid changes in fluctuations in respiratory sinus arrhythmia and high frequency HRV. Sympathetic neural activity can alter cardiac HRV only slightly beat to beat. Reduced HRV is an indicator of cardiac risk

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and death from all causes.[24] It has also been linked to anxiety and emotional disorders in children.[25,26,32]

Heart rate variability reflects the capacity of the central autonomic network, which includes the prefrontal cortex, central nucleus of the amygdala, hypothalamus, and brainstem to adapt to environmental demands and regulate emotions.[27]

This study intends on testing the following null hypotheses:

H0 Null hypothesis: Osteopathic interventions focused on autonomic balance do not attenuate the sympathetic response to nociception from cold pressor testing.

H1 Alternate hypothesis: Osteopathic interventions focused on autonomic balance attenuate the sympathetic response to nociception from cold pressor testing.

If the null hypothesis is disproven, it benefits the profession in helping patients to recover from a sympathetic challenge or painful incident in a timelier manner by using the osteopathic techniques described. Financially, this can impact the length of stay for a hospitalized patient who may, for example, be recovering from a traumatic incident.

Methods

Potential subjects were recruited from the general population of the College of Osteopathic Medicine of the Pacific-Northwest campus by posting flyers and sending recruitment e-mails. Potential subjects completed a questionnaire regarding their health history. All male and female subjects who were determined to be healthy using the questionnaire were included in the study.

Exclusion Criteria

Subjects were excluded if they used any medications affecting the nervous system such as sympathomimetic medication. Medications requiring exclusion from the study included the following: albuterol, arformoterol, ephedrine sulfate, epinephrine, formoterol fumarate, isoproterenol, levalbuterol, metaproterenol sulfate, pirbuterol acetate, salmeterol xinafoate, terbutaline sulfate, aminophylline, dyphylline, theophylline, pseudoephedrine, and phenylephrine. Anyone using blood pressure medications, anti-anxiety medications, and all illegal drugs were also excluded.

Medical condition exclusions included the following:

- Respiratory disease - asthma or chronic obstructive pulmonary disease and pulmonary hypertension.
- Endocrine/metabolic disease - thyroid or adrenal disorders, rheumatoid arthritis, Down's syndrome.
- Neurologic Diseases - current migraine headache, Parkinson's disease, prior cerebrovascular accident, thoracic outlet syndrome.
- Cardiovascular disease - congestive heart failure and high blood pressure, previous myocardial infarction.
- Psychiatric diseases - anxiety and depression, post-traumatic stress disorder, or physical abuse history.
- Surgery within the past 3 weeks, acute illness within the past 3 days, or motor vehicle accident within the past 7 days are exclusions.

In addition, crushing or traumatic injuries to either hand, vascular surgery of the arm or hand, or carpal tunnel syndrome with or without prior surgery were exclusions.

IRB approval and consent was obtained for 21 subjects, 11 females and 10 males, who met inclusion criteria. Two subjects withdrew before the study started, leaving 19 subjects to participate in the study design, 9 males and 10 females. None of the 19 subjects withdrew after the data collection started. The study ran from May 14, 2015 to June 9, 2015, and all data collection sessions were performed in the OMT lab at the College of Osteopathic Medicine of the Pacific-Northwest campus. HIPPA compliance was maintained throughout the study.

Subjects were randomized into two groups: group A, consisting of 10 female subjects, received Alpha Stim sham first and OMM second, and group B, consisting of 9 male subjects, received OMM first and Alpha Stim sham second. The average age of the subjects was 28.36 years. A randomly assigned number, generated by the PI, was given to each subject on a key tag to identify them in the research design, and log of the subject's name and key tag number was kept on the PI's password protected computer. She remained blinded to this log for the entire data collection phase. All subjects were given general knowledge of the intent of the study, such as "we are comparing how the nervous system recovers with two different interventions" during the consent phase, but further details were withheld. Information was purposely withheld regarding the purpose of the study to avoid placebo effect. The participants were unaware of other subjects in the study, and therefore blinded to each other as well.

The subjects were not evaluated with an osteopathic structural exam prior to the treatment. In this study design, subjects were treated with the same two osteopathic techniques and a sham Alpha Stim treatment regardless of diagnosis. All interventions were gentle

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and involved minimal risk to a healthy subject. Subjects were informed that they may voluntarily withdraw from the study if they found any of the treatment interventions or the ice bath too uncomfortable.

Osteopathic manipulative intervention treatments included CV-4 and OA decompression. The physician who is also the principle investigator performed all of the osteopathic manipulative treatments. The treatment for each technique is described below. The PI performed all the sham interventions on all of the subjects as well for reliability of data collection.

CV-4 Technique

1. Physician was seated at the head of the supine research subject.
2. Pillow was removed.
3. Physician placed hands palm up on the subject's occipital area medial to the occipitomastoid suture so that the thenar eminences are parallel. The thenar eminences provide cushion for the occiput and should be comfortable for the subject.
4. Physician became aware of the subjects' inherent cranial motion, and synchronized with it. Cranial extension was encouraged via slight pressure (less than 1 pound) on the occiput towards the physician seated at the head of the table, where cranial flexion, or occipital motion towards the feet of the patient, was discouraged.
5. Subject's amplitude of cranial motion decreased gradually until a "still point" was reached.
6. The "still point" was a point at which the cranial rhythmic impulse was neither in flexion or extension phase and a warmth and therapeutic pulse was felt in the subject.
7. The physician continued to hold this still point until flexion and extension returned.
8. Physician placed the subject's head back on the table gently.[7,5]
9. Technique took approximately 90 seconds, and all subjects received the same time for consistency of the study.

Occipital-atlantal (OA) Decompression

1. Physician sat the head of the research subject.
2. The subject was supine on a treatment table.
3. Pillow was removed.
4. Physician placed both palms under the subject's head in the occipital region.
5. Physician placed the pads of both index and middle fingers of both hands on the posterior aspect of the cranium (sub-occipital triangle) and slid the fingers down until they were resting against the posterior arch of the atlas (C1 vertebrae).
6. Physician applied a caudad pressure through both index fingers with less than 1 pound of force.
7. Physician applied a cephalad pressure though both middle fingers to separate the condylar parts of the occiput from the C1 vertebra.
8. Physician maintained this position while subject took several deep breaths.
9. Physician monitored the region through index and middle fingers until a warmth, softening of tissue and muscle relaxation was palpated and cranial rhythmic impulse returned.
10. Physician removed hands and gently set head on table.[4]
11. Technique took approximately 90 seconds, and all subjects received the same time for consistency of the study.

A sham intervention of a micro current electrical stimulation treatment (Alpha Stim) was used in which the device is attached via ear probe to the ear lobe but the device was not turned on. Alpha Stim 100 is a micro current electrical therapy (MET) device, which is used for the management of pain, anxiety, depression, and insomnia. It does so through a modified square, bipolar waveform of 0.5, 1.5 or 100 pulses per second (Hz), 10-600 millionths of an ampere at a 50% duty cycle.[28] MET results are long lasting and cumulative. This study used the device to provide a single-blind sham treatment. It is a small and compact unit that is portable. It has various designs of leads, and for this sham treatment, we used the ear clip electrode without the device being turned on or operational. There is no indication to the subject that the device is not operational. The device does not make noise when operational, therefore, there was no indication to the subject that this was a sham treatment. The ear probe did not interfere with cranial rhythmic impulse in the subject. The advantage to a blind sham treatment is that the subjects perceive there was an intervention when none was present. This acts like a placebo for control purposes.

For data collection, this study used a novel device called an emWave 2, which is a biofeedback device that has a color-coded display of green, yellow, or red, indicating the real-time amount of heart rate variability the subject is currently experiencing. When the emWave 2 is used as a biofeedback device, the subject uses the color display to indicate their level of heart rate variability. In this study, however, we wished to keep the subject blinded to the biofeedback nature of the device. Therefore, we used the real-time computer graph display to determine the amount of time spent in each color zone.

The sympathetic challenge in this study was achieved through skin exposure to an ice bath, held between 7 to 0 degrees Celsius for a maximum of 6 minutes. A temperature between 7 and 0 degrees Celsius optimizes the sympathetic challenge to the system.[29] In other studies on the subject of frostbite, there is no concern for freezing or frostbite in subjects with ice submersion in this temperature range.[30]

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The ice was continuously replenished to maintain the temperature in the above range, and a digital thermometer confirmed the temperature. The temperature was checked between each subject to assure temperature control.

Equipment

- EmWave 2 monitoring device
- Omron HEM-FL31 automatic sphygmomanometer
- Stopwatch with second hand
- Ice bath
- Remi digital thermometer for ice bath
- Hill osteopathic treatment table
- Alpha Stim 100 (Electromedical Products International) micro current stimulation device
- Hot Hands brand hand warmers
- Avery split ring key tags

Protocol

Subjects were scheduled for 3 blocks of time lasting 20 minutes each, with 2 occurring on the same day and the final on a separate day. The 2 time blocks on the same day were separated by a 20-minute rest interval to give the subject time to recover from the first ice bath. All data collection information was held on a password-protected computer only accessible by the principle investigator.

In this crossover design study, both groups initially had a 3-minute baseline (BL) recording of blood pressure, heart rate, and heart rate variability using the emWave device and the ear clip monitor with no ice stimulus. The ear clip attachment of the emWave device was fixed to the right ear lobe of each subject and no readings were obtained until adequate connectivity was established. Both groups had continuous monitoring of the HRV with the emWave device, as well as heart rate and blood pressure monitoring at 90-second intervals.

This established each subject's baseline and eliminated subjects if BP or HR was in excess of acceptable limits prior to the study (BP 180/90, HR 110). The left hand of the subject was placed in the ice bath for 3 minutes. The HRV reading was recorded by the first research assistant as a percentage of time in the red, yellow, or green zones (averages of spectral data), while the BP and HR were recorded from the left arm by a second assistant unless contraindicated (1 subject). The second assistant was also the timekeeper. The use of assistants allowed the PI to do interventions necessary, such as OMT and the sham Alpha Stim treatment. None of the participants were able to view any of the readings and the sound was turned off, thus eliminating biofeedback effects of the emWave device. The protocol with each monitoring session, including HR, HRV, and BP, was as follows:

- 3 minutes baseline (Baseline =BL)
- 3 minutes hand in ice bath and continued monitoring for additional 3 minutes (BL with Ice = BLI)
- 20 minute break

Group A

- 3 minutes hand in ice bath with Alpha Stim and continued monitoring for 3 minutes (AS with Ice= AS)
- Subject filled out questionnaire
- Leave and return on day 2 for second intervention

Group B

- 3 minutes hand in ice bath with OMT (90 seconds OA decompression, 90 seconds CV-4 and continued monitoring for additional 3 minutes (OMT with ice = OMT)
- Subject filled out questionnaire
- Leave and return on day 2 for second intervention

Both groups received the osteopathic interventions of OA decompression and Compression of the Fourth Ventricle (CV IV) performed by the same physician for 90 seconds for each technique while the subject's hands were in the ice bath for 3 minutes. Both groups had the sham Alpha Stim treatment, in which the Alpha Stim device was attached via ear clip to the subject and the subject was blinded to the device not being operational.

Subjects were allowed to rest for 20 minutes between data collection intervals on the same day, and had the option of using a hand warmer at this time. The risk to subjects was minimal. There was discomfort involved in the form of burning, itching, mild pain, and numbness, but no risk for frostbite.[30] Group A received the Alpha Stim intervention first, and Group B received the OMM intervention first. All received the Baseline, and Baseline with Ice, before the intervention or sham.

A crossover design was used to in which the blinded control group then becomes the intervention group and intervention group then becomes the blinded control group. This second intervention was performed on a separate day for all but 3 subjects. All interventions were separated by 20-minute recovery intervals. The crossover design was created to increase the power of the study design. All phases of this trial were performed in the OMT lab at the College of Osteopathic Medicine of the Northwest. HIPPA compliance was maintained throughout the study.

At the end of the monitoring both the intervention and the control group were asked to fill out a questionnaire to assess the participants perceptions of recovery from both intervention and

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the blinded sham. In addition, the state of well-being for both intervention and blinded sham groups was assessed post study. The questionnaire was identical after both arms of the study. There were 2 subjects who, for unknown reasons, did not fill out the questionnaire in one portion of the study.

Protection Against Risks

A first aid kit and AED device was available during the study and hand warmers should the individual require them. With regard to protection against risk from osteopathic treatment, osteopathic cranial manipulative medicine is well tolerated and gentle to the patient with minimal movement of the operator's hands and no quick motions. The PI was the only operator and is a licensed physician with 23 years of experience in the field of osteopathic manipulative medicine. If the subject were to experience prolonged adverse effect from the treatment outside evaluation with a primary care physician not involved in the study would be made available and the subject would have been withdrawn from the study. Adverse events would be immediately reported to the IRB. In the event of a medical emergency the emergency services would be called and the patient transported to the nearest emergency room, which was in the immediate vicinity.

Results

Evaluation and Variable Design

Multiple variables were analyzed in this research study, including the subject's demographics, which can be seen in Table 1. A total of 19 subjects completed the study design phase, and the average age of each subject was 28.36 years. Of the 19 subjects, 9 were males and 10 females. For the purposes of this study, group A comprised the females and group B comprised the males. Of the 19 subjects, 11 were medical students at the college (57.89%), one was faculty (5.26%), and 7 were employees (36.84%).

Table 1 – Subject Demographics

Analysis Variable: Age			
N	Mean	Std Dev	Median
19	28.3684211	4.2322902	27.0000000

Sex	Frequency	Percent	Cumulative Frequency	Cumulative Percent
f	10	52.63	10	52.63
m	9	47.37	19	100.00

T-test analysis was used to compare all the variables at each of the 90 second recording intervals (data points) collected over the 6-minute period in which subjects were in the ice bath. These data collection points are numbered 1-4. Data collection points 1 and 2 were during the intervention, whether OMM or sham and 3 and 4 were while in ice bath but after intervention had ended. Subjects were compared to themselves as all participated in all portions of the study. The comparisons were as follows:

- OMM Heart Rate (OMMHR) – Alpha Stim Heart Rate (ASHR)
- OMM Systolic Blood Pressure (OMMSBP)-Alpha Stim Systolic Blood Pressure (AS SBP)
- OMM Diastolic Blood Pressure (OMMDBP) – Alpha Stim Diastolic Blood Pressure (AS DBP)
- OMM Heart Rate Variability (OMMHRV) – Alpha Stim Heart Rate Variability (AS HRV)

Similarly, OMM was compared to Baseline with Ice and Alpha Stim was compared to Baseline with Ice with the same 4 x 90 second data point intervals during intervention and sham. The same variables of heart rate, blood pressure and heart rate variability were recorded. Heart rate variability was recorded as the percentage of time in the green plus blue zones as recorded by the EmWave device. Table 2 is the T-test graph comparison of the OMM versus Alpha Stim evaluation.

The TTEST Procedure Difference: OMMHR1 - ASHR1

Table 2 –Std Dev = Standard deviation, CL = confidence level, N= Number, OMMHR1 = Osteopathic manipulative treatment heart rate #1 and ASHR1= AlphaStim heart rate #1

N	Mean	Std Dev	Std Err	Min	Max
19	-2.7368	13.5107	3.0996	-24.000	33.000

Mean	95% CL Mean		Std Dev	95% CL Std Dev	
-2.7368	-9.2488	3.7751	13.5107	10.2088	19.9799
DF		t Value		Pr > |t|	
18		-0.88		0.3889	

The distribution of difference graph is a histogram that subtracts the OMM intervention heart rate from the Alpha Stim intervention heart rate and plots the percent of individuals that fell within each category. For example, the bar on the far left indicates that approximately 15% had a negative value between -12 and -24 when the two variables were subtracted. The green box below the graph indicates the 95% confidence interval, and since it includes 0, we can neither rule in nor rule out the hypothesis being tested. The blue diamond is the mean value.

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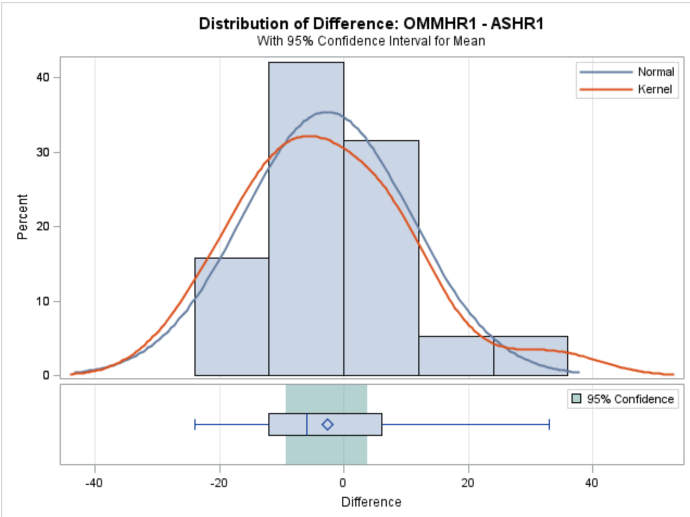
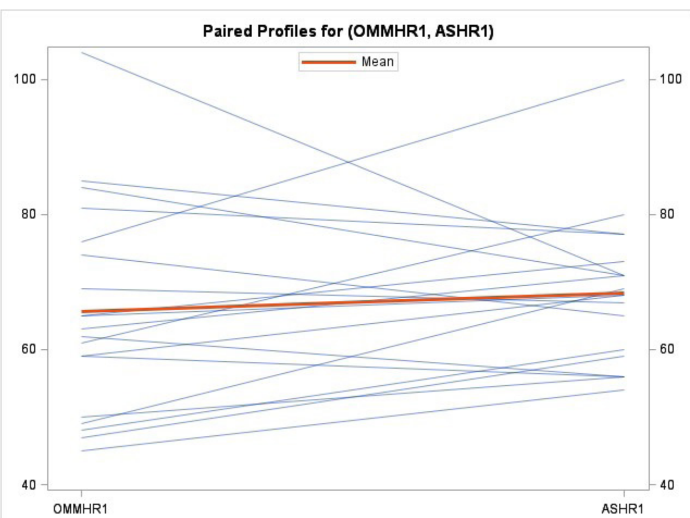
Table 3 – Distribution of Difference: Osteopathic Manipulative Medicine Heart Rate 1 to Alpha Stim Heart Rate 1. Kernel = Non-parametric data smoothing curve



The kernel is essentially a non-parametric data smoothing (curve fitting) function that can often fit the data better than a normal (bell-shaped) function especially when there is reason to believe the data are not normally distributed (multimodal). The kernel "over-fits" the data when there are too few data points to really know for sure how the data are distributed.

Table 4 – Paired Profiles of Osteopathic manipulative treatment heart rate #1 to Alpha Stim heart rate #1



OMM HR beats per minute AS HR beats per minute

In Table 4, the paired profile plot, each line is one subject and the heart rate of the OMT intervention is on the left while the heart rate of the Alpha Stim intervention is on the right. The bold orange line is the mean. In this case, the mean is sloping from the right to the left, indicating that the OMT intervention demonstrated a lower heart rate.

Table 5- Agreement of Alpha Stim heart rate #1 to Osteopathic manipulative treatment heart rate #1

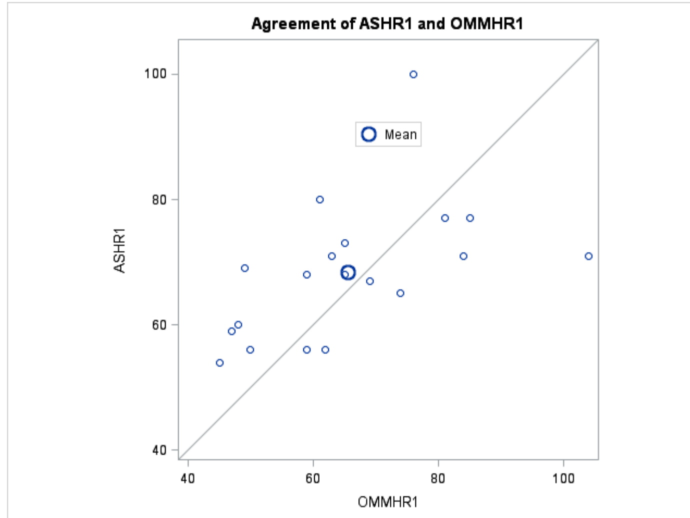


Table 5 is a one to one agreement plot between Alpha Stim heart rate one and OMM heart rate one. Each dot indicates a subject, and those falling above the 45-degree line indicate subjects with a higher heart rate with Alpha Stim intervention as compared to OMM intervention.

Table 6 - Q-Q plot Osteopathic manipulative treatment heart rate 1 to Alpha Stim heart rate 1

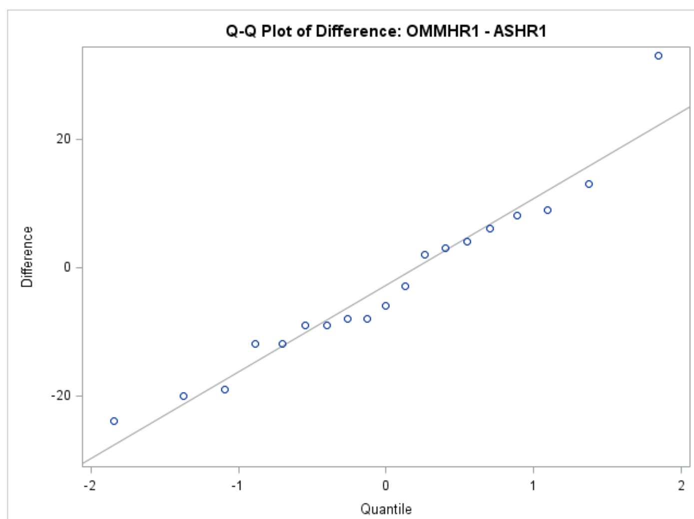


Table 6 is a quartile-to-quartile plot graph. Each point on the graph indicates a subject.

The hypothesis being tested assumes that the data follows a normal bell-shaped curve. If all data point were exactly lined up on the 45-degree line the data would be suspect, but because the points approximate but do not line up on the line this indicates they

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follow the normal bell-shaped curve. As the data points vary normality is assumed.

The survey results were analyzed with a means procedure for all questions after intervention, whether Alpha Stim or OMM. The same 5 questions were asked for both using a 1-5 Likert scale, with 1 meaning disagree and 5 meaning agree. All but 2 of the 19 subjects were analyzed, eliminating those who did not fill out one arm of the survey. The questions were as follows:

1. I found my hand in the ice water painful.
2. I felt the treatment intervention helped in my recovery from the pain.
3. I found the treatment intervention to be stressful.
4. I felt a sense of physical well-being from the treatment intervention.
5. I would recommend the treatment intervention to others.

The comparison of the survey questions is seen in Table 7.

The MEANS Procedure

Table 7 – Post survey results pommq = post OMM questionnaire and pasq = post Alpha Stim questionnaire

Variable	N	Mean	Std Dev	Median
pommq1	18	4.1666667	1.0431852	4.0000000
pommq2	18	3.6111111	0.8498366	3.5000000
pommq3	18	1.2777778	0.6691132	1.0000000
pommq4	18	3.8888889	0.9002541	4.0000000
pommq5	18	3.8888889	0.8323524	4.0000000
pasq1	17	4.2941176	1.0467035	5.0000000
pasq2	17	3.1764706	0.9510057	3.0000000
pasq3	17	1.0588235	0.2425356	1.0000000
pasq4	17	3.0000000	0.7905694	3.0000000
pasq5	17	3.1176471	1.1114379	3.0000000

Of note, the mean for question 1, state as "I found having my hands in the ice water painful," was rated as more painful for the Alpha Stim arm of the study at 4.29, as compared to the OMM arm of the study at 4.16. In addition, there was a slight difference in question 2 stated as "I found the treatment intervention helped in my recovery from pain" with the mean for the OMM arm being slightly higher at 3.61 than the Alpha Stim arm at 3.17. From these results, the OMM interventions may improve the subject's perception of painful stimuli. The fifth question, "I would recommend the treatment intervention to others," was also rated higher in the OMM arm at 3.88 than the Alpha Stim sham at 3.11.

Mean differences and P value determinations were calculated for each 90-second data collection point (1-4) for each of the paired T Test comparisons

Discussion

Summative evaluation and structured analysis was obtained using the ordinal data from groups A and B. Initial evaluation of BP, HR and HRV comparisons between the osteopathic treatment interventions and sham intervention at the 90 second data collection points 1-4 indicate a trend toward disproving the null hypothesis, and proving the alternate hypothesis. Both hypotheses are listed below for review.

H0 Null hypothesis: Osteopathic interventions focused on autonomic balance do not attenuate the sympathetic response to nociception from cold pressor testing

H1 Alternate hypothesis: Osteopathic interventions focused on autonomic balance attenuate the sympathetic response to nociception from cold pressor testing

The power of this small pilot study cannot rule in or rule it out definitively either hypothesis. However, the directions of the mean comparisons are very consistent, even though the magnitude of the differences vary. The direction of the mean differences of each paired t-test in the hypothesis testing results trend toward the alternate hypothesis, and as such suggest OMM interventions do affect autonomic balance. As can be seen by the mean comparisons, the trends do not go in the opposite direction, suggesting OMM is an effective clinical tool for autonomic imbalances. Essentially, the small sample size and statistical noise make this a pilot study only. The theory that OMM does decrease sympathetic tone and increase parasympathetic tone is sound.

The blood pressure and heart rate variables were consistently lower with OMM intervention; however, the HRV values were inconsistent. This may be due to the limitations of the emWave device, limitations of the method for stimulating the sympathetic nervous system, or the patient population and sample size.

The questionnaire's results suggest that OMM seems to help mitigate the peripheral insults from a subject's perspective, and is well tolerated. This can be seen in the subjects' perceptions that during the OMT intervention, pain of the ice bath seems less noticeable, and with the Alpha Stim sham, the ice bath seemed more painful. A larger sample size would be helpful in confirming these findings.

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Limitations of Study Design

The most significant limitation for this study was the limited data from only 19 subjects. The future recommendation is for a larger study size using multiple sites if possible to increase the power of the study and diversity of study population, as close to 58% of subjects were medical students undergoing final exams which may induce increased sympathetic tone at baseline. An observation was noted in using ice water to create the sympathetic challenge among athletes. Response was variable depending on the subject's experience. Athletes for example, crave ice baths as a method for recovering from multiple trauma during contact sports. The athletic subjects in this group of individuals did not have the expected result from the ice bath and instead had only minimal rise in heart rate or blood pressure, and HRV. This was an observation only, and the group was not analyzed as a subset. This group of individuals potentially has learned to modulate their nervous system and ice was not perceived as a painful experience. In future study designs either eliminating the contact sport population from the design or choosing methods such as tilt tables or peroneal nerve stimulation to create the sympathetic challenge might eliminate this observed pitfall.

Another limitation of the study is the emWave2 device. While an easy, portable, and inexpensive way to monitor heart rate variability, it was developed as a biofeedback tool, and as such, rapidly cycles between spectral data. In this study, the PI chose to use this tool instead of an electrocardiogram (ECG) machine due to its portability and potential for use in non-clinical settings for data collection. The design study utilized an "off label" indication of the device. Comparison studies on the emWave and ECG HRV would be useful for future research. Finally, limitation in the emWave ear clip to monitor HRV was problematic and presented some difficulty in picking up the signal if the subject was cold (i.e., recently had come in from the outside), or had pendulous ears.

Conclusion

Historically, osteopathic physicians have used trial and error, common sense, and a keen understanding of anatomy to determine what osteopathic treatment was needed in each patient. Reasons for selection of a technique to treat a specific problem were passed on from generation to generation due to efficacy in specific situations. Technology has advanced to allow researchers deeper understanding of how osteopathic treatment interfaces with human physiology. This pilot study shows promise that techniques such as the CV-4 and OA decompression can alter physiology to improve recovery from a sympathetic challenge.

The benefit to society and the profession has potential impacts on how osteopathic manipulative medicine is practiced and for what conditions. It has the potential to change the way osteopathic manipulative medicine is taught as well with an evidence basis for techniques. It has previously been practitioner experience and patient reporting of benefit that have justified the use of the treatment. Moving osteopathic theory to evidence base rather than trial and error benefits the osteopathic profession as a whole and the above benefits outweigh the minimal risks in this study. The larger benefit is in decreasing the burden on the health care system by reducing hospital days and recovery time from a traumatic injury.

Future studies are indicated to confirm the physiologic effects of these treatments. In addition, this study has shown that relatively inexpensive electrophysiologic devices that are readily available for use in physicians' offices with little or no preparation can be utilized to monitor heart rate variability. These devices can mitigate the expense and inconvenience of using an ECG machine in future studies. This may encourage more osteopathic physicians to undertake similar research. Western U IRB #14/IRB/003

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