

Study Protocol and Statistical Analysis Plan

Effects of osteopathic manipulative treatment on neuromuscular control of the head-neck system

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Study Objectives

Primary Objectives: To develop and to demonstrate the utility of sensitive and objective clinical research tools for the assessment of motor control of the head-neck system by:

- 1) Quantifying position and force control of the head-neck system in chronic neck pain (NP) participants before and after osteopathic manipulative treatment (OMT).
- 2) Comparing motor control performance for position and force control of the head-neck system between healthy individuals and NP participants.

Secondary Objective:

- 1) To quantify differences in patient-oriented outcome measures (e.g., pain, disability, fear avoidance, etc.) in chronic NP participants before and after OMT.

Design and Outcomes

This study protocol was designed to apply our measurement tools to participants with NP using a cross-over design with a delayed treatment group to examine the effects of OMT on neuromuscular control of the head-neck system, and a matched control group to examine the differences between NP participants and controls (Figure 1). At each test session, study participants will undergo an assessment of motor control using force and position controlled tasks. In addition to motor control performance, patient-oriented outcome measures (e.g., self-reported pain, disability, fear avoidance, etc.) will be collected.

Interventions and Duration

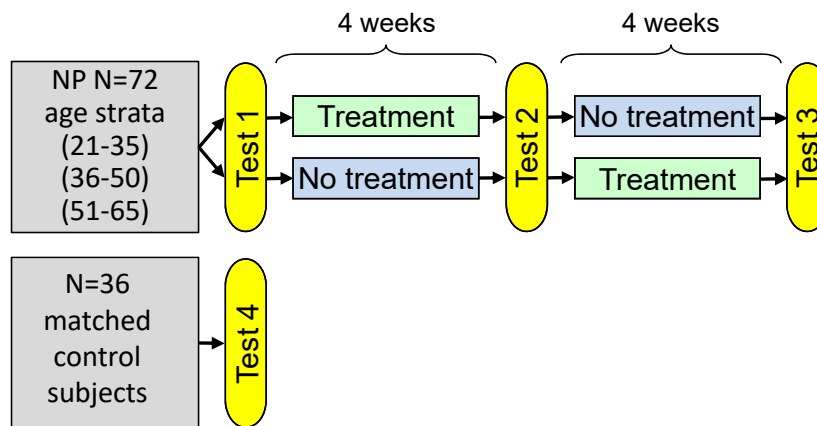


Figure 1. Experimental design implementing a cross-over design with a delayed treatment group and matched controls.

NP participants will undergo four sessions of OMT over a 4 week period. Each NP participant will receive high velocity low amplitude (HVLA) spinal manipulation. Soft tissue, muscle energy, myofascial, or articulatory techniques could be used if the physician deems the designated HVLA technique to be ineffective. Due to the cross-over design used to complete the primary objectives, NP participants will be tested at multiple time points (Figure 1) and will be in the study for approximately 8 weeks. Control subjects will be tested only once and will not undergo OMT treatment.

Sample Size and Population

A total of 108 participants, between the ages of 21-65, will be recruited, including individuals with chronic NP (n=72) and asymptomatic healthy controls (n=36). NP participants will be stratified by age

and gender, and randomized into either an immediate treatment group (OMT starts soon after being enrolled) or a delayed treatment group (OMT starts after 4 weeks. Additionally, matched controls will be stratified in the same fashion as those in the NP group.

STATISTICAL CONSIDERATIONS

General Design Issues

Primary Hypotheses:

Hypothesis 1: Position and force control of the head-neck will be better in asymptomatic individuals (matched controls) than NP participants, prior to NP participants receiving OMT.

Hypothesis 2: Position and force control of the head-neck will improve in participants with NP after 4 weeks of treatment (performance measures will improve). This improvement will be greater than any learning effect.

Secondary Hypotheses:

Hypothesis 1: Patient-oriented outcome measures will improve in participants with NP after 4 weeks of treatment. There will be a correlation between the change in clinical outcomes and the change in position and force control of the head-neck in participants with NP after 4 treatments.

These hypotheses will be answered using a stratified cross-over design in which there are immediate and delayed OMT groups. Data analyses will be performed across the entire group (not within stratum). Stratification is used to achieve matched groups. However, both gender and age can be used as covariates in the analyses. The cross-over design was chosen to reduce the influence of confounding covariates by allowing each participant to serve as their own control (Jones and Kenward, 2003). Stratification will be used to control for the possible confounding influence of age on motor control (Melzer et al., 2001, Rankin et al., 2000).

The primary outcome measures will be the motor control performance measures taken during position and force control experiments. The secondary outcome measures will be patient-oriented outcome measures such as level of pain (NPRS), disability (Neck disability index), and medications use. We have recently conducted a reliability study demonstrating the between-day reliability of these measures using Intra-class correlation coefficients (ICC) for error and coefficients of multiple correlations (CMC) for frequency response curves. The reliability of all tasks was excellent (ICC and CMC > 0.9), except for position stabilization, which was fair to good (ICC = 0.72, CMC = 0.73).

Sample Size and Randomization

To estimate the necessary sample size, we performed power analysis based on the data from previous studies that employed tasks similar to the proposed position and force control tests. (Revel et al., 1994) conducted a RCT, in which they compared changes in the head repositioning accuracy after a proprioceptive rehabilitation and a control program in patients with NP. They used 30 patients in each group and found the group difference of 2 degrees at the end of the program, with the standard deviation of 2.6 degrees. This gives a normalized effect size of 0.78. In terms of force control, (Descarreaux et al., 2007) compared the variability in generating isometric force in neck flexion and extension between 14 patients with whiplash and 34 healthy subjects. They expressed variability as an average absolute error from the target level. Whiplash patients exhibited error that was 2% greater in terms of the maximum voluntary exertion when compared to a population of healthy subjects with the standard

deviation in the population of 2%, giving a normalized effect size of 1.00. Based on the above analysis, we will recruit 36 subjects for each of the 3 groups allowing us to detect a more conservative effect size of 0.67 at $\alpha = 0.05$, power = 0.80.

Treatment Assignment Procedures

NP participant will be stratified by age and gender and randomized into either an immediate treatment group (OMT starts soon after being enrolled) or a delayed treatment group using a computer-generated sequence. Additionally, matched controls will be stratified in the same fashion as those in the NP group.

To assure random assignment of subjects, we will apply a quota (or reverse) sampling procedure. In this procedure, subjects are being enrolled and randomized until a minimum of 2 subjects completes the study in every stratum. This procedure allows enrollment of more subjects to achieve the targeted number of participant, irrespective of the expected drop-out rates ranging from 8% to 13% for similar studies (Bronfort et al., 2001, Cambron et al., 2010, Haas et al., 2010, Licciardone et al., 2013). To avoid the possibility of a greatly unbalanced design, randomization will be performed in blocks of 6 subjects.

If a subject withdraws or is excluded during the study (i.e., for poor treatment adherence), randomization will continue for age/gender appropriate subjects in blocks of six into the two treatment arms (immediate versus delayed treatment).

Definition of Populations

Hypothesis testing will be analyzed using the group allocation as depicted in Figure 1. This allocation calls for three groups:

- 1) Immediate OMT – This group will consist of individuals with chronic NP and will be treated soon after being enrolled in the study.
- 2) Delayed OMT – This group will consist of individuals with chronic NP and will be treated approximately 4 weeks after being enrolled in the study.
- 3) Matched Control – This group will consist of asymptomatic individuals.

Interim Analyses and Stopping Rules

There will be no interim analyses of the data. Barring any unforeseen circumstances, there are no plans for the adjustment of testing procedures during the project. Basic analyses of the procedures have been performed in the planning year (feasibility and safety studies) and were deemed satisfactory. Data will be analyzed after all participants have completed the study protocol. If any serious or unanticipated adverse event occurs, data collection will cease until a safety review is convened (either routine or ad hoc) to determine whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Further, this study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the research study; or (4) other situations occur that might warrant stopping the research study.

Outcomes

Upon completion of the data collection period, the outcome measures will be analyzed by the team's biostatistician. Data analysis will take approximately 3 months to complete. Findings will be reported to the Independent Monitoring Committee (IMC) for review and

adjudication. The review and adjudication process will be completed in 1 month. The IMC will be blinded to group assignment during the review and adjudication process.

Primary Outcome

The primary outcomes of the study are the motor control performance measures. Motor control will be tested in the laboratory setting during each of the “Test” periods as described in Figure 1.

Secondary Outcomes

The secondary outcomes of the study are the patient-oriented outcome measures. These measures will be assessed as follows:

Each laboratory assessment:

- Full questionnaire (PROMIS-29 v1.0, Oswestry disability questionnaire, Fear Avoidance Beliefs questionnaire, questions to recheck exclusion criteria & concomitant medications)

Weekly treatment visit:

- Condensed questionnaire (PROMIS-29 v1.0, & concomitant medications)

Weekly “off-treatment” assessment:

- Condensed questionnaire (PROMIS-29 v1.0, & concomitant medications)

Data Analyses

All analyses will be performed using R 3.0.2, Minitab 16 for Statistics, and/or SAS 9.3. Descriptive analyses will include calculations of means and proportions as appropriate for outcomes and assessment of normality for continuous variables. If the assumptions of normality are not met, we will either use transformations or nonparametric statistical methods as appropriate. Exploratory methods will be carried out, using boxplots, Q-Q plots, strip-plots, scatter plots, interaction plots, profile plots, residual plots as appropriate. We will perform correlation analyses, ANOVA, general linear models with fixed and random effects, and/or logistic regression (polytomous if appropriate) depending on hypothesis and type of outcome variable (Rosner, 2000). Because the study involves repeated measurements on the same NP subject (36 in each treatment group at 4 time points), we will also compute measures of association between time point responses of a given outcome. We will use pair-wise odds ratios and Pearson correlations to measure temporal association between two different time points. These measures will provide an indication of how the association between responses of a given outcome could be modeled over time in regression models. To assess the intervention effect on outcome variables (objective and clinical measures), repeated measures regression models appropriate for the outcome type will be used, e.g., nlme package (R), GLM (Minitab), GLIMMIX and GEE (SAS). For example, GEE models are an extension of the classical logistic regression model that takes into account the correlation of an outcome measured repeatedly over time within a subject (Zeger et al., 1988). Linear mixed effect models for longitudinal continuous outcomes adjust for the heterogeneity of subjects, which can be due to unmeasured subject-level random effects that account for the correlation within subject responses across time (Zeger and Liang, 1986). The estimated treatment effect is adjusted for these individual differences and regression estimates have an individual as well as population level interpretations. Twelve subjects per group enables us to detect standardized effect size of 0.84 with power of 80% (Hulley and Cummings, 1988). Hotelling's T^2 -type tests based on differences from the baseline will be used as multivariate extensions of the univariate

paired t-test as appropriate. Covariates under consideration will include age, gender, learning effect (extracted from the delayed treatment group), initial status (baseline measures), and other yet to be determined covariates. The Rao-Pathak-Koltchinskii sequential resampling methods will be used to assess the performance characteristics of statistical methods as needed (Pathak and Rao, 2013).

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