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HEALTH SCIENCE CENTER AT FORT WORTH
1970

ABSTRACT

White, Heath D., D.O., M.S. Physiologic and Anatomic Changes in Carpal Tunnel Syndrome: Is Osteopathic Manipulative Treatment an Effective Non-surgical Alternative Therapy? Master of Science (Clinical Research and Education – OMM), May 2005, 110 pp., 4 tables, 5 figures, references, 46 titles.

Objective: Carpal tunnel syndrome (CTS), caused by compression of the median nerve within the carpal tunnel, has a prevalence that ranges between 0.53 and 16.3 with medical costs exceeding $2 billion annually. The goal of this clinical trial was to assess for physiologic and anatomic changes in CTS in response to OMT. Physiologic changes were measured with nerve conduction studies (NCS). Anatomic changes were measured with magnetic resonance imaging.

Methods: This prospective, randomized, controlled, blinded clinical trial planned to evaluate 50 subjects randomized between two treatment groups, OMT and placebo sub-therapeutic ultrasound. Eligibility criteria included adults between 21 and 70 with a clinical diagnosis of CTS and increased conduction latency of the median nerve. Outcome measures were median motor and sensory conduction distal latencies. Subjects receive six treatments. NCS were conducted at entry to the study (baseline), midpoint, and endpoint.

Results: Thirty-seven of a planned 50 subjects were randomized to groups. Thirty-one subjects were included in the final data analysis. Preliminary analysis found no significant difference in NCS values over the three testing intervals. Evaluation for

effect(s) of multiple treatment providers by analyzing the single treatment provider with the greatest number of subjects found significant improvements in some NCS values for the OMT group. This study was funded by the Osteopathic Research Center, and approved by the UNTHSC Institutional Review Board.

Conclusions: The results of this preliminary analysis indicate the possibility for improvement of CTS with OMT, but no conclusive statements about the efficacy of OMT can be made. This preliminary study enabled us to identify multiple areas in the research design and methodology that may be improved, and provides the framework for future studies.

PHYSIOLOGIC AND ANATOMIC CHANGES IN CARPAL TUNNEL SYNDROME: IS OSTEOPATHIC MANIPULATIVE TREATMENT AN EFFECTIVE NON-SURGICAL ALTERNATIVE THERAPY?

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THESIS

Presented to the Graduate Council of the University of North Texas Health Science Center at Fort Worth in Partial Fulfillment of the Requirements for the Degree of

MASTER OF SCIENCE

By:

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ACKNOWLEDGEMENTS

I would like to thank the department of Osteopathic Manipulative Medicine and my graduate committee for the support they provided during this long endeavor. I would like to specifically thank Dr. Stoll, my major professor, and Dr. Cruser, my fellowship director, committee member, and source of infinite research knowledge, for the utmost support, patience, and guidance that they provided from the beginning to the end of this research. And finally, I would like to thank Bobbie Ann for her editorial comments and advice as well as extreme patience during our many conversations about this research and thesis.

This study was funded in full by the Osteopathic Research Center (ORC), which is located at the University of North Texas Health Science Center at Fort Worth.

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CHAPTER I

BACKGROUND & SIGNIFICANCE

EPIDEMIOLOGY

The first published report of carpal tunnel syndrome (CTS) was in 1854, and it is now the most commonly reported entrapment neuropathy in the general adult population.[1] Although the true prevalence of CTS in the United States is not clear, it is estimated that 40 million individuals with symptoms do not seek professional help.[2] Findings of prevalence studies in Sweden, Italy and the Netherlands do not differ widely from those few done in the U.S.[3,4,5] These studies have found CTS prevalence to be between 0.53 and 16.3%.[6,7,8]

A large number of clinical studies have been conducted which consistently document the characteristics of the patient population with CTS. CTS may be found in either gender, but it occurs most frequently in women. Examination of various prevalence studies found an average female to male ratio of 3.6:1.[3,4,5,6,8,9] Rosenbaum et al found that approximately 70% of patients with CTS were female and 30% male. Although it occurs less often in men, CTS is typically more severe for men. In both men and women, this disease is most prevalent between 40 to 60 years of age and is rarely diagnosed before 20 or after 80 years of age.[2] CTS has been found to be 1.8 times more likely to occur in white than in non-white populations. The cause of this racial difference is currently unknown but may include differences in disease awareness and medical care access for evaluation and treatment as well as occupation-related reasons.[7]

Multiple risk factors for CTS have been identified, including female gender, obesity, age greater than 30 years, repetitive motor activity, and the presence of systemic diseases such as diabetes mellitus, rheumatoid arthritis and hypothyroidism. Female gender, obesity (BMI >30), and age of 40 to 60 years have been shown to be independent risk factors for CTS. The literature identifies diabetes mellitus as a risk factor for CTS, but further analysis is needed due to the relationship between obesity and diabetes mellitus.[9] Repetitive motor activity has long been implicated as a risk factor for CTS with little definitive support in the medical literature. One correlation to support this relationship is the finding of a higher prevalence of CTS among blue-collar than white-collar workers and among those workers using excessive wrist/hand motion and force.[4]

The debilitating effects and medical costs of CTS place a large economic burden upon society. Medical costs secondary to CTS have been estimated to exceed $1 billion per year. This estimate includes an excess of 200,000 surgical procedures performed annually, as well as office visits and medical therapies.[10] Not included in this estimate are the millions spent on ergonomic efforts to prevent, lessen or alleviate this condition. Beyond the direct economic costs, indirect costs are associated with the labor force. Carpal tunnel syndrome causes economic hardship for both the employer and employee, resulting in millions of lost revenue because of disease management, litigation, lost productivity, lost wages and retraining. This disease has consistently been described by the Bureau of Labor and Statistics (BLS) as requiring the greatest time away from work when compared to all major work-related injuries or illnesses. Amount of time away from work is used by the BLS as an indicator of severity of occupational injury. In 2001, the

BLS reported that 1.6% of work-related injuries involving time away from work were caused by CTS.[11] The annual incidence of CTS among full-time employees varies greatly depending upon geographic location, which may reflect differences in occupation types, industrial and governmental standards, and medical practices. The incidence of work related CTS in the medical literature varies from a low of 24.5 cases per 100,000 workers to in excess an 1,000 cases per 100,000 workers.[2]

CLINICAL HISTORY & EXAMINATION

Carpal tunnel syndrome is defined as "a constellation of signs and symptoms caused by compression of the median nerve within the carpal tunnel of the wrist." This entrapment neuropathy most commonly presents with insidious development of paresthesias below the wrist in the median nerve sensory distribution of the hand. Patients report that paresthesias characteristically present nocturnally, upon awakening in the morning, or with repetitive or prolonged activities of the hand. When patients experience nocturnal awakening, relief is usually obtained by shaking (also called the "Flick sign") or rubbing of the hand(s). CTS usually begins as a unilateral disease, most commonly in the dominant hand, and symptoms frequently progress to bilateral by the time patients present to a physician. Hand pain typically accompanies paresthesias and is more likely to radiate proximally into the forearm and shoulder. The pain is typically intermittent, but in some cases it is the predominant symptom. Isolated neck, shoulder, or proximal arm pain are rarely symptoms of CTS unless accompanying distal arm symptoms of CTS are

present. CTS may further present with median motor abnormalities causing clumsiness and weakness of the involved hand(s). Motor abnormalities may progress to severe thenar atrophy and weakness, but this does not typically occur until late stages of the disease process.[2,12]

The primary pathologic process underlying CTS is compression of the median nerve within the carpal tunnel of the wrist. This compression, caused by a variety of etiologies, leads to a cyclic amplifying condition of inflammation, edema and increased pressure within the carpal tunnel. This cycle begins with obstruction of venous and lymphatic return, and causes arterial ischemia and nerve fiber destruction with disease progression. Carpal tunnel syndrome is an idiopathic disease in the majority of cases, but a variety of conditions may predispose a person to this disease. These conditions may include increased or decreased carpal tunnel volume, aberrant anatomy, trauma or mass lesion. Systemic diseases, such as diabetes mellitus, rheumatoid arthritis, acromegaly and hypothyroidism, are commonly associated with CTS. Pregnancy is frequently complicated with symptoms of CTS in as much as 20% of this population. The symptoms typically begin in the third trimester and resolve rapidly postpartum.[2,13]

DIAGNOSTIC TOOLS

Because there are no absolute clinical standards or definitive tests for CTS, its diagnosis requires a combination of different clinical tools and methods in addition to a detailed history and physical exam, including, provocative tests, imaging, and

electrodiagnostic studies. The diagnosis of CTS can be made based upon a clinical exam. However, a formal diagnosis should utilize a combination of diagnostic tools and techniques in addition to the clinical exam because of the variety of clinical presentations of CTS, the presence of other neuropathies and diseases which may mimic CTS, the inability to monitor disease progression, and the likelihood of false-positives and false-negatives on clinical exam.

Provocative tests, most commonly including Phalen's, Tinel's and median nerve compression test, are additional tools used during the physical exam when patients present with intermittent symptoms of CTS, but without objective neurological dysfunction on exam. These tests deliberately stress a compromised median nerve to elicit symptoms of pain, anesthesias, paresthesias, and/or dysesthesias as perceived in CTS. Phalen's sign, developed by Phalen in 1951, utilizes wrist flexion for a sustained period to elicit the signs of CTS. Phalen originally reported the test positive in 74% to 80% of his patients with CTS. Numerous studies since then report a wide range of sensitivities (10% to 88%) and specificities (47% to 100%). Tinel's sign, using percussion over the median nerve at the wrist to elicit symptoms of CTS, was first reported in 1915 by Tinel after it was noticed that percussion over a post-traumatic neuroma caused paresthesias. Phalen reported the test positive in 60% to 73% of his patients with CTS. Since that time, multiple studies have reported a wide range of sensitivities (26% to 79%) and specificities (40% to 100%). Median nerve compression test, developed by Jungo in 1969, elicits signs of CTS with sustained pressure over the carpal tunnel. Though there is a wide range of sensitivities (23% to 100%) and

specificities (29% to 100%) for the median nerve compression test, this test may in clinical practice be more reliable than Phalen's and Tinel's. Based on the sensitivities and specificities within the literature, the provocative tests cannot unequivocally provide the diagnosis of CTS. When used collectively, these tests are very valuable in the early course of CTS when median nerve conduction latencies are normal and when used in combination with other diagnostic tools.[2,12,14]

Multiple different imaging techniques, including radiography, ultrasonography, computed tomography, and magnetic resonance imaging have been used to examine the carpal tunnel and median nerve. These techniques are valuable because of their ability to show a variety of abnormalities within the wrist. Despite this ability, none of these techniques have been demonstrated to be reliable in the diagnosis of CTS or for routine evaluation of suspected CTS. Wrist and hand radiography is a very rapid and inexpensive screening tool, which are useful in evaluation of suspected traumatic injury, osseous disease and diseases affecting the articular joints, such as rheumatoid arthritis or osteoarthritis. However, radiographs provide very limited information for patients with CTS.[2]

Ultrasonography (US), which uses high frequency sound waves, provides longitudinal and axial images of the wrist allowing identification of the structures in the wrist and hand. The median nerve, flexor retinaculum, and flexor tendons are easily identified using US. Studies with US have identified certain abnormalities within the carpal tunnel in patients with CTS, including palmar bowing of the flexor retinaculum and swelling of the median nerve as seen by a greater cross-sectional area.[2]

Computer tomography (CT) provides cross-sectional images of the carpal tunnel in the axial plane, allowing for identification of structures contained within the wrist. Visualization of these structures also allows identification of any pathologic processes. Multiple studies have tried to build a relationship between the cross-sectional area of the carpal tunnel and the development of CTS, but many of these studies have presented conflicting data regarding that relationship. CT of the wrist provides excellent visualization, but it provides little diagnostic value and magnetic resonance imaging is usually preferred over CT.[2]

Magnetic resonance imaging (MRI) provides 1,000-fold contrast resolution compared to CT scanning devices. Although MRI tends to be more expensive than CT, it provides better visualization of soft tissue structures such as muscles, bones and in this case the contents of the carpal tunnel. A variety of different pathologies can be noted on MRI, such as osseous disease, fractures, ganglia, ligamentous injuries, tenosynovitis and articular disease. Some of these pathologies may be noticed with less expensive imaging techniques such as US and CT, but the diagnostic accuracy is greatly increased using MRI.

In addition to these major pathologies, several frequent abnormalities within the carpal tunnel have been identified with MRI in patients with CTS. Abnormal signal intensity and swelling of the median nerve is commonly identified in this population and reflects the presence of neuronal edema. Clinical studies have quantitatively demonstrated these MRI findings in patients with CTS as compared to control subjects, but currently the diagnostic value of these findings is limited. Flattening of the median

nerve and palmar bowing of the flexor retinaculum have also been identified with MRI in patients with CTS, but studies have found this to be an insensitive finding. As with CT, carpal tunnel size has been evaluated for its relationship with CTS. Some studies have found statistically significant relationships between carpal tunnel size and CTS when compared to control groups, but these findings do not give MRI the sensitivity to be utilized as a diagnostic test.[2]

As stated earlier, there are no absolute clinical standards or definitive tests for CTS, but electrodiagnostic testing that is interpreted in the appropriate clinical context along with a clinical exam provides the most definitive diagnostic information. Electrodiagnostic tests are used to obtain objective neurologic information that may be used for a variety of reasons other than assisting in the diagnosis of CTS. For example, these tests document disease severity, evaluate alternative neurologic pathology as the etiology of the symptoms, and provide a quantitative baseline assessment of CTS which may be used to evaluate therapy.[2]

Electrodiagnostic testing, which involves nerve conduction studies (NCS), assesses the health of the nervous system by evaluating the ability of the neuromuscular system to send electrical signals. NCS produce an electrical stimulus which causes nerve depolarization and the transmission of an electrical gradient along the path of the nerve in afferent and efferent directions. The conduction time (latency period) between the stimulus site and recording site is then measured as a quantitative assessment of neuronal function.[2,15]

In patients with CTS, NCS characteristically show an increase in the distal median sensory and motor latency periods. These findings indicate a slowing of nerve conduction. Quantitatively, this increase in latency can be used to define the severity of the CTS. CTS initially causes injury to the sensory nerve fibers with minimal effects on the motor nerve fibers. These findings are seen in NCS as abnormal sensory conduction latency and normal motor conduction. With disease progression, abnormalities in conduction latency extend to motor as well as sensory fibers.[2,12,15]

The practice parameters for electrodiagnostic testing have been jointly established by the American Association of Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation. These parameters provide the recommendations for the use of electrodiagnostic studies to confirm the diagnosis of CTS. The NCS recommendations for suspected CTS are 1) evaluation of median sensory distal latency across the wrist, 2) comparison of median sensory distal latency to ipsilateral radial or ulnar sensory distal latency, 3) median motor distal latency, and 4) comparison of median motor distal latency to ipsilateral radial or ulnar motor distal latency.[16]

NCS are an invaluable tool used in the diagnosis of CTS, and because of their sensitivity, some debate exists over the use of these tests as an exclusive diagnostic tool. Electrodiagnostic testing may be an invaluable tool, but its role as the "gold standard" and an exclusive diagnostic tool for CTS is not supported by the current literature. CTS is a syndrome defined by clinical manifestations and the removal of a clinical exam from the diagnostic criteria is not only contradictory to the definition but would also lead to a

large number of false-positive diagnoses. With the possibility of surgery as a therapeutic intervention, these false-positive diagnoses would have serious implications. In addition, there is no correlation between the symptoms of CTS and the severity of electrodiagnostic abnormalities.[2,12,15]

TREATMENTS

The traditional treatment of CTS involves a progressive program of conservative to invasive treatments. These treatments have a variable rate of success depending upon the patient and the severity of disease. The treatment program usually beings with conservative management and progresses to invasive therapies as the severity of the disease worsens. The current treatments available include, but are not limited to, splinting; oral medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, pyridoxine, and steroids; ultrasound; physical therapy and exercise; injectable steroids; and surgical excision of the transverse carpal ligament.

Splinting of the wrist is the most commonly prescribed initial therapy for patients with CTS. Multiple designs for wrist splints have been proposed, but those splints in a neutral position have been found to produce the most symptomatic relief and have the lowest intracarpal tunnel pressure measurements. Splinting has been shown to produce statistically significant improvements in symptoms and in some trials has shown improvement in objective measures. Wrist splints are typically worn at night if nocturnal

symptoms are present, but they may also be worn during the day if symptomatic during that time period.[2,12]

Oral medications are also a common initial therapy for CTS and usually begin as a two to four week trial of NSAIDs, diuretics, pyridoxine, and/or steroids. NSAIDs are commonly prescribed to patients with CTS, but no benefit from these medications has been found in placebo, double-blinded, controlled clinical trials. Diuretics are less commonly prescribed to patients with CTS, and as with NSAIDs, no benefit has been found in controlled clinical trials. Pyridoxine, or vitamin B_6, is anecdotally supported by many clinicians and in some poorly designed clinical trials, but the efficacy of this vitamin has not been demonstrated in a well-controlled clinical trial. A short, low dose prescription of oral steroids produced statistically significant improvements in symptoms in the same studies, but no objective changes were found. The incidence of relapse following completion of the steroid is common, and the benefit of long-term oral steroids, chronic or intermittent, is currently unknown.[2,12]

Ultrasound therapy to the wrist has been proposed as a beneficial therapy to patients with CTS. Some small controlled trials have supported this hypothesis, showing improvement in symptoms as well as electrodiagnostic tests, but other small studies have found no benefit to this therapy. Some studies have even indicated that ultrasound therapy produces a documented placebo effect in patients with CTS.[2,17,18]

Physical therapy and exercise constitute a modality of treatment that aims to improve the physical conditioning of the body. Exercise and forms of physical therapy, such as stretching, are commonly prescribed during clinical practice as an adjunctive

therapy for CTS, but only minimal literature from clinical studies exists to validate these therapies. The use of aerobic exercise as a primary therapy for CTS was found in only one study. The results of objective and subjective measures from this study found that aerobic exercise was a beneficial treatment for CTS.[19] No clinical studies evaluating the use of stretching as a primary or adjunctive therapy for CTS could be found. Traditional physical therapy has been evaluated in post-surgical patients but not as a primary or adjunctive therapy in mild-to-moderate CTS.

Injectable steroids constitute an invasive therapy initiated in patients with CTS that have failed to improve after conservative therapy. The injection of corticosteroids into the carpal tunnel has been shown to produce statistically significant improvements in the symptoms of CTS and electrodiagnostic findings. The time period of improvement varies from less than a month to greater than two years depending upon the literature. The vast majority of patients receive benefit immediately, but this tends to taper off by six months to a year later for most patients. The dose of steroids used in the literature varies, but a controlled study found no significant difference between low-dose and high-dose steroids. Comparison between local and systemic steroids found that local injection produced greater improvement in symptoms, which lasted for a longer period of time than oral steroid.[2,12,20]

Surgical excision of the transverse carpal ligament provides a last resort therapy for patients who have failed other, more conservative therapies. The use of a surgical therapy is ultimately the patient's preference and should be strongly considered as a treatment option in those patients presenting with signs of axonal injury, i.e. constant

numbness, loss of sensation, and muscular atrophy. This procedure involves complete incision of the transverse carpal ligament through either an open palmar incision or with an endoscope. The efficacy of both procedure types appears to be same based on multiple outcome studies. Carpal tunnel release produces statistically significant improvement in the symptoms of CTS in the vast majority of patients. Objective evaluations also improve, but at a slower rate than symptomatology. NCS normally improve towards baseline, but may never reach this level. Also, grip and pinch strength measurements tend to return to baseline in six months to a year. As with any surgical procedure, carpal tunnel release carries certain surgical risks or complications that may include injury to nerves, excessive scaring, loss of strength or sensation, and incomplete relief of symptoms. The rates of complications vary in the literature, but one report of 10,640 cases produced a complication rate of 2.6% to 5.6% with surgeons who had performed less than 25 operations and less than 1% in surgeons who had performed over 100 operations.[2,12,20]

OSTEOPATHIC MANIPULATIVE TREATMENT

Modern medicine offers numerous conservative and invasive treatments to manage the symptoms of CTS. Despite the presence of these potentially efficacious therapies, there are few studies to document long term effects and none of these therapies can provide an absolute cure for this disease. Hence, the presence of additional conservative therapies is always beneficial to patients since this is a potentially

debilitating disease. This thesis project involved the examination of osteopathic manipulative treatment (OMT) as an additional conservative therapy that can be used in combination with current medical treatments. OMT, which is a form of manual medicine, is used by osteopathic physicians to improve physiologic function and to support homeostasis through the treatment of somatic dysfunction.

The Glossary of Osteopathic Terminology defines somatic dysfunction as "impaired or altered function of related components of the somatic (body framework) system: skeletal, arthrodial, and myofascial structures, and related vascular, lymphatic, and neural elements."[21] Within the framework of this definition, the osteopathic physician relies and draws on three physiologic and anatomic models, Fluid, Musculoskeletal, and Neurologic, to shape a treatment approach. The Fluid Model emphasizes the physiologic movement of blood and lymph through the respective arterial, venous, and lymphatic pathways in order to optimize circulation, cellular metabolism, and fluid balance. The Musculoskeletal Model emphasizes how the musculoskeletal structure is intimately interrelated to function, and how dysfunctional biomechanics may cause multiple negative consequences throughout the somatic system. The Neurologic Model emphasizes how somatic dysfunction can lead to somatic and autonomic neurologic dysfunction.[22-26]

The use of OMT to treat CTS applies the Fluid, Musculoskeletal, and Neurologic models to formulate a treatment plan aimed at enlarging the carpal tunnel, removing impediments to venous and lymphatic drainage, improving somatic and autonomic neurologic function, and minimizing patterns of myofascial restrictions (somatic

dysfunction). In order to accomplish these goals, the osteopathic physician addresses somatic dysfunction in areas of the body beyond the wrist, including the general areas of the affected wrist, arm, shoulder, neck and upper back.

OMT to the wrist is specifically designed to stretch the transverse carpal ligament and enlarge the dimensions of the carpal tunnel. The enlarged carpal tunnel should reduce compressive forces on the median nerve to improve its function and reduce the symptoms of carpal tunnel syndrome. Treatment of the arm and shoulder should align joints and reduce patterns of fascial tension such that impediments to central venous and lymphatic fluid return will be reduced, myofascial pain will be reduced and peripheral neural entrapments will be released. OMT to the neck and upper back will align these musculoskeletal structures such that nerve roots and brachial plexus impingements may be alleviated and autonomic neural traffic will be optimized. All of these treatments are aimed at improving median nerve conduction, increasing carpal tunnel dimensions, reducing edema, and improving hand and arm function.

MANUAL MEDICINE LITERATURE

Research on the use of manual medicine for CTS has been reported as efficacious in some literature. However, there are too few prospective, randomized, blinded, controlled clinical trials to provide adequate evidence that this reported efficacy is true. The studies reported in the literature have used different designs, different outcome measures, and different interventions to evaluate manual medicine, but each study has

numerous methodologic flaws that prevent generalized conclusions about this therapy from being made. The following is a detailed review of the available literature on manual medicine and its use as a therapy for CTS. This literature served as a guide in the development of the research protocol used in this study. Different aspects of each study were used to formulate a methodology that would be most sound and stand up to peer review. Corrections were made to the limitations of previous studies, and flaws in methodology, statistical analysis, and use of outcome measures were addressed.

An extensive search of the literature was performed with Ovid MEDLINE and OSTMED® using a variety of search terms, including manual medicine, manipulation, OMT, Osteopathic medicine, and Chiropractic manipulation. In addition, other source material was identified in the references of the literature found in the electronic search. This literature search revealed a total of 17 articles, 10 osteopathic and 7 chiropractic, evaluating the efficacy of manual medicine treatments for CTS. Among these 17 reports there were 4 abstracts (all osteopathic), 7 case reports (3 osteopathic and 4 chiropractic), and 6 clinical trials (3 osteopathic and 3 chiropractic).

The earliest identified literature that evaluates the use of manual medicine as a treatment for CTS is found in the chiropractic literature. These articles are single case reports only. These articles are primarily descriptive and provide very little information except for some clinical insight and possibly guidance in future research.[27-30]

The largest portion of the literature on CTS and manual medicine is in a series of five osteopathic publications by Sucher et al. These articles by Sucher include three articles written as case reports, two clinical trials, and one abstract. The three articles

published as a collection of case reports documented the treatment of CTS with OMT in a total of ten subjects. These case reports evaluated the effectiveness of OMT using NCS. A complete, detailed OMT protocol was not given in these case reports, but particular emphasis was placed on describing specific stretching techniques for the wrist. These techniques are theorized to increase the dimensions of the carpal tunnel and relieve fascial restrictions within, which should decrease pressure on the median nerve and help relieve the symptoms of CTS. To assess the effectiveness of these stretching techniques, one article with a collection of five case reports, measured the anterior-posterior and transverse dimensions of the wrist using MRI. Statistical analysis of the NCS and MRI findings was not performed, but positive results were reported in both of these outcome measures. Other than describing OMT techniques at the wrist and providing some guidance for protocol development in future studies, these case reports do little to establish the efficacy of OMT as a therapy for CTS.[31-33]

The first article that Sucher et al. presented as a clinical study consisted of four experimental groups. In this study, there were nine subjects (11 wrists) with carpal tunnel in Group A, four subjects (four wrists) with CTS in Group B, five subjects (five wrists) with CTS in Group C, and 13 normal, asymptomatic volunteers (20 wrists) in Group D. This study used no randomization process in assigning subjects to experimental groups. Group A received OMT, self-stretching exercises, and was available for post-treatment follow-up. Group B did not receive any therapeutic intervention and was not available for follow-up. Group C used a therapeutic stretching appliance developed by Sucher and was available for follow-up. Group D received no therapeutic intervention and required no

follow-up. The authors of this study provided no methodology for blinding subjects, treatment providers, or those that collected outcome measures. NCS were used to evaluate therapy in Groups A and C. Palpatory examination of the wrist using a restriction scale was made on each subject in all groups by the author of the study as a method to quantify the degree of motion restriction at the wrist. The OMT, self-stretching exercise, and stretching appliance protocols were not described. The findings of this study are very difficult, if not impossible to interpret because of the lack of a clear methodology. The data of only selected cases from groups A and C are presented and no statistical analysis was performed in this study. The efforts to grade motion restriction using a palpatory examination appear novel and logical, but these findings are purely subjective, with no efforts to blind the examiner. This study provides no significant findings that may assist in the evaluation OMT as a therapy for CTS because of the flawed design.[34]

Sucher et al. conducted a second clinical study to test the earlier hypothesis that OMT could increase the dimensions of the carpal tunnel. This mechanistic study evaluated the ability to stretch the transverse carpal ligament in cadaver upper extremities. This study, done in two parts, was published as a full length article and later as an abstract. Sucher used fresh-frozen cadaver upper limbs, 7 in the first part and 20 in the second part, for this evaluation by drilling pins into the medial and lateral carpal bones and measuring for changes in the distance between the pins. Weights were suspended from the pins using pulleys to provide horizontal distraction of the transverse carpal ligament. Different quantities of weights were added over specific time intervals

followed by repeat measurements of the distances between the pins. In addition to the weights, some cadaver limbs were subjected to the same OMT as described in the previous literature by Sucher et al. This was followed by repeat measurements of the distances between pins. This evaluation was performed on a small number of cadaver upper limbs and statistical analysis of the data was not performed. Multiple different factors, including the type of cadaver limb, amount of weight, and the use of manipulation, were inconsistently used in this study and make the change in one cadaver limb difficult to compare to the rest of the limbs. This study demonstrated the ability of the transverse carpal ligament to stretch and maintain this length, but again, full interpretation of the results is not possible because of flawed methodology.[35,36]

In addition to Sucher, Ramey et al. evaluated the treatment of CTS with OMT on six subjects using NCS, MRI, pain and distress (PAD) scale, analog pain scale, and wrist range of motion. The results of this study were published in abstract and full length article form. The OMT protocol used by Ramey provided treatment to the cervicothoracic spine and tenderpoints in the forearm but excluded treatment to the wrist and hand. The treatment provider was not identified and blinding efforts were not addressed. The study did not have a control group and all subjects enrolled in the study received the OMT protocol, of which only minimal details describing the OMT protocol were given. Outcome measures were taken for both wrists, with the exception of the PAD scale, but it is unknown whether the subjects had unilateral or bilateral CTS. Statistical analysis was only performed on the five subjects with improvement in symptoms. Statistically significant findings of those five subjects were found in the sensory amplitude of NCS,

analog pain scales, and wrist range of motion. No significant findings were seen in the remaining NCS, PAD scales, and carpal tunnel MRI measurements of signal intensity and dimensions. Full interpretation of these findings, even in comparison to the previous work by Sucher, is difficult because of the extremely small number of subjects, an OMT protocol that did not include treatment the wrist, and the lack of statistical analysis on those subjects that did not display improvement.[37,38]

Another osteopathic study which included a two month follow-up was conducted by Strait et al. and Huu et al. This study was reported in the literature as two abstracts, but was never published as full length articles. This study compared a standard care group to a standard care and OMT group. In this study, 23 subjects were randomized between the two groups (ten control subjects and 13 OMT subjects) in the original study, and on follow-up, 20 of the original extremities (nine control extremities and 11 OMT extremities) were evaluated. The OMT protocol was described as systemic OMT, which was applied every two weeks for two months. These studies revealed more improvement in self-rating of pain, NCS, and the presence of provocative tests in the OMT group, but because of the lack of statistical analysis, it is unknown whether this improvement was significant or if there were significant differences between the experimental groups. These improvements were found to be sustained over a two month period, but again, no statistical findings was reported.[39,40]

The earliest chiropractic clinical study, which was published as two full length articles, was by Bonebrake et al. This two-group, single-blinded clinical trial consisted of an initial study with a six month follow-up. History and clinical examination defined the

inclusion criteria for this study. NCS were not used for inclusion criteria or evaluation of change in the initial evaluation or follow-up. Bonebrake did not randomized subjects between the experimental groups, which consisted of 1) a chiropractic group of CTS patients and 2) a comparison group of asymptomatic volunteers without CTS. The chiropractic group received hard tissue manipulation of the cervical, thoracic and lumbar spine, upper and lower extremities, shoulder girdle, and ribcage from the primary author of the articles. These subjects also received soft tissue manipulation to the oral area, trunk, neck and upper and lower extremities. The study methodology gave neither a specific interval nor time frame for the manipulation protocol. In selected cases, subjects in the chiropractic group received dietary modifications, supplements, a daily exercise regimen, or ultrasound. These later therapies were inconsistently applied to selected subjects. The comparison group received no therapeutic interventions. At the conclusion of the study, 38 subjects (32 female and six male) were enrolled in the chiropractic group and 13 subjects (seven female and six male) were enrolled in the control group. Outcome measures, including anthropometry of the hands, strength measures, electromyograph (EMG) signals, range of motion, task performance, and ratings of pain and distress (PAD) were collected for both groups initially and for the chiropractic group post-intervention and at the six month follow-up. The outcome measures were collected independently in a blinded fashion by a technician. Statistical analysis was performed on all outcome measures. Comparison of the two groups found significant differences between groups in some of the strength measurements, some of the range of motion measurements, task performance, and PAD scales. The pre- and post-treatment

comparison found significant improvements within the chiropractic group for some of the strength measurements, some of the range of motion measurements, and PAD scales.[41]

The six month follow-up evaluation used the same outcome measures, which were used to evaluate a total of 22 subjects (17 female and five male) that returned for follow-up. The outcome measures were again collected by an independent technician, but blinding could not be achieved because only subjects from the chiropractic group were re-evaluated. No efforts were made to control for treatments that subjects received between the post-intervention measurements and six month follow-up. Findings at the six month follow-up evaluation reveals significant sustained improvement for a six month period in some strength measurements, some range of motion measurements, and PAD scales.[42]

The findings of the study conducted by Bonebrake, both initial and follow-up, show statistically significant improvements in certain outcome measures, but full interpretation of these findings is difficult because of significant flaws in the methodology. In this study, 34 different outcome measures were used which drastically increases the chance of Type I error and makes interpretation of any significant findings complicated. In addition, NCS were not used as inclusion criteria or to evaluate the progress of therapy.[41,42]

In addition to Bonebrake, Davis et al. conducted a chiropractic clinical trial which was published as a full length article. Davis used a two-group, randomized, single-blinded trial of nine weeks duration with a one-month follow-up evaluation. The randomization scheme, which was conducted by computer, assigned subjects to two

experimental groups: 1) a medical group which received a scheduled ibuprofen regimen and cock-up nocturnal wrist splints, and 2) a chiropractic group which received high-velocity, low-amplitude thrust procedures to the upper extremities and vertebrae of the cervical and thoracic spine as well as soft tissue massage to these regions. Evaluation of therapy for these two groups was made by assessing change over time using questionnaires of physical and mental distress, general health status questionnaires (SF-36), NCS, and vibrometry. Davis had a sample size calculated for statistical power and statistical analysis procedures were performed on all outcome measures. In this chiropractic study, 91 subjects were randomized between the two groups (46 in the medical group and 45 in the chiropractic group). Of the 91 subjects randomized, 70 subjects completed the nine week protocol and 67 subjects returned for the one-month follow-up evaluation. Analysis of the outcome measures revealed significant improvement in physical and mental distress, NCS, and vibrometry, but no differences were found between the two experimental groups. The methodology used by Davis is the most sound of all the manual medicine literature discussed here, but improvements in design could have been made with the addition of a placebo or sham group, more emphasis on electrodiagnostic testing, and removal ultrasound therapy from the chiropractic group[43]

Overall, the available published literature of clinical trials and clinical case reports provides some promising evidence towards the efficacy of manual medicine as a treatment for CTS. However, this literature is extremely limited and the majority of the

present studies have significant design flaws which must be addressed before a proper interpretation of the data can be made.

CHAPTER II

METHODOLOGY

INTRODUCTION

The overall goal for this study was to take the first step in building an evidence-based scientific body of knowledge concerning the impact of osteopathic manipulative treatment (OMT) on carpal tunnel syndrome (CTS) and to establish a plausible model for testing in larger more definitive studies. The ultimate goal is to evaluate the efficacy of a conservative, biomechanical, non-surgical treatment for CTS. This study used a prospective, randomized, controlled, blinded design to examine whether OMT is an effective treatment for CTS when compared to a sub-therapeutic ultrasound placebo.

Osteopathic manipulative treatment may favorably impact CTS through several mechanisms including 1) mechanical expansion of the carpal tunnel resulting in decreased mechanical compression of the median nerve, 2) decreased tension within upper extremity fascial strain patterns that may be compressing low pressure lymphatic and venous vessels and contributing to fluid congestion and edema within the carpal tunnel, and 3) decreased minor upper extremity neural impingements at the nerve roots, brachial plexus, median or ulnar nerves that may be causative of other upper extremity symptomatology and may contribute to the "Double Crush Syndrome" of the median nerve at the wrist.

Based upon this understanding of the theoretical mechanisms of OMT on CTS, three hypotheses were developed for this study.

- Hypothesis 1: OMT will decrease the median motor and sensory distal latency.
- Hypothesis 2: OMT will increase the transverse and anterior-posterior diameters and the cross-sectional area of the carpal tunnel.
- Hypothesis 3: OMT will reduce the presence of water (edema) in the carpal tunnel.

Outcome measures were selected specifically to test these hypotheses. Figure 1 below depicts the design utilized in this study.

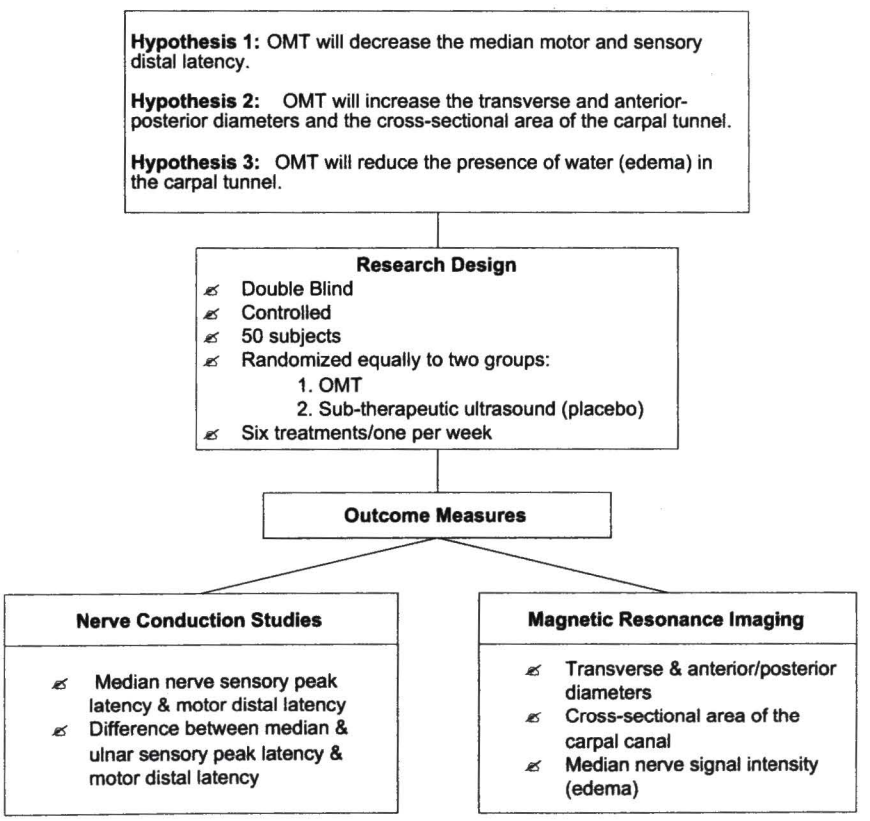


Figure 1: Research Design

For the purpose of this study, the primary outcome measures are: 1) median motor distal latencies and 2) sensory distal latencies measured by nerve conduction studies (NCS). The secondary outcome measures are: 1) changes in the transverse and anterior/posterior diameter, as well as cross-sectional area of the carpal tunnel and 2) edema of the carpal tunnel and median nerve measured by quantification of the mean T2 weighted magnetic resonance imaging (MRI) signal intensities of these respective structures.

SUBJECT SELECTION AND RECRUITMENT

A power analysis was performed in consultation with the Department of Biostatistics at the University of North Texas Health Science Center (UNTHSC). The primary outcome measure of median motor distal latency was used to estimate the sample size needed to detect a 20% change in median motor distal latency with a power of 0.80 at an alpha level of $a = 0.05$. The effect size was based on previous research by Kilmer, Ramey, and Eisen.[15,37,44] The number of subjects per group to detect this amount of change in NCS would be approximately 400 subjects per group. Because this number is unrealistic for a preliminary study and the strict power calculations were beyond the scope of this study, a total of 50 subjects between two groups were chosen. This sample size does not protect against Type II error, i.e. not finding a change when there was one. The interior dimensions and signal intensities within the carpal tunnel from MRI were considered secondary outcome measures for the power analysis. As with the primary

outcome measure, the secondary measures were not powered to meet the predicted calculations.

The research protocol, informed consents and advertisements were approved by the UNTHSC Institutional Review Board prior to starting the study. Subjects were recruited by referral from the Internal Medicine and Family Medicine clinics at the UNTHSC/Texas College of Osteopathic Medicine (TCOM). The Internal Medicine and Family Medicine clinics combined had approximately 170 patients from April 2002 to March 2003. Subjects were also recruited by flyers, newspaper ads and email at the UNTHSC clinics and campus. Once a subject was recruited for the study, written informed consent for the research protocol was obtained.

Inclusion criteria for participation in this study were: 1) age 21 to 70; 2) clinical diagnosis of carpal tunnel syndrome; 3) NCS consistent with CTS: median nerve sensory distal latency greater than 2.2 ms, a difference between median and ulnar sensory distal latency greater than 0.3 ms, median nerve motor distal latency greater than 4.2 ms, and/or a difference between median and ulnar motor distal latency greater than 1.5 ms.[15]

Inclusion NCS were performed immediately after obtaining informed consent to verify that subjects met the electrodiagnostic inclusion criteria for the study. Those subjects who did not meet the inclusion criteria for NCS were excluded from the study. After acceptance into the study protocol, subjects were randomly assigned to one of the two treatment groups and demographics were recorded. All clinic visits and treatment sessions took place in the Osteopathic Manipulative Medicine (OMM) clinic. All MRI

sessions took place at Monticello Diagnostic Imaging Center which is located two blocks from the OMM clinic.

Exclusion criteria for participation in this study were: 1) severe CTS that had progressed to muscle atrophy; 2) pregnancy; 3) previous wrist surgery; 4) systemic diseases which included but not limited to: diabetes mellitus, thyroid disorders, rheumatoid arthritis, Paget's bone disease, gout, myxedema, multiple myeloma, acromegaly, hepatic disease, dialysis patients, and other disease in which peripheral neuropathies are common; 6) secondary causes of CTS including, but not limited to, ganglion cyst, mass, tendonitis, or accessory muscle(s).

Exclusion criteria for participation in the MRI portion of the study protocol were: 1) cardiac pacemaker; 2) hip prosthesis; 3) metallic foreign body in the immediate vicinity of affected writs; 4) other conditions which serve as a medical contraindication to MRI as determined by the radiologist/MRI staff.

STUDY PROTOCOL

Table 1 (below) presents the study protocol schedule. All subjects were enrolled in the study via the inclusion/exclusion criteria and consent process by a clinical research coordinator (CRC). The inclusion/exclusion screening data was collected by the CRC, who was trained by the Principal Investigator (PI). The PI also reviewed all collected data as well. Subjects received $10 for their travel time and expenses for each study visit.

GROUP	Weeks / Data collection/Treatment	1	2	3	4	5	6	7	8	9	10
Group A OMT	Demographics	X									
	History & Physical	X									
	Nerve Conduction Studies	X					X			X	
	MRI		X								X
	OMT			X	X	X	X	X	X		
Group B Sub-therapeutic Ultrasound (Placebo)	Demographics	X									
	History & Physical	X									
	Nerve Conduction Studies	X					X			X	
	MRI		X								X
	Sub-therapeutic Ultrasound			X	X	X	X	X	X		

Table 1: Study Protocol

Two experimental groups were used in this study. These two groups consisted of: 1) an OMT group and 2) a placebo sub-therapeutic ultrasound (PSTU) group, and are described in the Experimental Groups and Interventions section in more detail. Identical outcome measures were taken from each group over the same time intervals. Subjects were randomized at the time that clinical eligibility for participation was confirmed. The CRC, PI, subjects, and radiologist were blind to the treatment group assignment. A Predoctoral Fellow in the Department of OMM at UNTHSC/TCOM administered all sessions of OMT and sub-therapeutic ultrasound under the direction of the PI.

Subjects began and ended the study in sets of six to facilitate scheduling and provide for periods of potentially unavoidable delay. At the first visit, the CRC explained the study and the informed consent to the subjects. Following the informed consent and screening NCS, the CRC collected demographic data, including birth date, age, gender, marital status, weight, height, race/ethnicity, occupation, and education. Other information collected included workers compensation claim status, past and current medical illnesses, surgery history, current medications, allergies, and current treatment

for CTS. This data was kept on a Demographic Sheet in the chart for all consented subjects.

At the 2nd visit, all subjects eligible for an MRI were given an MRI to exclude any secondary causes of CTS and to document the baseline values of the transverse and anterior/posterior diameters, cross-sectional area of the carpal tunnel, and signal intensity of the carpal tunnel and median nerve. A board certified radiologist provided a complete report to the PI of any abnormal findings as well as the data required for analysis of the MRI findings.

The study protocol called for six treatment sessions, one per week from the 3rd through the 8th week/visit. NCS were performed at the 6th and 9th visits to correspond to the midpoint and endpoint. A post-treatment MRI was performed during the 10th visit for comparison with baseline values.

EXPERIMENTAL GROUPS AND INTERVENTIONS

This proposed clinical trial involved two experimental groups: Group A – OMT & Standard of Care and Group B – PSTU & Standard of Care. The details of each intervention are described below. All interventions occurred one time per week for six weeks, while the outcome measures were taken at the intervals shown in Table 1. All subjects were randomly and equally assigned to groups. A Predoctoral Fellow in the Department of OMM at UNTHSC/TCOM provided the OMT or PSTU to Groups A and B respectively. Standard of care for both groups was provided by each subject's primary

care physician. Standard of care included any therapy routinely provided for CTS in the medical community. These therapies included but were not limited to nonsteroidal anti-inflammatory drugs (NSAID's), wrist splints, exercises or steroid injections. Surgery is considered standard of care, but it was considered exclusion criteria for this study. The use of any standard of care by each subject was recorded in the chart and re-evaluated at each treatment visit. The PI, CRC and treating Predoctoral Fellows met monthly for training/review of procedures and evaluation of consistency.

A Predoctoral Fellow provided OMT to Group A for approximately 30 minutes with a standard treatment protocol utilizing variations of the four (4) OMT types described below. This protocol was used to systematically address any somatic dysfunction in the regions of the body which are hypothesized to be associated with CTS and provided flexibility for the fellow to decide which treatment was most clinically appropriate. The protocol was similar to that used in standard osteopathic clinical practice.

1. High Velocity/Low Amplitude (HVLA): This is a direct treatment technique in which all planes of motion of the joint are engaged toward the restrictive barrier. At this point of localization, a high velocity/low amplitude force to overcome the restrictive barrier is applied. In some cases this may be associated with an audible noise but is not a required for successful treatment.
2. Muscle Energy: This technique is used to treat areas of somatic dysfunction in a direct fashion to engage restrictive barriers. The patient is positioned in a manner where the restrictive barrier is engaged. The patient provides an isometric muscular

contraction against the force provided by the operator for approximately three to five seconds. The patient then relaxes the muscular contraction and operator moves the patient into a new restrictive barrier. This is repeated approximately three to five times.

3. Myofascial Release Treatment: This technique is the manual application of forces to myofascial structures in an indirect, direct or combined fashion and in a manner used to release tense and optimize musculoskeletal functional positioning.
4. Strain/Counterstrain: This technique uses treatment of tender points to relieve somatic dysfunction. The operator contacts the tender point and gently positions the body to a point of minimal myofascial tension around the tender point until the patient reports a significant decrease in the tenderness. This position is held for 90 to 120 seconds and then gently returned to a resting position.

The treatment protocol was designed to address three main regions of the body. The goals and rationale for treatment according to region are:

1. Wrist carpal bones and myofascial structures, forearm myofascial structures and interosseous membrane

a. *Wrist carpal bones and myofascial structures:* The carpal bones and myofascial structures of the wrist form the carpal tunnel, through which digital muscle tendons and the median nerve pass. Compression of the carpal tunnel is considered the primary cause of CTS and is the site of surgical intervention. Therefore, somatic dysfunction of the wrist is a cause of CTS and treatment of the carpal bones and

myofascial structures of the wrist should relieve the compressive effects, and hence the somatic dysfunction, in the carpal tunnel.

b. *Forearm myofascial structures and interosseous membrane:* The myofascial structures of the forearm often exhibit somatic dysfunction in CTS and may act as an additional site of compression of the median nerve. Treatment of the myofascial structures of the forearm alleviates fascial restrictions along the pathway of the median nerve.

2. Shoulder Girdle, 1st rib, Sibson's fascia and pectoralis minor

a. *1st Rib:* The brachial plexus passes between the clavicle and 1st rib in its pathway to the upper extremity. Somatic dysfunction causing an elevation of the 1st rib may lead to a compressive effect on the brachial plexus and result in dysfunction in the median nerve at the shoulder girdle with potentiation of causing CTS through the "double crush" effect.

b. *Sibson's fascia:* The terminal lymphatic drainage of the upper extremities passes through the cervicothoracic fascial diaphragm (Sibson's fascia) at the thoracic inlet. Dysfunctional strain patterns in Sibson's fascia cause obstruction to lymphatic flow and decrease the efficiency of lymphatic return which can result in edema and stasis of interstitial fluids.

c. *Pectoralis Minor:* The pectoralis minor crosses anterior to the brachial plexus and arterial, venous and lymphatic supply of the upper extremities. Therefore, somatic dysfunction of the pectoralis minor and surrounding myofascial structures can have

adverse effects on the homeostatic mechanisms of the neural, arterial, venous and lymphatic systems of the upper extremity.

3. Cervical and thoracic vertebrae

a. *Cervical vertebrae (including Cervicothoracic junction):* The nerve roots C_5-C_8 and T_1 exit the spinal column in the lower half of the cervical spine and upper thoracic spine to form the brachial plexus. Each of the nerve roots C_5-C_8 and T_1 contribute nerve fibers toward the formation of the median nerve in the terminal branches of the brachial plexus. Somatic dysfunction of the cervical vertebrae and the surrounding muscular and fascial structures can affect the functioning of the nerve roots as they exit the spinal column and, therefore, cause dysfunction of the median nerve. Somatic dysfunction of the cervicothoracic junction can also induce a strain pattern into Sibson's fascia, thus compromising return of lymphatic drainage from the body (See 2.a. for relevance and treatment of Sibson's fascia).

b. *Thoracic vertebrae:* The sympathetic innervation of the upper extremities arises from thoracic vertebrae T_2-T_8. Somatic dysfunction of upper thoracic vertebrae and the corresponding ribs may alter sympathetic tone to the upper extremities and produce nerve dysfunction, and lymphatic and venous congestion. In addition, the inferior most nerve roots of the brachial plexus exit in relation to the upper thoracic vertebrae (See 3.a. for relevance and treatment).

Placebo groups are an important component in osteopathic manipulative medicine research. OMM may generate various intentional positive benefits, but it may also generate a positive clinical response because of ancillary and possibly uncontrollable

influences from: 1) increased physical contact ("the power of touch"); 2) greater attention and interaction with the treating physician; 3) an expectation by the patient of a therapeutic effect. A placebo group was included to control for these effects and account for possible confounding variables. This permitted the analysis to consider the possible placebo effect as a variable in detecting significant change attributable to the OMT.

Group B received PSTU from a Predoctoral Fellow to the general areas of the wrist, arm, shoulder, neck and back in addition to current standard care as outline by the subject's primary care physician. PSTU treatments addressed the same anatomical regions as the OMT for approximately the same amount of time. Ultrasound gel was not used, as the subject received treatment through the clothes with an intensity of 0.1 W/cm^2 and 10% pulsed mode (the lowest setting and with the greatest cycle interruption). Subjects were unaware that the treatment was sub-therapeutic. The subjects received PSTU treatments at the same frequency and duration as Group A during the 3^{rd} through 8^{th} visits.

NERVE CONDUCTION STUDIES

This study used electrophysiologic evaluation of CTS to test Hypothesis 1. This evaluation using electrodiagnostic testing measured the median motor and sensory distal latencies. All testing was performed with a XLTEK's NeuroMax 1002. Current practice parameters recommend that a physician perform NCS. For this study, however, a

registered nurse and a CRC were trained to perform the NCS. The PI reviewed and interpreted the findings.

Electrodiagnostic testing for CTS was performed using NCS to measure the distal latency of the median nerve through the carpal tunnel. Numerous techniques have been described in the literature to evaluate both sensory and motor fibers of the median nerve, with sensory evaluation as the most sensitive predictor of CTS.[2] All subjects underwent electrodiagnostic testing of both median and ulnar motor and sensory distal latencies across the wrist. Sensory testing for both nerves involved stimulating at the mid-palm and recording orthodromically at a point 8 cm proximal to the stimulation point over the respective ulnar and median nerves. The median motor nerve distal latency was measured by stimulating the median nerve at the wrist at a point 8 cm proximal to the recording electrode placed over the mid-point of the Abductor Pollicis Brevis muscle. The ulnar motor nerve distal latency was similarly measured by stimulating the ulnar nerve at the wrist at a point 8 cm proximal to the recording electrode placed over the mid-point of the Abductor Digiti Minimi. A ground electrode was placed on the dorsum of the hand. All results recorded represented the most rapid and largest responses obtained from a supra maximal stimulus. Sensory nerve action potential latency was recorded at its peak. Motor unit action potential latency was recorded at its onset. All sensory wave form amplitudes were measured from peak to peak while all motor wave form amplitudes were measured from onset to peak.

All subjects' hands and wrists being studied were warmed for five minutes with an electric heating pad to achieve a temperature between 32 and 36 degrees Celsius to

avoid temperature variations that could have negatively impacted the electrodiagnostic testing. Temperature was measured with a calibrated surface temperature strip which was applied to the palm prior to electrodiagnostic testing.

MAGNETIC RESONANCE IMAGING

This study used MRI to test Hypotheses 2 and 3. MRI was selected to measure anterior-posterior (A/P) and transverse diameters and the cross-sectional area of the carpal tunnel. Also, it was selected to measure changes in edema in the median nerve and carpal tunnel using signal intensity.

MRI tests provide the resolution necessary to evaluate these outcome measures, and the necessary clinical information to screen subjects for secondary causes of CTS. The MRIs were done at Monticello Diagnostic Imaging Center under the supervision of Paul Marsh, D.O. Dr. Marsh is certified by the American Osteopathic Board of Radiology and the Clinical Magnetic Resonance Society, and completed a post-graduate MRI fellowship in 1996 at Christ Hospital in Cincinnati, Ohio.

Various types of magnetic resonance images were obtained, including T_1 and T_2 turbo spin axial images, volume gradient echo images in the axial plane, and fat suppressed proton density axial images. The wrist was placed in a dedicated wrist coil at the isocenter of the magnetic field. The radiologist ensured consistency in the wrist image slice utilized for analysis through identification and orientation around boney wrist landmarks, including the hook of the hamate and the trapezium. The same scan

parameters at pre and post MRI were utilized to ensure consistency of image slice. Based on the protocol developed, a consistent image slice was obtained and deviation on the post image proximal or distal to the level of the pre image was minimized.

When acceptable wrist MRI images were obtained, as determined by the MRI tech, the consulting radiologist recorded several measurements. The MRI processing computer and software allowed the radiologist to mark and measure the greatest A/P and transverse dimension, as well as outline any region of interest (ROI) and automatically calculate signal intensity and area for the ROI. To account for background signal during each MRI scan, a ROI outside the wrist was sampled. This ROI was used for standardization of changes in signal noise, small movements of the wrist during the scan, and minor changes in wrist position with respect to the isocenter of the magnet between pre-and post-treatment scans.

The internal dimensions of the carpal tunnel were identified and circumscribed by utilizing multiple specific and reproducible boney and ligamentous landmarks within the wrist. The maximum A/P diameter of the carpal tunnel was measured from the anterior border of the transverse carpal ligament to the anterior boney cortex inner margin of the dorsal arch of the tunnel. The maximum transverse diameter was measured from the boney cortex inner margin of the hook of the hamate to the boney cortex inner margin of the trapezium.

ROIs, including the outer circumference of the median nerve and the inner circumference of the carpal tunnel, were obtained to calculate the mean signal intensity within the ROI. The measurements of relative signal intensity were recorded on heavily

water-weighted fat suppressed data sets. In the event that chemical fat suppression was not possible, Short Tau Inversion Recovery images were obtained. These data sets provided an indicator of free water or free protons in the region and were indirectly an indication of edema that was otherwise difficult to detect.

DATA ANALYSIS

This study was guided by three hypotheses: 1. OMT will decrease the median motor and sensory distal latency, 2. OMT will increase the transverse and anterior-posterior diameters and the cross-sectional area of the carpal tunnel, and 3. OMT will reduce the presence of water (edema) in the carpal tunnel. The study was designed to be a phase II clinical trial of the efficacy of osteopathic manipulative treatment in treating CTS. Each hypothesis was tested after the data were examined to ensure the necessary assumptions were met for the statistical test applied. The approach to this study was exploratory, developmental, and model building.

Analyses were performed using traditional methods provided in the Advanced Statistics component of SPSS-PC™. The outcome measures selected for the study have been found to be valid, reliable, and sensitive to the target observations.[2,15,16] We used statistical tools that control for unequal numbers and the amount of within group variance relying in part on Lipsey, 1990.[45]

The hypotheses for this study called for an analysis of change between baseline, midpoint and endpoint NCS for each group as well as analysis of these NCS measures

between groups. Paired t-tests were used to compare baseline, midpoint and endpoint NCS values for each treatment group independently. Analysis of covariance (ANCOVA) was used to compare the baseline, midpoint and endpoint NCS values between groups. Analysis of the MRI assessed for change between baseline and endpoint for A/P and transverse diameters, cross-sectional area of the carpal tunnel, and signal intensity of the median nerve and carpal tunnel. The study design also called for analysis of the baseline and endpoint MRI measures between groups. Paired t-tests were used to compare baseline and endpoint MRI measures for each treatment group independently. ANCOVA was used to compare the baseline and endpoint MRI measures between groups.

In order to provide a full description of the population and the outcomes, and to examine the data prior to hypothesis testing, we utilized exploratory data analysis techniques (EDA). EDA is an approach/philosophy for data analysis that employs a variety of techniques such as scatter plots, box plots, and other descriptive statistical tools to examine and describe the data in a rich and full manner. EDA enables the researcher to maximize insight into a data set, uncover underlying structure, extract important variables, detect outliers and anomalies, test underlying assumptions, develop parsimonious models, and determine optimal factor settings (Tukey, 1977).[46]

Correlation analysis was performed on NCS to determine their interrelationships. Correlation coefficients were calculated for the relationship between dimensional changes on MRI in the transverse and A/P diameters, and the cross-sectional area and edema. Chi-Square analyses and t-tests were computed to test for differences between the

groups that may be attributable to demographics such as gender, age, and ethnicity. Independent t-tests were also used to compare disease severity between groups.

SUMMARY

This work was conducted within the national Osteopathic Research Center at the UNTHSC. The Principal Investigator in this study, Scott Stoll D.O., Ph.D., is the Executive Director of the ORC, an organization that was created to foster this type of quality clinical trial while training the next generation of clinical researchers.

CTS is very prevalent in the general population and places a significant burden upon society. One in ten adults are afflicted with CTS and pay a high price in time lost from work, medical bills, disability, chronic pain and suffering. All too commonly, these individuals resort to surgery, which does not always resolve their symptoms.

The osteopathic profession has long felt that it has a unique and powerful treatment approach that can significantly improve the signs and symptoms of this potentially crippling disease. However, the profession has been unable to completely and rigorously test the conservative, biomechanical, non-surgical, unique approach of OMT. This exploratory/developmental clinical trial was designed to fill this void through the application of the very best clinical research methodology.

At the completion of this proposed study we hope to have: 1. pilot data in support of our hypotheses, 2. a plausible physiologic model of clinical efficacy for OMT and, 3. a sound experimental protocol that can be appropriately utilized in a larger, more

definitive, clinical trial. The course we will follow in the future is to apply this clinical data to the physiologic model, modify the model as appropriate and design the next most appropriate clinical trial. This design will further evaluate the efficacy of and mechanism by which this conservative, biomechanical, non-surgical approach may help patients with CTS.

CHAPTER III

RESULTS

INTRODUCTION

The study was conducted from September of 2003 to November of 2004 after approval by the Institutional Review Board at the University of North Texas Health Science Center at Fort Worth. The process of recruitment and screening to randomization and study completion is shown in Figure 2 in Appendix A. Approximately 125 subjects were screened by telephone in response to referrals from the clinics, flyers, and campus-wide emails. Following the initial screening, 50 subjects (~ 40%) were screened with nerve conduction studies (NCS) of which 38 subjects (76%) were accepted into the study protocol. After the baseline magnetic resonance imaging (MRI), which was used for screening, one subject was excluded from the study for suspected de Quervain's tenosynovitis. Overall, 37 subjects (74%) were randomized to the two experimental groups following the NCS and MRI screening. Five subjects (14%) did not complete the trial. Of the 32 subjects who completed the trial, 14 (38%) were in the osteopathic manipulative treatment (OMT) group and 18 subjects (49%) were in the placebo sub-therapeutic ultrasound (PSTU) group.

The 32 subjects who completed the trial were retained for statistical analysis. The five subjects that failed to complete the study were not considered for statistical analysis because of incomplete data. These subjects had been randomized to the OMT group, which gave that group a higher rate of attrition than the PSTU group. Only baseline

outcome measures had been collected from them, and together they received an average 1.8 treatments. In addition, despite completing the study protocol and intervention, one additional subject in the PSTU group was excluded from data analysis because of clerical errors which caused parts of the data to be lost. Taking into account these 6 exclusions, the final database used for statistical analysis included 31 subjects, 14 in the OMT group and 17 in the PSTU group.

APPROACH TO THE DATA MANAGEMENT AND ANALYSIS

This study used a mixed factorial model, with two experimental groups and four dependent variables as outcome measures. The study logistics, data set, and data analysis presented several challenges: 1) Dropping the six subjects that had incomplete data required a comparison of the original enrolled 37 subjects with the remaining 31 subjects to determine if the full data set sufficiently represented the clinical population of interest in this study; 2) The mixed factorial design with two groups, three testing intervals, and multiple outcome measures which taken as single variables would not be clinically coherent but taken together would be meaningful, offered extensive possible scenarios for analyses; 3) The controversy over whether one single treatment provider might achieve better outcomes than multiple providers begged to be assessed if possible; and 4) The small sample size presented a risk for a Type II error of accepting the null hypothesis when it may be false, or not detecting a significant change or difference even though one might actually exist.

We have responded to these challenges by 1) Determining whether dropping the 6 incomplete data subjects from the original group of 37 enrolled subjects changed the characteristics of the sample; 2) Using several different but appropriate statistical analysis tools and combining the interpretation of the results with the output from exploratory data analysis techniques; 3) Analyzing a subset of the subjects who were treated by only one treatment provider; and 4) Carefully discerning whether the statistical inferences from analysis of variance tests, tests for differences in means, and correlational analyses support plausible clinical explanations of the findings. In the following sections each of these challenges are addressed.

DESCRIPTION OF THE POPULATION DEMOGRAPHICS

During the course of the study, various demographic descriptors of the subjects were collected to compare with the general clinical population of CTS patients and to make comparisons between the experimental groups. These demographics were evaluated in the 37-subject data set and 31-subject data set. A complete listing of the demographic findings for the 37-subject data set and 31-subject data set are found in Appendix B and Appendix C respectively. Of primary importance to this study is the 31-subject data set, which was used to test the hypotheses for this study.

The demographics of the 37-subject data set were analyzed to determine if the six subjects dropped from the data set were significantly different from the final study population (31). The 37-subject data set had a mean age of 44.1 ± 12.7 yrs, mean height

in meters of 1.65 ± 0.10 m, mean weight in kilograms of 80.4 ± 20.8 kg, mean body mass index (BMI) of 29.4 ± 7.21, and mean length of time since diagnosis of 3.18 ± 4.42 years. Analysis of these demographics using independent t-tests found a significant difference between experimental groups in age ($t=-2.169$, $p=0.037$) and height ($t=2.190$, $p=0.036$), but not in weight, BMI, or length of time since diagnosis. A comparison of genders using these demographics found a significant difference in only height ($t=5.932$, $p<0.0001$) and weight ($t=2.766$, $p=0.009$). Additionally, gender, hand dominance, hand treated, ethnicity, and hand(s) with disease were analyzed for differences between the experimental groups with no significant differences found.

The six subjects who were dropped from the data set, 5 OMT subjects and 1 PSTU subject, had a mean age of 34.4 ± 6.95 years, mean height in meters of 1.72 ± 0.07 m, mean weight in kilograms of 69.3 ± 6.87 kg, mean BMI of 24.1 ± 3.43, and a mean length of time since diagnosis of 1.72 ± 2.86 years and consisted of 2 males and 4 females. These six subjects appear to be younger, lighter in weight, have a smaller BMI, and had the disease for a shorter period of time compared to the complete 37-subject data set.

The 31-subject data set had 14 OMT subjects and 17 PSTU subjects. Analysis of the demographic frequencies found a mean age of 45.7 ± 12.8 years, mean height in meters of 1.65 ± 0.10 m, mean weight in kilograms of 82.3 ± 21.8 kg, mean BMI of 30.3 ± 7.32, and mean length of time since diagnosis of 3.37 ± 4.59 years. The subjects were primarily Caucasian (90.0%) and the majority of the subjects were female (71.9%). The right hand was dominant in 87.1% of the subjects, 83.9% of the subjects had bilateral

CTS, and more right hands were treated (54.8%) than left hands. The left hand was treated in four subjects, 1 OMT subject and 3 PSTU subjects, because of previous carpal tunnel release surgery to the right wrist. All four subjects were right hand dominant and had bilateral CTS.

Analysis of age, height, weight, BMI, length of time since diagnosis, gender, hand dominance, hand treated, ethnicity, and hand(s) with disease for differences between experimental groups using independent t-tests found no significant differences. Analysis between genders for age, height, weight, BMI, and length of time since diagnosis revealed statistically significant differences for height ($t=6.018$, $p<0.0001$) and weight ($t=2.950$, $p=0.006$). The male subjects tended to be taller (1.76 ± 0.08 vs 1.60 ± 0.06 m) and heavier (98.2 ± 17.4 vs 75.5 ± 20.1 kg) than the females. Also, males on average, but not at a level of statistical significance, were younger (42.6 ± 13.2 vs 47.0 ± 12.7yrs), had a higher BMI (31.7 ± 6.36 vs 29.7 ± 7.76), and had the disease for a shorter period of time (1.59 ± 1.41 vs 4.02 ± 5.18 yrs). Bar graphs and histograms of the 31-subject data set demographics can be found in Appendix D. Bar graphs and box plots by treatment group for the 31-subject data set demographics can be found in Appendix E.

There were significant differences between groups in the 37-subject data set in age and height, but these differences were lost when the six subjects with incomplete data were excluded from the data set. The significant differences in height and weight between genders in the 37-subject data set were also found in the 31-subject data set. The other non-significant findings of the 37-subject data set remained non-significant in the 31-subject data set.

NERVE CONDUCTION STUDIES

The primary interest in this study was whether any significant change occurred in the median motor and sensory distal latencies in the OMT group. In order to evaluate for these changes, and test Hypothesis 1, four different NCS measurements were taken: 1) median motor latency (MML), 2) median/ulnar motor latency difference (MLDiff), 3) median sensory latency (MSL), and 4) median/ulnar sensory latency difference (SLDiff). It is important to note that the term "severity" is used in this thesis to mean that NCS values typically have a range from low to high, which may be described as mild, moderate or severe. There is currently no clinical standard which provides a severity scale for CTS. The standards used in current clinical practice for the diagnosis of CTS use NCS measurements from either within a local population or from the literature. Examining the severity NCS in this paper means evaluating whether the NCS scores worsened or improved.

In the 31-subject data set, the mean baseline MML was 4.91 ± 0.96 ms, mean baseline MLDiff was 1.65 ± 0.99 ms, mean baseline MSL was 2.32 ± 0.27 ms, and the mean baseline SLDiff was 0.32 ± 0.28ms. We looked for any differences between experimental groups in baseline NCS using independent t-tests. A significant difference was found in only the MLDiff ($t=-2.654$, $p=0.014$). A positive trend could be seen in the MML that suggests clinical importance even though almost 7% of the time this might have occurred by chance alone ($t=-1.907$, $p=0.068$). On visual comparison of the means between experimental groups, the PSTU group seemed to have more severe CTS on

average, i.e. a higher latency period, but at a statistically significant level for only MLDiff.

Evaluation of the baseline NCS between genders found no significant difference, nor could any important trends be identified on visual examination of the means. The females in this study population had CTS for a significantly longer period of time than the males (4.02 ± 5.18 yrs vs 1.59 ± 1.41, t=-2.001, p=0.055), but this does not seem to correlate, in this population, with disease severity. The baseline measurements in the 37-subject data set were similar to the 31-subject data set on visual comparison. In the 37-subject data set, the only significant difference between groups was found in MLDiff (t=-2.521, p=0.018) and no significant difference between genders could be found. Complete analysis findings of the baseline NCS for the 37-subject data set and 31-subject data set are found in Appendix B and C respectively.

We analyzed the 31-subject data set to determine if there were significant differences within the experimental groups between baseline and endpoint, between baseline and midpoint, and between midpoint and endpoint in MML, MLDiff, MSL and SLDiff using paired t-tests. No statistically significant differences in any of the median nerve distal latency measurements were found for the OMT or PSTU groups between any of the testing intervals. Paired t-test tables are provided in Appendix F. Line graphs representing the score for each of the testing intervals for MML, MLDiff, MSL, and SLDiff can be seen below (Figure 3).

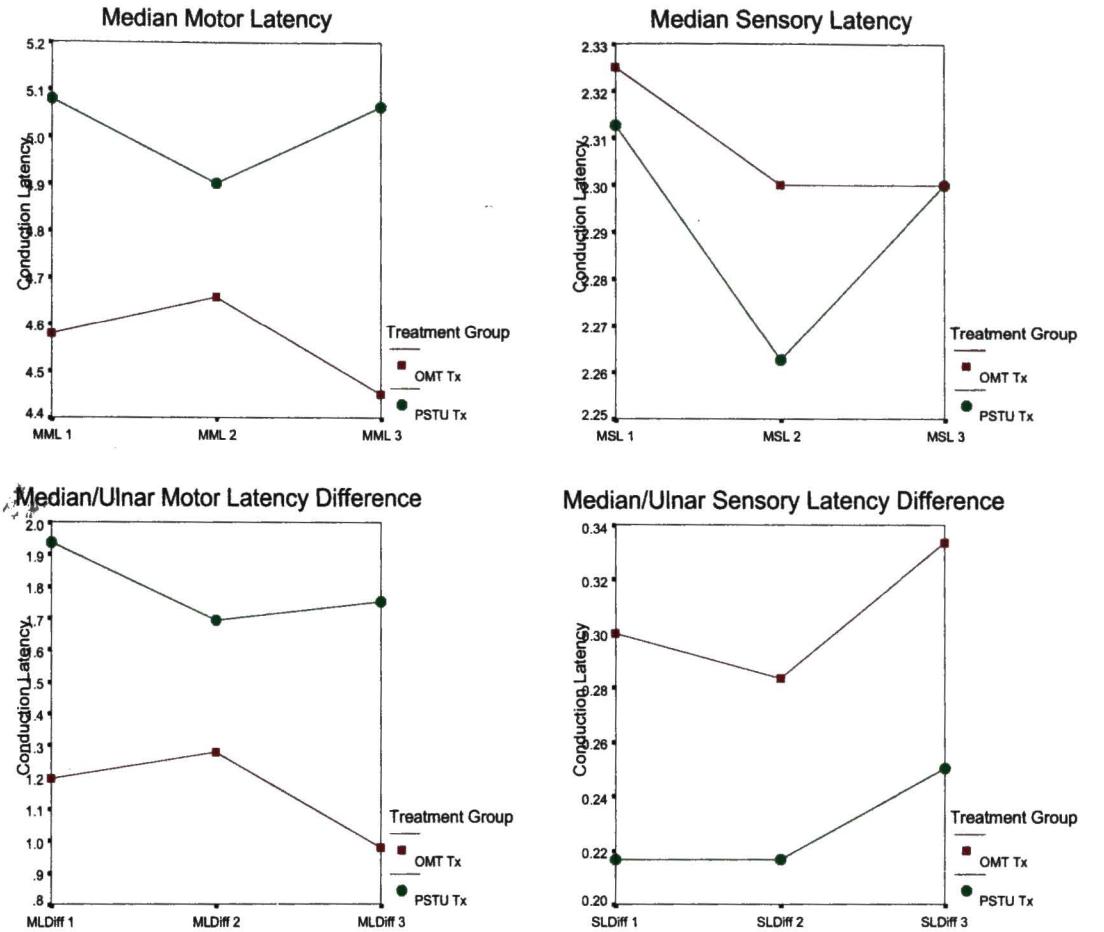


Figure 3: Line Graphs (31-subject data set)

Statistical analysis was performed for between group differences using analysis of covariance (ANCOVA). In the 31-subject data set, ANCOVA with the treatment group as the fixed factor, the post-treatment NCS value as the dependent variable, and the pre-treatment NCS value as the covariate, revealed no significant difference between the groups on any of the outcome measures (MML, MLDiff, MSL and SLDiff). Tables for the ANCOVA at each time interval for MML, MLDiff, MSL, and SLDiff can be found in Table 2 below.

Analysis of Covariance (ANCOVA) – 31-Subject Data Set OMT Group vs PSTU Group at Each Interval				
31	Depend. Var.	Covariate	F	Sig.
MML	Endpoint	Baseline	0.394	0.536
	Endpoint	Midpoint	3.209	0.085
	Midpoint	Baseline	0.332	0.569
MLDiff	Endpoint	Baseline	0.023	0.881
	Endpoint	Midpoint	1.760	0.197
	Midpoint	Baseline	1.144	0.294
MSL	Endpoint	Baseline	0.162	0.693
	Endpoint	Midpoint	0.001	0.975
	Midpoint	Baseline	1.243	0.282
SLDiff	Endpoint	Baseline	0.208	0.657
	Endpoint	Midpoint	1.347	0.270
	Midpoint	Baseline	0.699	0.417

Table 2: ANCOVA (31-subject data set)

ANALYSIS BY TREATMENT PROVIDER

During the study, four different treatment providers (Providers A through D) provided therapy to both groups. Forty-eight percent of the final data set (7 in the OMT group, and 8 in the PSTU group) received all study interventions from a single provider, Provider A. Another six (19.4%) subjects were treated by only Provider B, 2 in OMT and 4 in PSTU. Another 6 subjects (19.4%) (4 OMT, 2 PSTU) received their interventions from a combination of both Providers A and B. The remaining 4 subjects (12.9%) received study interventions from either Provider C alone, or a combination of Providers C and D. Table 3 and Figure 4 below provide information on subjects by treatment group and provider.

Number of Subjects Treated by Treatment Provider			
31	OMT	Ultrasound	Total
Treatment Provider A	7 (22.6%)	8 (25.8%)	15 (48.4%)
Treatment Provider B	2 (6.5%)	4 (12.9%)	6 (19.4%)
Treatment Provider A & B	4 (12.9%)	2 (6.5%)	6 (19.4%)
Treatment Provider C	1 (3.2%)	1 (3.2%)	2 (6.5%)
Treatment Provider C & D	0 (0.0%)	2 (6.5%)	2 (6.5%)
Total	14 (45.2%)	17 (54.8%)	31 (100.0%)

Table 3: Treatment Providers (31-subject data set)

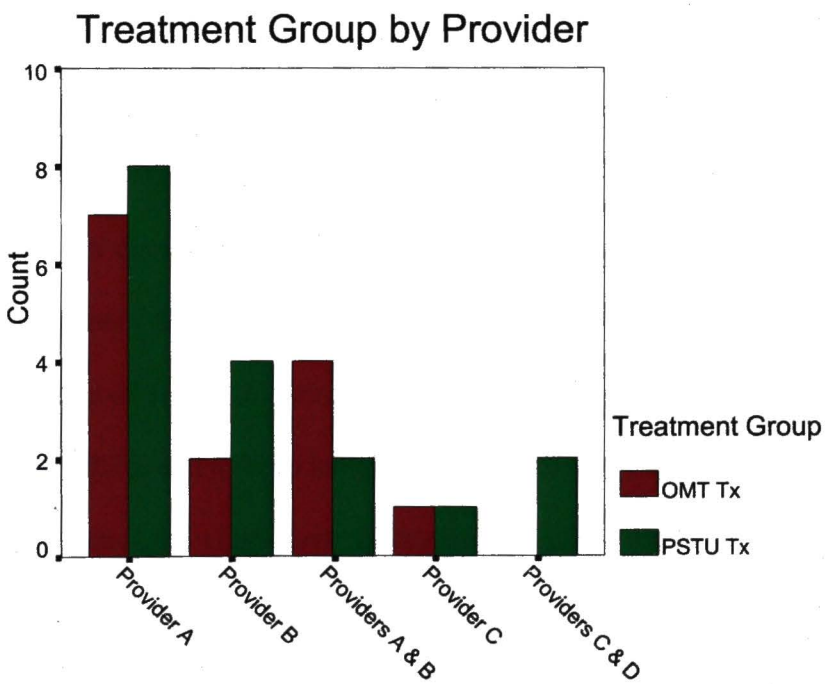


Figure 4: Treatment Group by Provider (31-subject data set)

Since different treatment providers were utilized in this study, the question is raised as to what effect(s) multiple treatment providers have on the study outcomes.

Because of the interest here as well as in other studies, we analyzed the outcome measures for those subjects who received study interventions from only Provider A. Fifteen subjects (48.3%) from the 31-subject data set received study interventions from Provider A, hence the single treatment provider with the greatest number of subjects. The number of subjects receiving interventions from only Providers B, C or D is too small to analyze independently. The results of an analysis of the subjects receiving interventions from only Provider A (15-subject data set) are presented below.

ANALYSIS OF 15-SUBJECT DATA SET

Demographics

The 15-subject data set consisted of 7 subjects in the OMT group and 8 subjects in the PSTU group. A complete listing of demographic findings for the 15-subject data set is found in Appendix G. These 15 subjects had a mean age of 45.1 ± 13.1 years, a mean height in meters of 1.63 ± 0.09 m, a mean weight in kilograms of 78.0 ± 21.2 kg, a mean BMI of 29.4 ± 7.75, and a mean length of time since diagnosis of 4.60 ± 5.88 years. Using independent t-tests, no significant difference was found between the experimental groups in these demographics. A comparison between genders found statistically significant differences in height ($t=4.415$, $p=0.001$) and weight ($t=2.625$, $p=0.022$) but not in age, BMI, and the length of time since diagnosis.

The subjects were all Caucasian and the majority of the subjects were female (73.3%). The right hand was dominant in 93.3% of the subjects, 86.7% of the subjects

had bilateral CTS, and more right hands were treated (60.0%) than left hands. A comparison of the 15-subject data set to all other Providers (16 subjects) combined found no statistically significant differences in any demographic descriptors (data not shown). Bar graphs and histograms of the 15-subject data set demographics can be found in Appendix H. Bar graphs and box plots by treatment group for the 15-subject data set demographics can be found in Appendix I.

Nerve Conduction Studies

The baseline frequencies for NCS revealed the mean baseline MML was 4.60 ± 0.78 ms, the mean baseline MLDiff was 1.36 ± 0.71 ms, the mean baseline MSL was 2.20 ± 0.23 ms, and the mean baseline SLDiff was 0.18 ± 0.34 ms. Comparison of the means using independent t-tests for between experimental groups and genders found no statistically significant differences in baseline NCS. A complete listing of baseline NCS findings can be found in Appendix G.

Analysis of the NCS data for differences at each testing interval within the OMT and PSTU groups independently was performed using paired t-tests. This analysis found differences at the midpoint and endpoint interval for MLDiff ($t=2.594$, $p=0.041$) in the OMT group. The MML at this same interval showed a positive trend towards significance ($t=2.394$, $p=0.054$). The MSL and SLDiff for the midpoint and endpoint interval were not significantly different. Statistical significance was also found in the baseline and endpoint interval for MML ($t=2.635$, $p=0.039$) in the OMT group, but no significant difference between baseline and endpoint in MLDiff, MSL, or SLDiff were found. No significant

difference was found between the baseline and midpoint interval in the OMT group or any of the intervals within the PSTU group. Line graphs representing the score for each of the testing intervals for MML, MLDiff, MSL, and SLDiff are provided Figure 5 below. Paired t-test tables are provided in Appendix J.

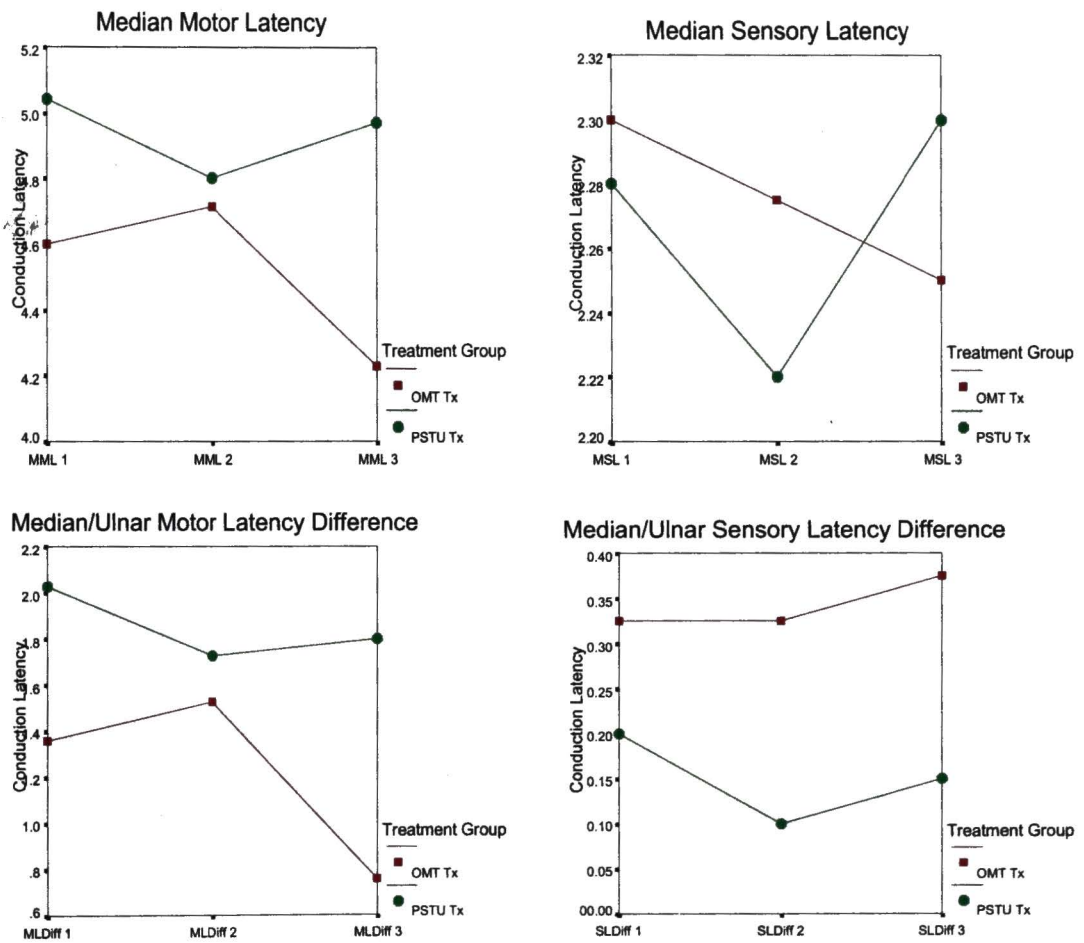


Figure 5: Line Graphs (15-subject data set)

Analysis of the 15-subject data set was performed using ANCOVA, with the treatment group as the fixed factor, the post-treatment NCS value as the dependent variable, and the pre-treatment NCS value as the covariate, to examine differences in the variances of scores for each group at each testing interval. The two groups differed

significantly on MML (F=7.061, p=0.022) and MLDiff (F=5.662, p=0.037) at endpoint, controlling for the midpoint. No significant difference was detected in MSL or SLDiff between the groups at endpoint, controlling for the midpoint. A possible positive trend was found in SLDiff (F=4.518, p=0.078) at midpoint, controlling for baseline but not at a level of significance. No significant difference was identified in the remaining NCS measurements at midpoint, controlling for baseline, nor was any significance found between experimental groups for the endpoint, controlling for baseline. A table for the ANCOVA at each time interval for MML, MLDiff, MSL, and SLDiff is found in Table 4 below.

Analysis of Covariance (ANCOVA) – 15-Subject Data Set OMT Group vs PSTU Group at Each Interval				
15	**Depend. Var.**	**Covariate**	**F**	**Sig.**
MML	Endpoint	Baseline	2.654	0.132
	Endpoint	Midpoint	7.061	0.022
	Midpoint	Baseline	1.095	0.316
MLDiff	Endpoint	Baseline	0.880	0.368
	Endpoint	Midpoint	5.662	0.037
	Midpoint	Baseline	1.420	0.256
MSL	Endpoint	Baseline	1.030	0.349
	Endpoint	Midpoint	3.411	0.114
	Midpoint	Baseline	0.994	0.352
SLDiff	Endpoint	Baseline	0.811	0.403
	Endpoint	Midpoint	1.654	0.255
	Midpoint	Baseline	4.518	0.078

Table 4: ANCOVA (15-subject data set)

Comparison of the 31-subject data set with the 15-subject data set provided a preliminary analysis of the effect(s) of multiple treatment providers in a clinical study. The comparison of these databases found no differences between groups in age, height,

weight, BMI or length of time since diagnosis. Although males differed from females in height and weight, they did not differ in mean age, BMI, or length of time since diagnosis. There seems to be, however, a slight difference, not at the .05 level, but of some interest to this exploratory preliminary study, between males and females in both groups in length of time since diagnosis (31-subject data set: t=-2.001, p=0.055; 15-subject data set: t=-1.791, p=0.097). The baseline NCS for the 31-subject data set revealed a significant difference in only MLDiff (t=-2.654, p=0.014), while the 15-subject data set found no difference between groups. No differences were found between genders in either database for baseline NCS.

A comparison of the 31-subject data set and the 15-subject data set reveals significant differences in NCS of the OMT group independently and between groups. This is of particular importance when analyzing for effect(s) of multiple treatment providers in a manual medicine clinical study. Analysis of the 31-subject data set found no significant difference within or between the experimental groups between baseline and endpoint, between baseline and midpoint, or between midpoint and endpoint in MML, MLDiff, MSL and SLDiff. In contrast, analysis of the 15-subject data set found significant differences in MML at the baseline/endpoint interval and MLDiff at the midpoint/baseline interval. Additionally, analysis for between group differences found significant results in MML and MLDiff at endpoint, controlling for midpoint.

MRI DATA ANALYSIS

The MRI portion of this study could not be finished by the date of submission. The collection of the data for this section remains to be completed, at which time a full analysis will be undertaken. Currently, 31 of the 37 sets of MRI data have been collected and await entry into the database. Upon completion of data collection and entry, a full analysis will be performed on this portion of the study with comparisons and correlations to the NCS section. The results of this analysis will ultimately be published in a peer reviewed journal.

CHAPTER IV

DISCUSSION

INTRODUCTION

The findings reported in this thesis represent only a portion of the analyses that will eventually be performed upon the study database. Therefore, the direction undertaken was to provide an initial analysis of the data to evaluate its resemblance to the general clinical population of carpal tunnel syndrome (CTS) and provide a limited evaluation testing the stated hypotheses. Because of the findings in this initial evaluation, an additional analysis was performed to evaluate for possible effect(s) of different treatment providers. Overall, the findings reported in this thesis provide a thorough overview and initial analysis which will ultimately be used to help formulate the final conclusions.

The total enrollment planned for this study was 50 subjects with CTS confirmed by nerve conduction studies (NCS). At the conclusion of this study, a total of 37 subjects had been consented and randomized to the treatment protocol. For the purpose of statistical analysis, six subjects were dropped from the data set, and a total of 31 subjects were used for complete statistical analysis. Exclusion of these six subjects gave an attrition rate of 16% for this study, which is mildly elevated from the expected rate. Although the study did not meet the planned enrollment and had a slightly higher attrition rate than expected, this had minimal consequence on the preliminary findings because strict power calculations were not adhered to. Despite these limitations, the 31-subject

data set provides a unique preliminary study which can be expanded for larger clinical trials.

DEMOGRAPHICS

The subject population that was used in this study is a good representation of the general clinical population. The majority of the subjects were female as expected, and the mean age of subjects fell within the general clinical population age range of 40 to 60 years. The vast majority of subjects were Caucasian, which approximates the general clinical population. The level of obesity found in this study closely approaches, but did not quite reach the point of increased risk for CTS in the general clinical population (BMI>30). It would be expected for this study population to have a BMI>30, but this may not have been found because diabetes mellitus, which itself is a risk factor for obesity, was considered part of the exclusion criteria. In the general clinical population, the length of time since diagnosis is currently unknown since evidence-based literature can not provide an estimate. Additionally, the length of time since diagnosis may depend heavily upon the annual incidence of CTS. The population in this study is hypothesized to resemble the general clinical population and the length of time since diagnosis may be considered mild to moderate, although this can not be validated. This conclusion is supported by the presence of a majority of subjects with bilateral CTS, since this disease usually begins unilaterally and progresses over time to a bilateral disease.

The demographic findings from each data set were compared not only to establish a resemblance to the general clinical population, but also to evaluate for any effects of excluding the six subjects who had incomplete data. Demographic findings were also used to establish whether a valid comparison could be made between the 31-subject data set and the 15-subject data set. Significant differences were found between experimental groups in only the 37-subject data set. Thus the exclusion of the six subjects with incomplete data left the 31-subject data set and the 15-subject data set with similar demographics.

Statistically significant differences in gender were found in height and weight in each database studied. The males were found to be taller and weigh more than the females, which based upon the general population would be expected and should have no bearing upon the results of this study. The exclusion of the six subjects with incomplete data had no effect upon differences in gender, nor did the exclusion of all other treatment providers in forming the 15-subject data set. In addition, a comparison of those subjects in the 15-subject data set with the remaining 16 subjects found no statistical difference in any of the demographics (data not shown), further establishing the similarity between the 31-subject data set and the 15-subject data set in terms of demographics.

The baseline NCS were evaluated in each database to establish the baseline disease severity since clinically a patient with more severe CTS could be more difficult to treat and less likely to show objective improvement in their disease. Differences in baseline NCS for the experiment groups were found in only median/ulnar motor latency difference (MLDiff) for the 37-subject data set and the 31-subject data set, and no

difference was found for the 15-subject data set. Additionally, no differences were found between genders for any of the databases. Thus, the conclusion can be drawn that in the 15-subject data set, differences in disease severity probably had no bearing upon the presence or absence of statistical findings in the outcome measures. However, in the 31-subject data set, since a difference was found in MLDiff and no differences were found in baseline, midpoint, and endpoint MLDiff NCS, there remains the question concerning the effects of disease severity on the absence of significant improvement in MLDiff NCS. This question is further exemplified by the presence of significant improvement in MLDiff in the 15-subject data set when no differences in disease severity were found in baseline NCS.

MISCELLANEOUS POINTS OF DISCUSSION

Clinical research in osteopathic manipulative treatment (OMT) presents a unique challenge to investigators because of the variety of different therapeutic approaches with different techniques which can be utilized, not only for each disease, but also for each subject. As is found in all other aspects of medicine, treating a patient is a combination of art and science. There are always variations in the treatment approach and a large portion of medicine is not restricted to specific protocols, so the use of a cookbook recipe as therapy does not suffice. Since OMT is in many aspects an art and has the potential of great variability, a clinical researcher has to choose whether to allow flexibility or set specific standards in the treatment protocol.

The treatment approach in this study was designed for a balance between flexibility and standardization. Since multiple treatment providers were used in this study, some degree of flexibility was necessary. Each treatment provider has certain OMT technique preferences that coincide with his or her level of skill or knowledge as well as comfort. In addition, each patient presents with different physical findings on examination, which when coupled with a different body habitus, necessitates the need for some degree of flexibility. In contrast, strong research design and analysis requires rigorous methods that can be standardized, particularly in a preliminary study such as this. More standardization across the protocol may be important in order to control for other factors and draw out the portion of the effect that truly belongs to the action of the OMT intervention. Only in this way can we compare various groups of clinically-unique patients in a study and draw solid, meaningful clinical conclusions from such studies.

In order to reach a balance between flexibility and standardization, the research design in this study dictated an OMT protocol with specific techniques to be used in specific regions without flexibility, as well as a variety of techniques that may be used in other regions where preference and skill may dictate a successful treatment. Standardized treatments were applied to the wrist, forearm and shoulder based upon previous OMT literature on CTS and because these treatments could be easily standardized between different treatment providers. Flexibility was allowed for treatment of the neck and upper back, where different techniques require different levels of skill. This ultimately allowed some balance between flexibility and standardization.

An additional challenge in OMT research is the issue of treatment dosage and frequency. Current clinical practice based upon anecdotal evidence suggests that efficacy may be derived by providing treatments with longer duration at a higher frequency, but aside from being impractical in the clinical setting, there is no evidence based research literature to support this. On the other hand, long periods between treatments might decrease the likelihood of achieving the desired clinical outcomes. So the question is: "What factors should determine the dosage and frequency for OMT?"

The problem is that the dosage and frequency of treatment in the clinical setting is usually based on subjective patient reports and physician reimbursement. Current evidence-based OMT literature does not provide standards or recommendations for dosage and frequency of treatment. Since no standards are found within the literature, the dosage and frequency of treatment in this study was drawn from the available manual medicine and CTS research literature collectively. At the conclusion of this study, it is not possible to make generalized statements regarding appropriate dosage or frequency based upon any of the study findings. Final conclusions and recommendations shall be reserved for future studies with larger numbers of subjects.

Another aspect of OMT clinical research which merits discussion, since it relates directly to this study, is the incorporation of a placebo or sham into the experimental design. In the era of modern medicine, medical therapies do not rely solely upon clinical experience as it has been done traditionally in the past. Current medical decisions are most often derived from evidence-based findings in the medical literature. These evidence-based findings formulate treatment guidelines which dictate the best therapeutic

options for the best medical care. In order to formulate these treatment guidelines from the evidence-based findings, the experimental design of clinical research must incorporate a placebo. This presents a unique challenge for all forms of manual medicine because there are no existing standards to validate any placebo used in the manual medicine literature. Since there are no existing standards, different manual medicine placebos are chosen arbitrarily in each clinical study. This potentially leads to a great degree of variability in how patients may respond to the placebo treatment and prevents comparisons across different studies.

In the current literature, a wide variety of manual medicine placebos have been utilized, including light touch musculoskeletal manipulation, sub-therapeutic ultrasound therapy, gentle massage techniques, and sham adjustments of minimal force to name a few. Sub-therapeutic ultrasound was chosen for this study for a variety of reasons. Most importantly, some evidence in the literature supports the use of ultrasound as a true therapy for CTS, forming the belief that this therapy was beneficial. Additionally, sub-therapeutic ultrasound has been used in other studies at our university and the protocol was very reproducible. Since no standards to validate this placebo are available, it is impossible assess whether any placebo effect found in this study would be similar to the effect found with a different placebo type.

LIMITATIONS

Before discussing the findings found in the outcome measures, a discussion of the limitations within the methodology of this study is merited. One of the overall goals of this study was to develop a sound methodology based upon previous studies, which took into account and corrected any methodologic design flaws. A variety of different methodologies were found in the literature and all attempts were made to remove inconsistencies in those methodologies, but despite our efforts, certain controlled as well as uncontrolled limitations were inherently present in this study.

Probably the most serious limitation in this study is the number of subjects that were recruited and retained through completion of the study. The number of subjects that were recruited in this study was not based on power calculations because the number estimated was beyond the scope of this preliminary study. This limitation alone has serious implications on the interpretation of the statistical findings. This limitation was further compounded by the lower than expected recruitment and retention numbers. Thus, since this study did not rely upon power for statistical analysis, and recruitment was lower than expected, any significant as well as non-significant findings should be interpreted with caution and efforts should be made not to make broad, generalizing statements concerning the overall results of this preliminary clinical trial.

Nerve conduction studies are traditionally performed in the clinical setting by a trained physician or technician. This was not the case in this study because of financial and logistical reasons. Alternatively, a clinical research coordinator (CRC) was trained by

the principal investigator, who has significant training and expertise with electrodiagnostic testing, to conduct a limited NCS as outlined by the outcome measures. This presents as a significant limitation in this study because of the lack of experience of the CRC in conducting these tests. When reviewing the raw data, multiple random NCS values were excluded from the database because of technical issues related to collection of the NCS. The majority of the excluded NCS values were the result of median sensory analysis, which is expected since evaluation of the sensory component of a nerve is more difficult than the motor component. This limitation not only has implications because of a lack of NCS provider experience, but also because it resulted in a significant decrease in the number of usable data points in an already under-powered study.

The goal of this study was to evaluate the effects of OMT in a heterogeneous population of patients with CTS that resembled the general clinical population. Despite all the efforts to enroll subjects from the surrounding community through newspaper ads and flyers within the clinic in order to form a heterogeneous population, the majority of the subjects were from either within the university or direct referrals from university employees. Thus, the subjects of this study do not truly represent a homogeneous population, but they also do not have the diversity that was desired. The implications of this limitation on the analysis of this study should be minimal to none, but this should be considered in future studies, with greater efforts to diversify the subject population to match the surrounding community.

In the clinical setting, CTS can be diagnosed with a variety of diagnostic tools in addition to a thorough review of the patient's history. The diagnosis of CTS in this study

was based upon a clinical diagnosis from the subject's private physician as well as a limited NCS. A thorough history, if completed by the treatment provider, was not always examined until after the subject was enrolled in the study. Ultimately, this may have allowed the possible enrollment of some subjects with a disease whose symptoms mimic CTS. To prevent this limitation in future studies, the inclusion parameters should include the use of additional objective measures that evaluate for CTS as well as a more thorough history.

The best methodologic design for clinical trials involves the use of an experimental group, a placebo or sham group, and a control group. The experimental design used in this study had only an experimental group and a placebo group, which limits this study by the absence of a non-experimental baseline point of reference. Since this was a preliminary study with a small number of subjects, the assumption was made that the severity of disease for most subjects would not change drastically during the course of their enrollment if they were not treated, so a control group was not used. This limitation should have a minimal effect upon our study, but future studies should prevent this by including a control group.

Since OMT is a therapy that has the potential to have an extremely high degree of variability among different treatment providers, the use of multiple providers will inherently represent a limitation to any OMT clinical trial. This study was originally designed to have only two treatment providers, which would have logistically allowed the study to be completed and would have minimized the effects of different treatment providers. Additionally, any effect from different providers could be delineated by a

separate analysis for each provider. But, at the completion of this study, five different treatment providers were utilized. This limitation was fully considered during data analysis and any conclusions drawn from the data accounted for this limitation.

NERVE CONDUCTION STUDIES

The ultimate goal of this study was to determine if OMT is effective in treating CTS. Multiple outcomes were measured, but NCS was the primary outcome measure of interest. Because NCS are the primary objective tool used to diagnose CTS in clinical practice, it was only logical that these tests should be used as outcome measures. The specific NCS used in this study, median motor latency (MML), median/ulnar motor latency difference (MLDiff), median sensory latency (MSL), and median/ulnar sensory latency difference (SLDiff), were selected from the evidence-based recommendations for clinical practice. To establish efficacy, the NCS were analyzed as repeated measures within the OMT and the placebo sub-therapeutic ultrasound (PSTU) groups independently, as well as between these two groups.

31-Subject Data Set

The analysis of the 31-subject data set found no significant differences in either the OMT group or the PSTU group between baseline and endpoint, between baseline and midpoint, or between midpoint and endpoint for MML, MLDiff, MSL and SLDiff. Additionally, no significant between group differences for any of the NCS were found

using ANCOVA with the treatment group as the fixed factor, the post-treatment NCS value as the dependent variable, and the pre-treatment NCS value as the covariate. These findings, if taken at face value, support the null hypothesis that OMT does not decrease the median motor and sensory distal latency in patients with CTS. But, before accepting the null hypothesis, the limitations that are present in this study should be fully considered and any possible effects accounted for.

15-Subject Data Set

The most obvious limitation that can be addressed from an analysis perspective is the presence of multiple treatment providers. This experimental design issue was re-evaluated because a separate subset analysis could be performed based on the one treatment provider that treated the greatest number of subjects. Analysis of the 15-subject data set, which contained only those subjects treated by Provider A, represented the largest number of subjects to receive interventions by one treatment provider. Thus, a preliminary analysis of the effects of multiple treatment providers was undertaken.

The analysis of the 15-subject data set found significant differences in the OMT group for MML between baseline and endpoint and MLDiff between midpoint and endpoint. Additionally, MML in the OMT group showed a positive trend towards a significant difference between midpoint and endpoint that may be considered to be clinically important and is certainly worthy of a follow-up study with a larger number of subjects. MML and MLDiff for the OMT group revealed a decrease in the mean latency period indicating an improvement in nerve conduction. In the analysis for between group

differences, significant results were found in both MML and MLDiff at endpoint, controlling for midpoint. The mean MML and MLDiff decreased in the OMT group and increased in the PSTU group, indicating improvement of the OMT group and worsening of the PSTU group. The lack of statistical significance in MML between groups at endpoint controlling for baseline and the presence of significance in MML between groups at endpoint controlling for midpoint has no explanation. The cause of this inconsistency will most likely only be determined through future studies that have a greater enrollment, thus a greater power for statistical analysis. Overall, interpretation of the results of the 15-subject data set is difficult. There are some positive findings, but the limitations described above still apply to this sub-set of data.

Sensory NCS

The lack of significant findings in the sensory component compared to the motor component is a concern, but actually expected because of the large number of sensory values which were dropped from the data set. The lack of significant findings in sensory latency for the OMT group, as well as between groups, may represent inaccurate results for the subject population. This finding may be primarily attributed to the limitation described above.

CONCLUSIONS & FUTURE CLINICAL STUDIES

The results of this study indicate the possibility for improvement of CTS through the use of OMT, but no conclusive statements about the efficacy of OMT can be made. Additionally, analysis of the MRI data has not been finished. When completed, this portion of the research design may allow further interpretation of the study data. This preliminary study provides the framework for future studies and enabled us to identify multiple areas in the research design and methodology that may be improved. This preliminary study led to the submission of a National Institute of Health R21 exploratory/developmental grant application aimed at continuing and expanding this research. The major limitation of this study was the lack of statistical power because of low enrollment numbers. The goal of future studies should be to correct the limitations of this study, determine the efficacy of OMT with additional formulation of a dose-response curve, determine the mechanism of OMT, and incorporate the use of OMT into the current standard of medical care and health policy related to CTS.

APPENDICES

LIST OF APPENDICES

APPENDIX A

Flow of Subjects Through Study

APPENDIX A

Flow of Subjects Through Study

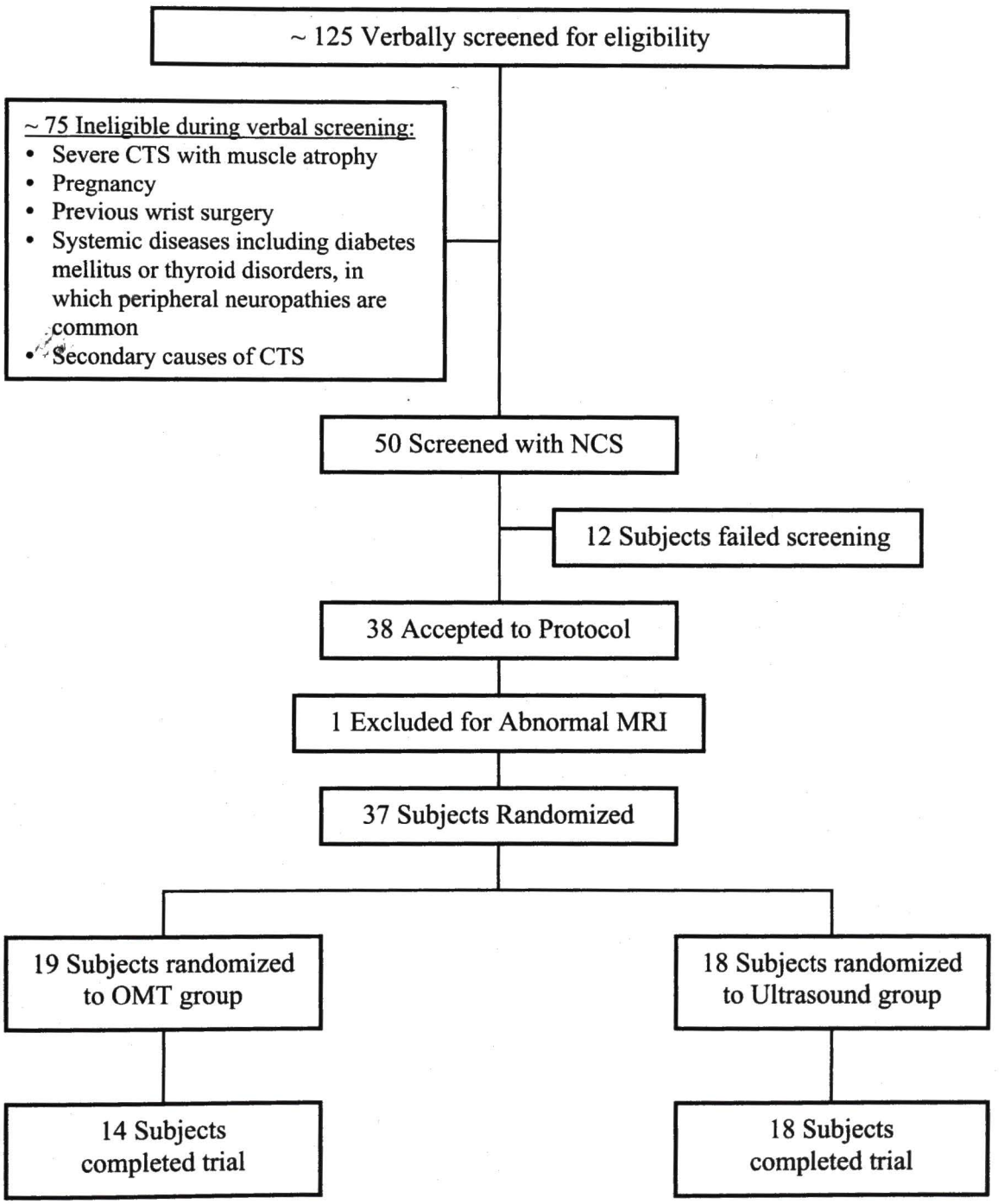


Figure 2: Flow of Subjects Through Study

APPENDIX B

37-Subject Data Set Demographics & Baseline NCS Frequencies

APPENDIX B

37-Subject Data Set Demographics & Baseline NCS Frequencies

Demographic Frequencies					
37	**Age**	**Height (m)**	**Weight (kg)**	**BMI**	**Yrs since Dx**
Mean	44.1	1.65	80.4	29.4	3.18
Std. Dev.	12.7	0.1	20.8	7.21	4.42
Min/Max	22/65	1.47/1.93	47.6/124.7	17.0/47.8	0.08/18.0

Demographic Frequencies & Pearson Chi-Square Analysis Between Groups						
37	**Ethnicity**					
	Cauc	**Afr Amer**	**Hisp**	**Chi-Square**	**df**	**Sig.**
OMT	16 (45.7%)	1 (2.9%)	1 (2.9%)	0.004	2	0.998
Ultrasound	15 (42.9%)	1 (2.9%)	1 (2.9%)			
Total	31 (88.6%)	2 (5.7%)	2 (5.7%)			
	Hand with Disease					
	Right	**Left**	**Both**	**Chi-Square**	**df**	**Sig.**
OMT	3 (8.3%)	0 (0.0%)	16 (44.4%)	1.203	2	0.548
Ultrasound	3 (8.3%)	1 (2.8%)	13 (36.1%)			
Total	6 (16.7%)	1 (2.8%)	29 (80.6%)			
	Hand Dominance					
	Right	**Left**	**Ambid**	**Chi-Square**	**df**	**Sig.**
OMT	14 (38.9%)	4 (11.1%)	1 (2.8%)	2.831	2	0.243
Ultrasound	16 (44.4%)	1 (2.8%)	0 (0.0%)			
Total	30 (83.3%)	5 (13.9%)	1 (2.8%)			
	Gender					
	Male	**Female**	**Chi-Square**	**df**	**Sig.**	
OMT	7 (18.9%)	12 (32.4%)	0.946	1	0.476 [a]	
Ultrasound	4 (10.8%)	14 (37.8%)				
Total	11 (29.7%)	26 (70.3%)				
	Hand Treated					
	Right	**Left**	**Chi-Square**	**df**	**Sig.**	
OMT	10 (27.0%)	9 (24.3%)	0.271	1	0.743 [a]	
Ultrasound	11 (29.7%)	7 (18.9%)				
Total	21 (56.8%)	16 (43.2%)				
a. Fisher's Exact Test used because of small sample size						

Demographic Frequencies & Independent t-test for Equality of Means Between Groups					
37	Group	Mean	Std. Dev.	t	Sig. (2-tailed)
Age	OMT	40.0	12.6	-2.169	0.037
	Ultrasound	48.8	11.5		
Height (m)	OMT	1.69	0.10	2.190	0.036
	Ultrasound	1.62	0.08		
Weight (kg)	OMT	80.1	20.2	-0.110	0.913
	Ultrasound	80.8	21.9		
BMI	OMT	27.8	5.06	-1.328	0.193
	Ultrasound	31.1	8.80		
Years since Dx	OMT	2.48	2.81	-0.913	0.370
	Ultrasound	3.87	5.60		

Demographic Frequencies & Independent t-test for Equality of Means Between Genders					
37	Gender	Mean	Std. Dev.	t	Sig. (2-tailed)
Age	Male	42.1	12.2	-0.635	0.530
	Female	45.0	13.1		
Height (m)	Male	1.76	0.08	5.932	<0.0001
	Female	1.60	0.07		
Weight (kg)	Male	93.6	18.7	2.766	0.009
	Female	74.4	19.1		
BMI	Male	30.3	6.50	0.507	0.616
	Female	29.0	7.60		
Years since Dx	Male	2.08	1.98	-0.862	0.395
	Female	3.57	5.00		

NCS Baseline Frequencies				
37	MML 1	Median/Ulnar MLDiff 1	MSL 1	Median/Ulnar SLDiff 1
Mean	4.98	1.67	2.38	0.32
Std. Dev.	0.92	0.95	0.31	0.27
Min/Max	3.6/7.7	0.0/4.4	1.8/3.1	-0.4/0.8

NCS Baseline Frequencies & Independent t-test for Equality of Means Between Groups						
37	Group	Mean	Std. Dev.	Min/Max	t	Sig. (2-tailed)
MML 1	OMT	4.76	0.65	3.8/6.0	-1.492	0.147
	Ultrasound	5.21	1.11	3.6/7.7		
Median/Ulnar MLDiff 1	OMT	1.29	0.61	0.5/2.4	-2.521	0.018
	Ultrasound	2.04	1.10	0.0/4.4		
MSL 1	OMT	2.41	0.33	1.8/3.1	0.623	0.539
	Ultrasound	2.34	0.29	1.9/2.8		
Median/Ulnar SLDiff 1	OMT	0.31	0.28	-0.4/0.8	-0.192	0.851
	Ultrasound	0.33	0.27	0.0/0.8		

NCS Baseline Frequencies & Independent t-test for Equality of Means Between Genders						
37	Group	Mean	Std. Dev.	Min/Max	t	Sig. (2-tailed)
MML 1	Male	4.92	1.15	3.6/7.7	-0.245	0.808
	Female	5.00	0.82	3.8/6.8		
Median/Ulnar MLDiff 1	Male	1.60	1.09	0.7/4.4	-0.275	0.785
	Female	1.70	0.91	0.0/3.3		
MSL 1	Male	2.42	0.35	1.9/3.1	0.507	0.617
	Female	2.36	0.29	1.8/2.9		
Median/Ulnar SLDiff 1	Male	0.33	0.28	0.0/0.8	0.220	0.828
	Female	0.31	0.28	-0.4/0.8		

APPENDIX C

31-Subject Data Set Demographics & Baseline NCS Frequencies

APPENDIX C

31-Subject Data Set Demographics & Baseline NCS Frequencies

Demographic Frequencies					
31	**Age**	**Height (m)**	**Weight (kg)**	**BMI**	**Yrs since Dx**
Mean	45.7	1.65	82.3	30.3	3.37
Std. Dev.	12.8	0.10	21.8	7.32	4.59
Min/Max	22/65	1.47/1.93	47.6/124.7	17.0/47.8	0.08/18.0

Demographic Frequencies & Pearson Chi-Square Analysis Between Groups						
31	**Ethnicity**					
	Cauc	**Afr Amer**	**Hisp**	**Chi-Square**	**df**	**Sig.**
OMT	12 (40.0%)	0 (0.0%)	1 (3.3%)	0.814	2	0.665
Ultrasound	15 (50.0%)	1 (3.3%)	1 (3.3%)			
Total	27 (90.0%)	1 (3.3%)	2 (6.7%)			
	Hand with Disease					
	Right	**Left**	**Both**	**Chi-Square**	**df**	**Sig.**
OMT	1 (3.2%)	0 (0.0%)	13 (41.9%)	1.726	2	0.422
Ultrasound	3 (9.7%)	1 (3.2%)	13 (41.9%)			
Total	4 (12.9%)	1 (3.2%)	29 (83.9%)			
	Hand Dominance					
	Right	**Left**	**Ambid**	**Chi-Square**	**df**	**Sig.**
OMT	11 (35.5%)	2 (6.5%)	1 (3.2%)	1.988	2	0.370
Ultrasound	16 (51.6%)	1 (3.2%)	0 (0.0%)			
Total	27 (87.1%)	3 (9.7%)	1 (3.2%)			
	Gender					
	Male	**Female**	**Chi-Square**	**df**	**Sig.**	
OMT	5 (16.1%)	9 (29.0%)	0.553	1	0.693 [a]	
Ultrasound	4 (12.9%)	13 (41.9%)				
Total	9 (29.0%)	22 (71.0%)				
	Hand Treated					
	Right	**Left**	**Chi-Square**	**df**	**Sig.**	
OMT	7 (22.6%)	7 (22.6%)	0.241	1	0.725 [a]	
Ultrasound	10 (32.3%)	7 (22.6%)				
Total	17 (54.8%)	16 (45.2%)				
a. Fisher's Exact Test used because of small sample size						

Demographic Frequencies & Independent t-test for Equality of Means Between Groups					
31	Group	Mean	Std. Dev.	t	Sig. (2-tailed)
Age	OMT Ultrasound	42.0 48.8	13.7 11.5	-1.492	0.146
Height (m)	OMT Ultrasound	1.68 1.62	0.12 0.08	1.794	0.084
Weight (kg)	OMT Ultrasound	84.2 80.8	22.3 21.9	0.411	0.684
BMI	OMT Ultrasound	29.3 31.1	4.94 8.80	-0.647	0.523
Years since Dx	OMT Ultrasound	2.72 3.87	2.87 5.60	-0.732	0.505

Demographic Frequencies & Independent t-test for Equality of Means Between Genders					
31	Gender	Mean	Std. Dev.	T	Sig. (2-tailed)
Age	Male Female	42.6 47.0	13.2 12.7	-0.873	0.390
Height (m)	Male Female	1.76 1.60	0.08 0.06	6.018	<0.0001
Weight (kg)	Male Female	98.2 75.5	17.4 20.1	2.950	0.006
BMI	Male Female	31.7 29.7	6.36 7.76	0.698	0.491
Years since Dx	Male Female	1.59 4.02	1.41 5.18	-2.001	0.055

NCS Baseline Frequencies				
31	MML 1	Median/Ulnar MLDiff 1	MSL 1	Median/Ulnar SLDiff 1
Mean	4.91	1.65	2.32	0.32
Std. Dev.	0.96	0.99	0.27	0.28
Min/Max	3.6/7.7	0.0/4.4	1.8/2.8	-0.4/0.8

NCS Baseline Frequencies & Independent t-test for Equality of Means Between Groups						
31	Group	Mean	Std. Dev.	Min/Max	T	Sig. (2-tailed)
MML 1	OMT	4.58	0.56	3.8/5.5	-1.907	0.068
	Ultrasound	5.18	1.13	3.6/7.7		
Median/Ulnar MLDiff 1	OMT	1.19	0.55	0.5/2.1	-2.654	0.014
	Ultrasound	2.02	1.13	0.0/4.4		
MSL 1	OMT	2.30	0.25	1.8/2.7	-0.330	0.745
	Ultrasound	2.34	0.30	1.9/2.8		
Median/Ulnar SLDiff 1	OMT	0.32	0.31	-0.4/0.8	-0.093	0.927
	Ultrasound	0.33	0.27	0.0/0.8		

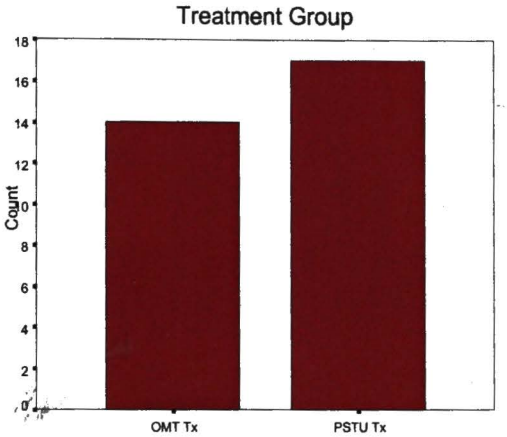
NCS Baseline Frequencies & Independent t-test for Equality of Means Between Genders						
31	Group	Mean	Std. Dev.	Min/Max	T	Sig. (2-tailed)
MML 1	Male	4.83	1.22	3.6/7.7	-0.268	0.791
	Female	4.94	0.86	3.8/6.8		
Median/Ulnar MLDiff 1	Male	1.61	1.14	0.7/4.4	-0.120	0.905
	Female	1.66	0.95	0.0/3.3		
MSL 1	Male	2.34	0.29	1.9/2.8	-0.239	0.814
	Female	2.31	0.27	1.8/2.8		
Median/Ulnar SLDiff 1	Male	0.35	0.29	0.0/0.8	-0.324	0.750
	Female	0.31	0.29	-0.4/0.8		

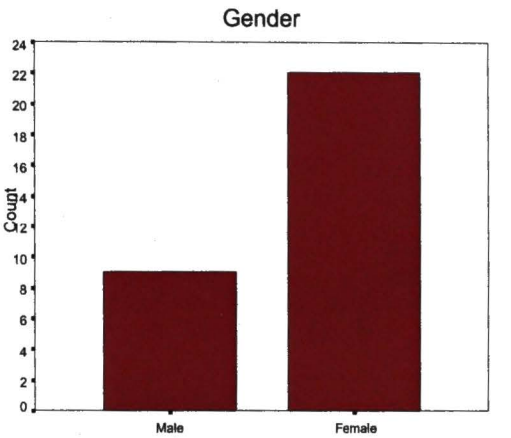
APPENDIX D

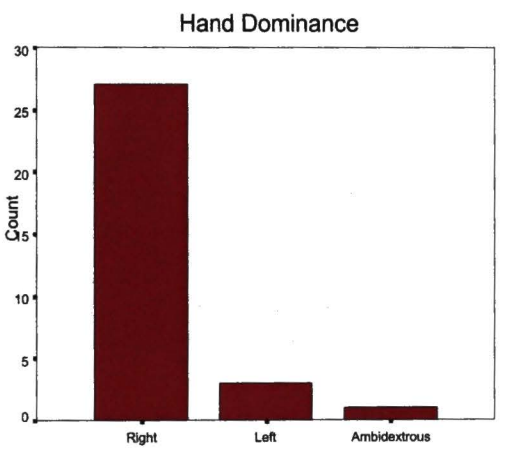
31-Subject Data Set Bar Graphs and Histograms

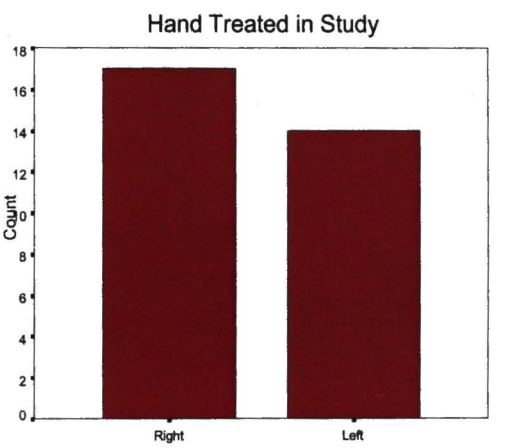
APPENDIX D

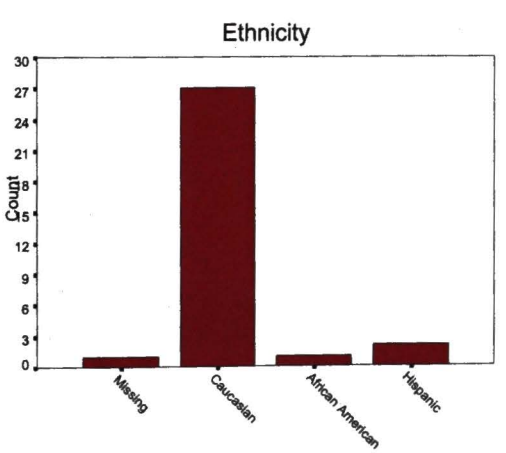
31-Subject Data Set Bar Graphs and Histograms

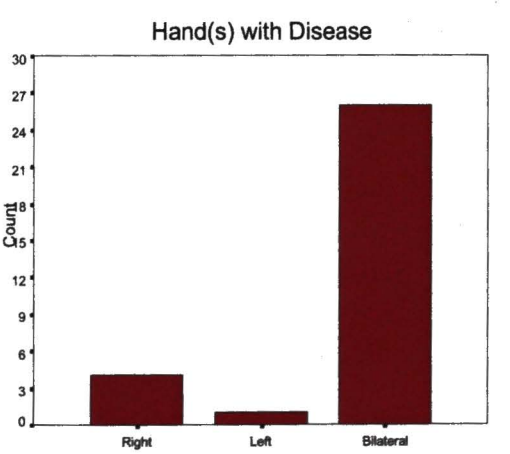


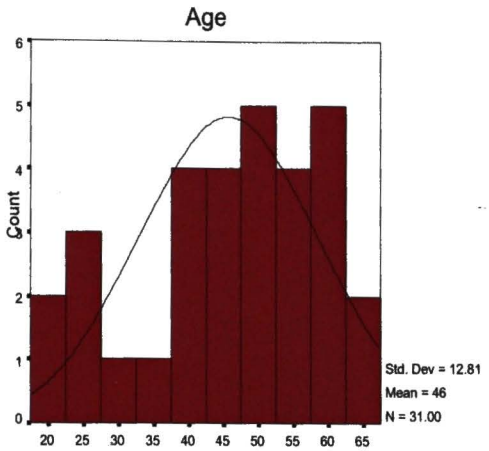








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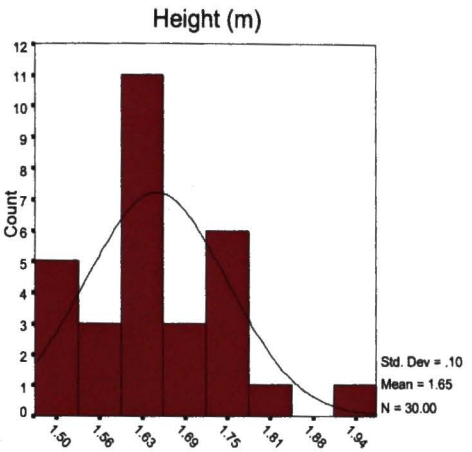
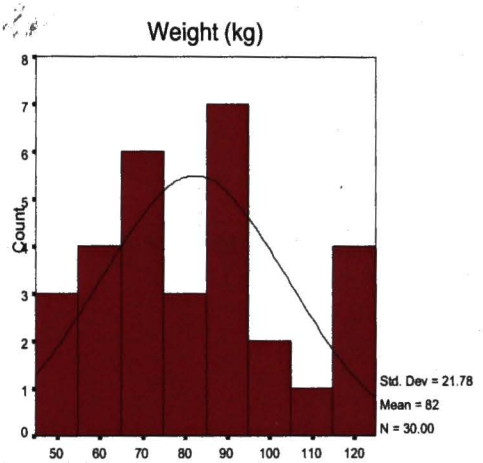

Height (m)
Count
Std. Dev = .10
Mean = 1.65
N = 30.00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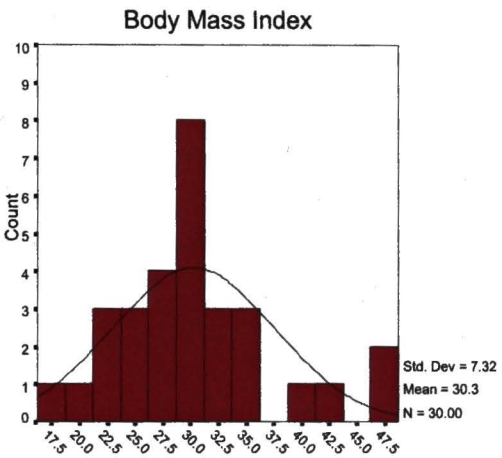
Body Mass Index
Count
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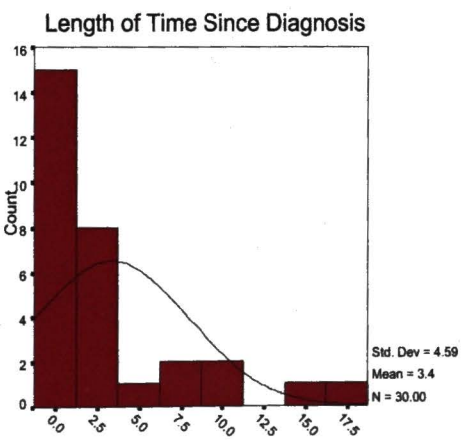
N = 30.00


Length of Time Since Diagnosis
Count
Std. Dev = 4.59
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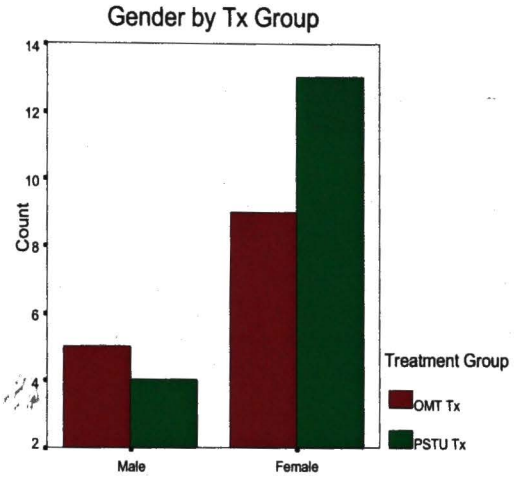
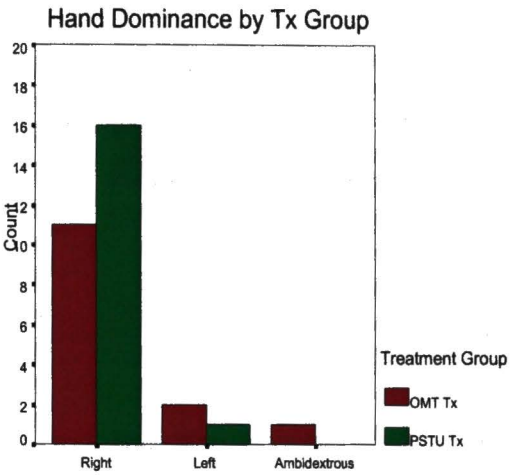
APPENDIX E

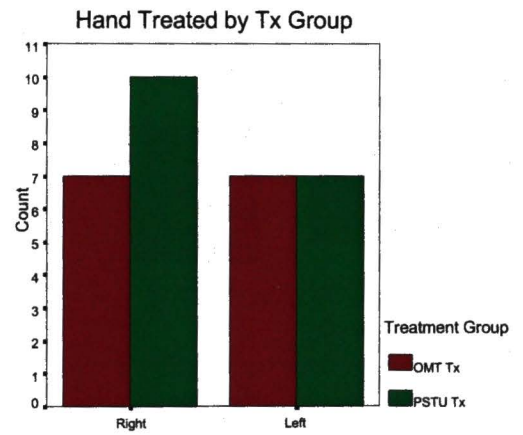
31-Subject Data Set Bar Graphs and Box Plots by Treatment Group

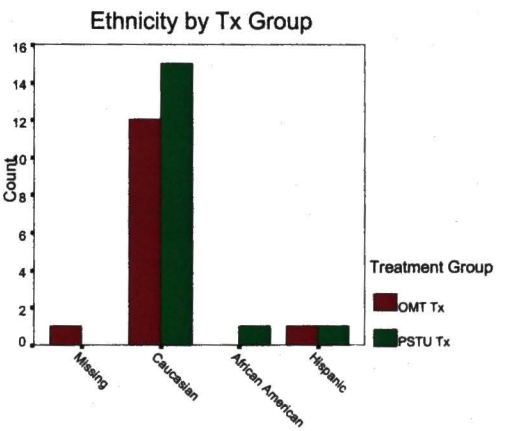
APPENDIX E

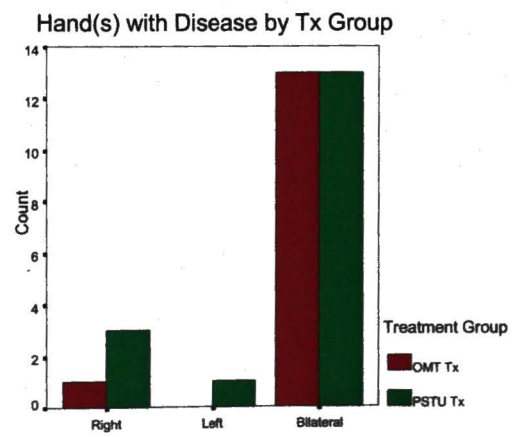
31-Subject Data Set Bar Graphs and Box Plots by Treatment Group



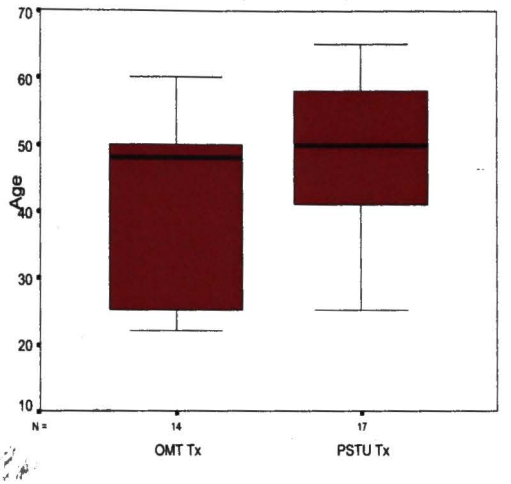




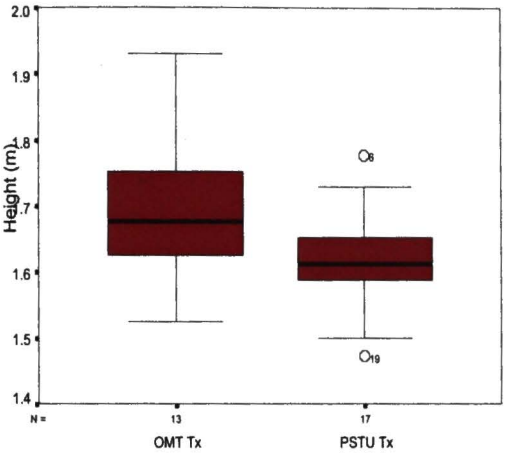




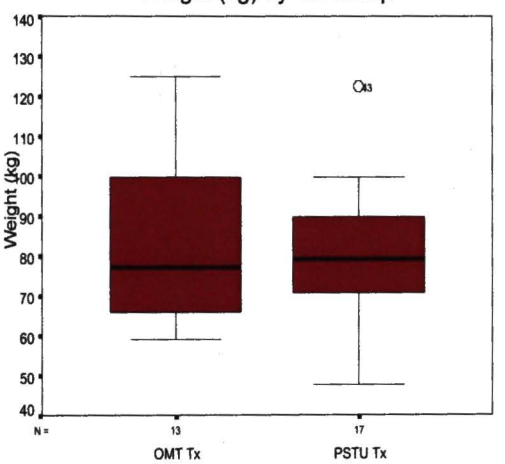
Age by Tx Group



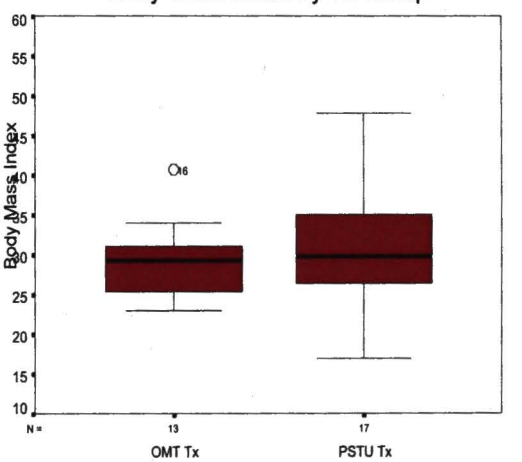
Height (m) by Tx Group



Weight (kg) by Tx Group

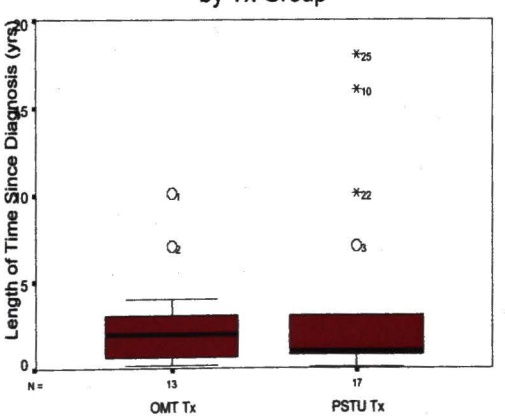


Body Mass Index by Tx Group



Length of Time Since Diagnosis

by Tx Group



APPENDIX F

31-Subject Data Set Paired t-test Tables

APPENDIX F

31-Subject Data Set Paired t-test Tables

Paired t-test: Baseline & Endpoint OMT Group NCS						
31	Mean	Std. Dev.	Mean Diff	Std. Dev.	t	Sig. (2-tailed)
MML 1	4.579	0.56	0.129	0.53	0.913	0.378
MML 3	4.450	0.69				
MLDiff 1	1.193	0.56	0.214	0.79	1.011	0.330
MLDiff 3	0.979	0.70				
MSL 1	2.311	0.17	-0.022	0.16	-0.426	0.681
MSL 3	2.333	0.20				
SLDiff 1	0.300	0.10	-0.071	0.21	-0.918	0.394
SLDiff 3	0.371	0.17				

Paired t-test: Baseline & Midpoint OMT Group NCS						
31	Mean	Std. Dev.	Mean Diff	Std. Dev.	t	Sig. (2-tailed)
MML 1	4.579	0.56	-0.079	0.59	-0.501	0.625
MML 2	4.657	0.63				
MLDiff 1	1.193	0.56	0.086	0.54	-0.590	0.565
MLDiff 2	1.279	0.70				
MSL 1	2.310	0.26	-0.040	0.18	-0.712	0.494
MSL 2	2.350	0.29				
SLDiff 1	0.320	0.33	-0.020	0.30	-0.210	0.838
SLDiff 2	0.340	0.21				

Paired t-test: Midpoint & Endpoint OMT Group NCS						
31	Mean	Std. Dev.	Mean Diff	Std. Dev.	t	Sig. (2-tailed)
MML 2	4.657	0.63	0.207	0.63	1.229	0.241
MML 3	4.450	0.69				
MLDiff 2	1.279	0.70	0.300	0.80	1.412	0.182
MLDiff 3	0.979	0.70				
MSL 2	2.300	0.24	0.000	0.09	0.000	1.000
MSL 3	2.300	0.19				
SLDiff 2	0.283	0.13	-0.050	0.08	-1.464	0.203
SLDiff 3	0.333	0.15				

Paired t-test: Baseline & Endpoint PSTU Group NCS						
31	Mean	Std. Dev.	Mean Diff	Std. Dev.	t	Sig. (2-tailed)
MML 1	5.079	1.19	0.014	0.51	0.105	0.918
MML 3	5.064	1.30				
MLDiff 1	1.936	1.19	0.186	0.73	0.951	0.359
MLDiff 3	1.750	1.52				
MSL 1	2.312	0.28	0.012	0.20	0.174	0.867
MSL 3	2.300	0.28				
SLDiff 1	0.300	0.26	-0.014	0.25	-0.152	0.884
SLDiff 3	0.314	0.35				

Paired t-test: Baseline & Midpoint PSTU Group NCS						
31	Mean	Std. Dev.	Mean Diff	Std. Dev.	t	Sig. (2-tailed)
MML 1	5.144	1.16	0.094	0.47	0.801	0.436
MML 2	5.050	1.22				
MLDiff 1	2.019	1.16	0.188	0.52	1.442	0.170
MLDiff 2	1.831	1.25				
MSL 1	2.312	0.28	0.050	0.15	0.935	0.381
MSL 2	2.263	0.30				
SLDiff 1	0.214	0.13	0.029	0.26	0.295	0.778
SLDiff 2	0.186	0.34				

Paired t-test: Midpoint & Endpoint PSTU Group NCS						
31	Mean	Std. Dev.	Mean Diff	Std. Dev.	t	Sig. (2-tailed)
MML 2	4.900	1.20	-0.164	0.50	-1.229	0.241
MML 3	5.064	1.30				
MLDiff 2	1.693	1.23	-0.057	0.70	-0.304	0.766
MLDiff 3	1.750	1.52				
MSL 2	2.240	0.28	-0.010	0.13	-0.246	0.811
MSL 3	2.250	0.27				
SLDiff 2	0.313	0.37	0.100	0.33	0.847	0.425
SLDiff 3	0.213	0.29				

APPENDIX G

15-Subject Data Set Demographics

APPENDIX G

15-Subject Data Set Demographics

Demographic Frequencies					
15	**Age**	**Height (m)**	**Weight (kg)**	**BMI**	**Yrs since Dx**
Mean	45.1	1.63	78.0	29.4	4.60
Std. Dev.	13.1	0.09	21.2	7.75	5.88
Min/Max	22/65	1.52/1.78	49.9/122.5	19.8/46.4	0.08/18.0

Demographic Frequencies & Pearson Chi-Square Analysis Between Groups						
15	**Ethnicity**					
	Cauc	**Chi-Square**	**df**	**Sig.**		
OMT	7 (46.7%)	------	---	------		
Ultrasound	8 (53.3%)					
Total	15 (100.0%)					
	Hand with Disease					
	Right	**Left**	**Both**	**Chi-Square**	**df**	**Sig.**
OMT	0 (0.0%)	0 (0.0%)	7 (46.7%)	2.019	2	0.364
Ultrasound	1 (6.7%)	1 (6.7%)	6 (40.0%)			
Total	1 (6.7%)	1 (6.7%)	13 (86.7%)			
	Hand Dominance					
	Right	**Left**	**Chi-Square**	**df**	**Sig.**	
OMT	6 (40.0%)	1 (6.7%)	1.224	1	0.467 [a]	
Ultrasound	8 (53.3%)	0 (0.0%)				
Total	14 (93.3%)	1 (6.7%)				
	Gender					
	Male	**Female**	**Chi-Square**	**df**	**Sig.**	
OMT	2 (13.3%)	5 (33.3%)	0.024	1	1.000 [a]	
Ultrasound	2 (13.3%)	6 (40.0%)				
Total	4 (26.7%)	11 (73.3%)				
	Hand Treated					
	Right	**Left**	**Chi-Square**	**df**	**Sig.**	
OMT	4 (26.7%)	3 (20.0%)	0.045	1	1.000 [a]	
Ultrasound	5 (33.3%)	3 (20.0%)				
Total	9 (60.0%)	6 (40.0%)				
a. Fisher's Exact Test used because of small sample size						

Demographic Frequencies & Independent t-test for Equality of Means Between Groups					
15	Group	Mean	Std. Dev.	t	Sig. (2-tailed)
Age	OMT	43.4	16.0	-0.459	0.654
	Ultrasound	10.8	10.8		
Height (m)	OMT	0.10	0.10	0.661	0.521
	Ultrasound	0.07	0.07		
Weight (kg)	OMT	17.4	17.4	-0.661	0.521
	Ultrasound	24.3	24.3		
BMI	OMT	3.91	3.91	-1.155	0.275
	Ultrasound	9.56	9.56		
Years since Dx	OMT	3.77	3.77	-0.678	0.509
	Ultrasound	7.40	7.40		

Demographic Frequencies & Independent t-test for Equality of Means Between Genders					
15	Gender	Mean	Std. Dev.	t	Sig. (2-tailed)
Age	Male	41.0	15.5	-0.726	0.481
	Female	46.6	12.6		
Height (m)	Male	1.73	0.07	4.415	0.001
	Female	1.59	0.05		
Weight (kg)	Male	97.5	22.3	2.625	0.022
	Female	70.2	15.7		
BMI	Male	33.0	10.0	1.115	0.287
	Female	27.9	6.71		
Years since Dx	Male	1.77	1.68	-1.791	0.097
	Female	5.63	6.58		

NCS Baseline Frequencies				
15	MML 1	Median/Ulnar MLDiff 1	MSL 1	Median/Ulnar SLDiff 1
Mean	4.60	1.36	2.20	0.18
Std. Dev.	0.78	0.71	0.23	0.34
Min/Max	3.8/5.5	0.5/2.1	1.8/2.4	-0.4/0.5

NCS Baseline Frequencies & Independent t-test for Equality of Means Between Groups						
15	Group	Mean	Std. Dev.	Min/Max	T	Sig. (2-tailed)
MML 1	OMT	4.23	0.72	3.8/5.5	-1.166	0.266
	Ultrasound	4.97	1.53	3.6/7.7		
Median/Ulnar MLDiff 1	OMT	0.76	0.77	0.5/2.1	-1.556	0.146
	Ultrasound	1.80	1.60	0.6/4.4		
MSL 1	OMT	2.25	0.13	1.8/2.4	-0.478	0.647
	Ultrasound	2.30	0.17	1.9/2.8		
Median/Ulnar SLDiff 1	OMT	0.38	0.17	-0.4/0.5	0.756	0.474
	Ultrasound	0.26	0.26	0.0/0.8		

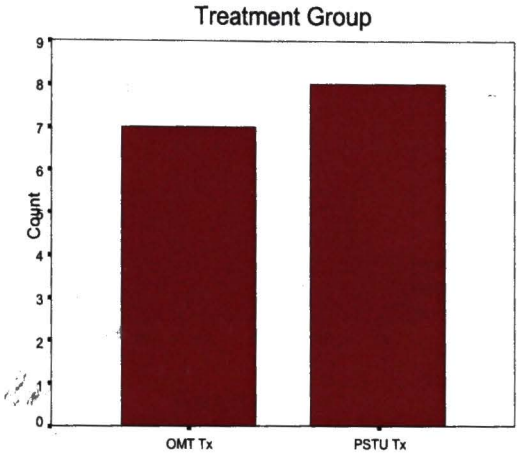
NCS Baseline Frequencies & Independent t-test for Equality of Means Between Genders						
15	Group	Mean	Std. Dev.	Min/Max	T	Sig. (2-tailed)
MML 1	Male	5.15	1.90	3.6/7.7	0.309	0.775
	Female	4.85	0.88	3.8/6.4		
Median/Ulnar MLDiff 1	Male	2.15	1.59	0.8/4.4	0.314	0.488
	Female	1.67	0.97	0.5/3.3		
MSL 1	Male	2.13	0.23	1.9/2.3	-0.528	0.612
	Female	2.23	0.30	1.8/2.8		
Median/Ulnar SLDiff 1	Male	0.17	0.15	0.0/0.3	-0.534	0.608
	Female	0.29	0.36	-0.4/0.8		

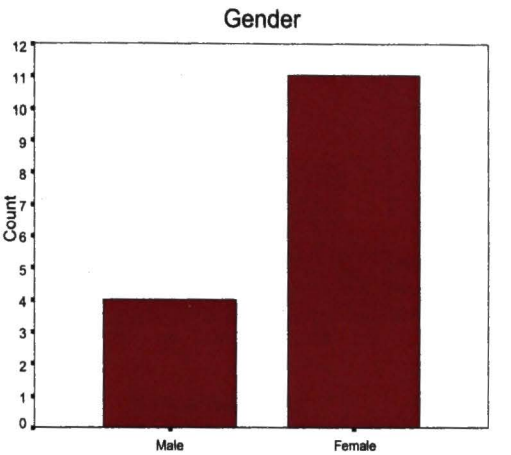
APPENDIX H

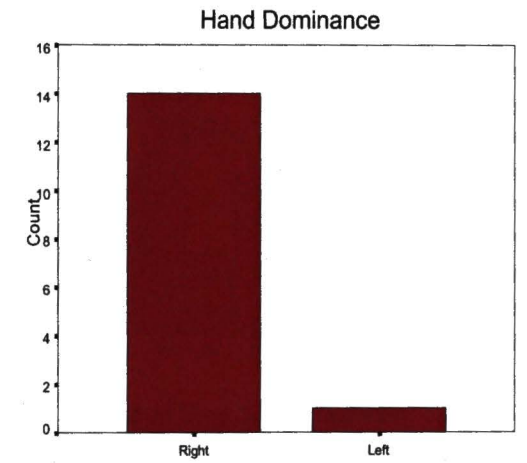
15-Subject Data Set Bar Graphs and Histograms

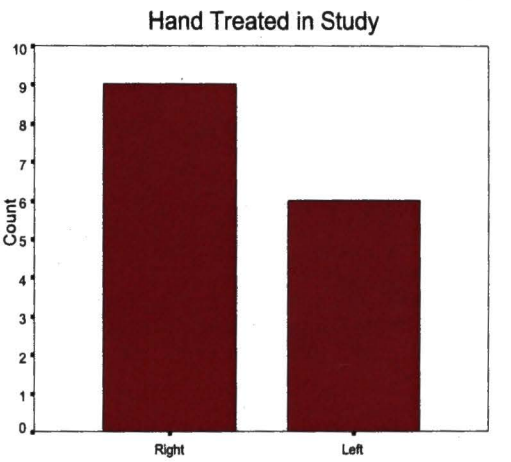
APPENDIX H

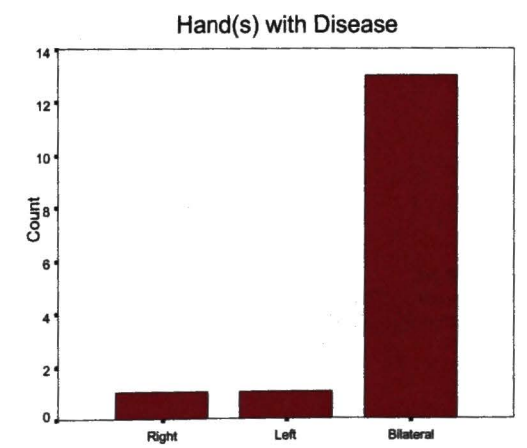
15-Subject Data Set Bar Graphs and Histograms

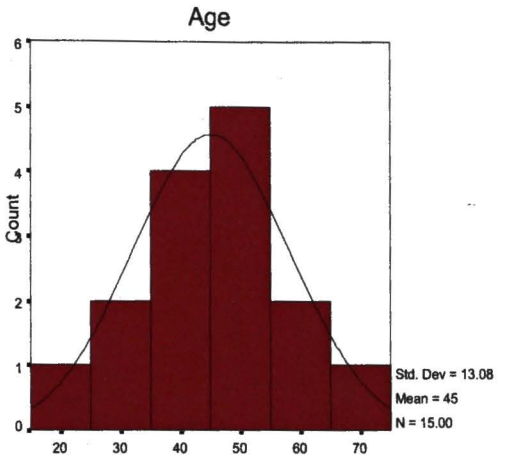


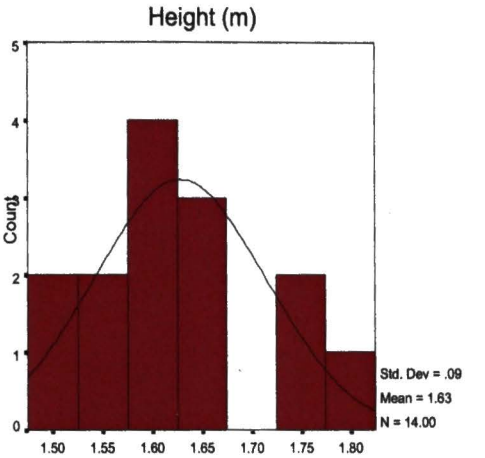


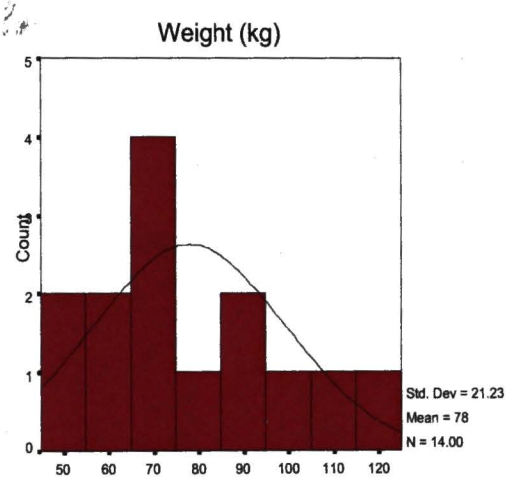


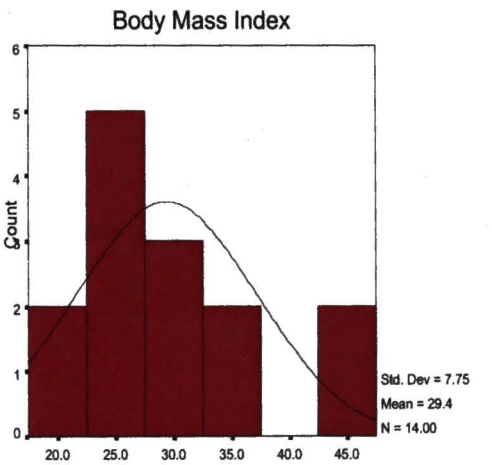





Age
Count
Std. Dev = 13.08
Mean = 45
N = 15.00


Height (m)
Count
Std. Dev = .09
Mean = 1.63
N = 14.00


Weight (kg)
Count
Std. Dev = 21.23
Mean = 78
N = 14.00


Body Mass Index
Count
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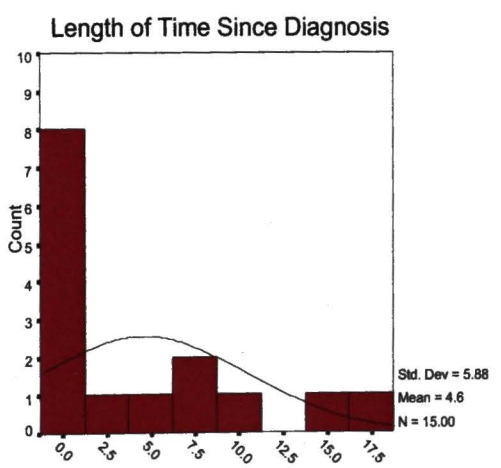
Mean = 29.4
N = 14.00

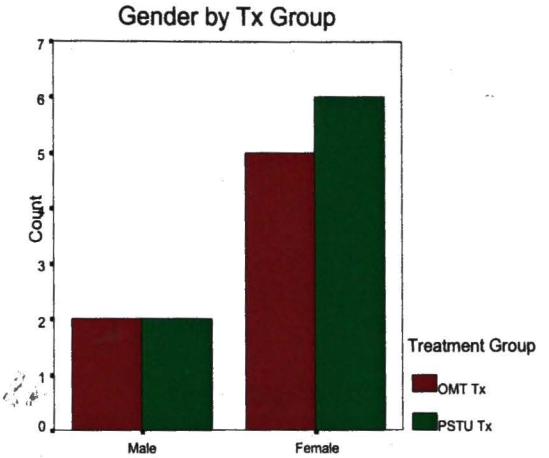

Length of Time Since Diagnosis
Count
Std. Dev = 5.88
Mean = 4.6
N = 15.00

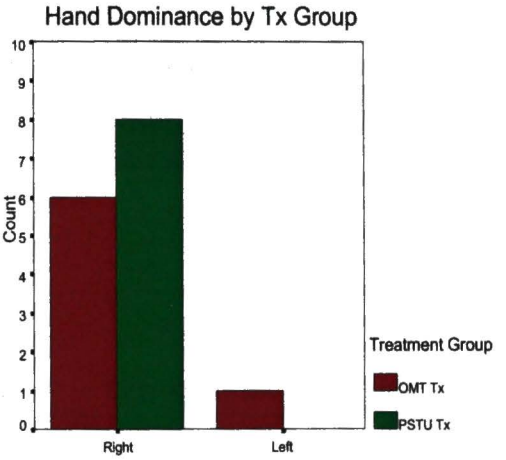
APPENDIX I

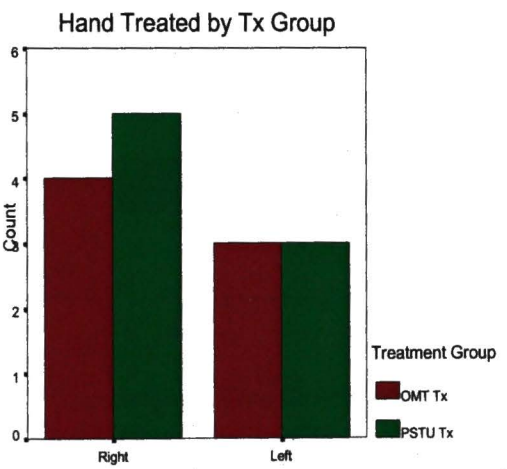
15-Subject Data Set Bar Graphs and Box Plots by Treatment Group

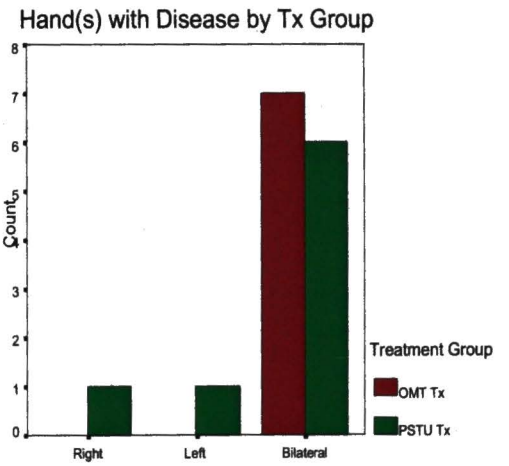
APPENDIX I

15-Subject Data Set Bar Graphs and Box Plots by Treatment Group

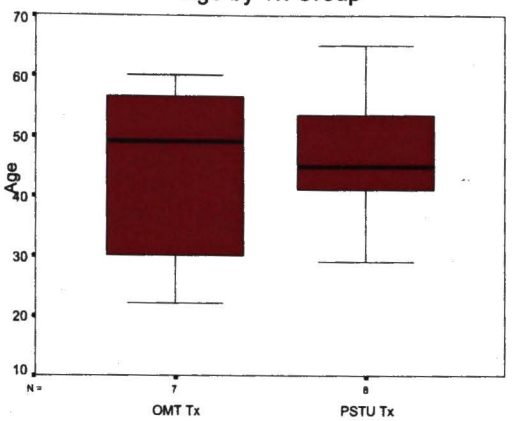




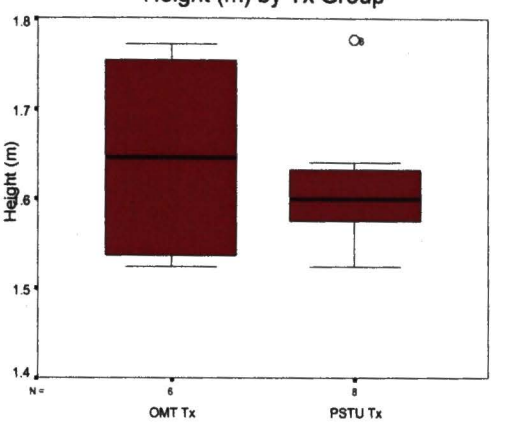




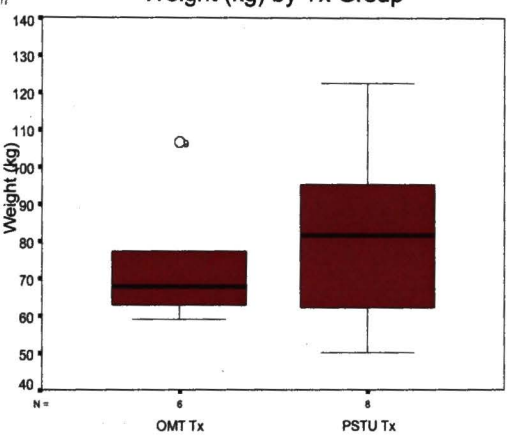
Age by Tx Group



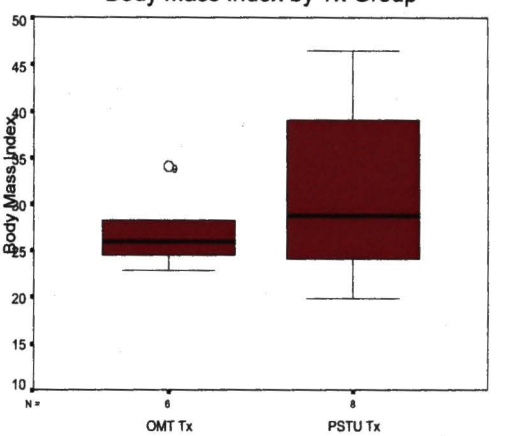
Height (m) by Tx Group



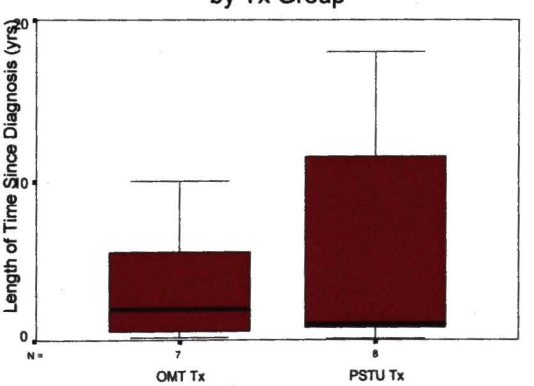
Weight (kg) by Tx Group



Body Mass Index by Tx Group



Length of Time Since Diagnosis by Tx Group



APPENDIX J

15-Subject Data Set Paired t-test Tables

APPENDIX J

15-Subject Data Set Paired t-test Tables

Paired t-test: Baseline & Endpoint OMT Group NCS (Provider A as only Treatment Provider)						
15	**Mean**	**Std. Dev.**	**Mean Diff**	**Std. Dev.**	**t**	**Sig. (2-tailed)**
MML 1	4.600	0.78	0.371	0.37	2.635	0.039
MML 3	4.229	0.72				
MLDiff 1	1.357	0.71	0.600	0.93	1.708	0.138
MLDiff 3	0.757	0.77				
MSL 1	2.300	0.08	0.050	0.06	1.732	0.182
MSL 3	2.250	0.13				
SLDiff 1	0.325	0.13	-0.050	0.24	-0.420	0.703
SLDiff 3	0.375	0.17				

Paired t-test: Baseline & Midpoint OMT Group NCS (Provider A as only Treatment Provider)						
15	**Mean**	**Std. Dev.**	**Mean Diff**	**Std. Dev.**	**t**	**Sig. (2-tailed)**
MML 1	4.600	0.78	-0.114	0.42	-0.716	0.501
MML 2	4.714	0.52				
MLDiff 1	1.357	0.71	-0.171	0.47	-0.969	0.370
MLDiff 2	1.529	0.47				
MSL 1	2.200	0.23	-0.060	0.21	-0.647	0.553
MSL 2	2.260	0.15				
SLDiff 1	0.180	0.34	-0.140	0.36	-0.858	0.439
SLDiff 2	0.320	0.11				

Paired t-test: Midpoint & Endpoint OMT Group NCS (Provider A as only Treatment Provider)						
15	**Mean**	**Std. Dev.**	**Mean Diff**	**Std. Dev.**	**t**	**Sig. (2-tailed)**
MML 2	4.714	0.52	0.486	0.54	2.394	0.054
MML 3	4.229	0.72				
MLDiff 2	1.529	0.47	0.771	0.79	2.594	0.041
MLDiff 3	0.757	0.77				
MSL 2	2.275	0.17	0.025	0.05	1.000	0.391
MSL 3	2.250	0.13				
SLDiff 2	0.325	0.13	-0.050	0.10	-1.000	0.391
SLDiff 3	0.375	0.17				

Paired t-test: Baseline & Endpoint PSTU Group NCS (Provider A as only Treatment Provider)						
15	**Mean**	**Std. Dev.**	**Mean Diff**	**Std. Dev.**	**t**	**Sig. (2-tailed)**
MML 1	5.043	1.42	0.071	0.26	0.719	0.499
MML 3	4.971	1.53				
MLDiff 1	2.029	1.33	0.229	0.42	1.429	0.203
MLDiff 3	1.800	1.60				
MSL 1	2.280	0.33	-0.020	0.19	-0.232	0.828
MSL 3	2.300	0.17				
SLDiff 1	0.320	0.30	0.060	0.15	0.885	0.426
SLDiff 3	0.260	0.26				

Paired t-test: Baseline & Midpoint PSTU Group NCS (Provider A as only Treatment Provider)						
15	**Mean**	**Std. Dev.**	**Mean Diff**	**Std. Dev.**	**T**	**Sig. (2-tailed)**
MML 1	5.212	1.40	0.162	0.35	1.312	0.231
MML 2	5.050	1.42				
MLDiff 1	2.188	1.32	0.212	0.45	1.349	0.219
MLDiff 2	1.975	1.40				
MSL 1	2.280	0.33	0.060	0.13	1.000	0.374
MSL 2	2.220	0.26				
SLDiff 1	0.200	0.14	0.100	0.14	1.414	0.252
SLDiff 2	0.100	0.18				

Paired t-test: Midpoint & Endpoint PSTU Group NCS (Provider A as only Treatment Provider)						
15	**Mean**	**Std. Dev.**	**Mean Diff**	**Std. Dev.**	**t**	**Sig. (2-tailed)**
MML 2	4.800	1.33	-0.171	0.34	-1.353	0.225
MML 3	4.971	1.53				
MLDiff 2	1.729	1.32	-0.071	0.40	-0.474	0.652
MLDiff 3	1.800	1.60				
MSL 2	2.220	0.26	-0.080	0.13	-1.372	0.242
MSL 3	2.300	0.17				
SLDiff 2	0.100	0.18	-0.050	0.24	-0.420	0.703
SLDiff 3	0.150	0.10				

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