Study Protocol and Statistical Analysis Plan

Osteopathic manipulative treatment and postural control: systems engineering approach

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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 postural control of the trunk by:

1) Quantifying postural control of the trunk in participants with low back pain (LBP) before and after a single osteopathic manipulative treatment (OMT).

2) Quantifying postural control of the trunk in participants with LBP before and after 4 OMT sessions.

Secondary Objective:

1) To quantify differences in patient-oriented outcome measures (e.g., pain, disability, fear avoidance, etc.) in LBP participants before and after 4 OMT treatments.

Design and Outcomes

This study protocol was designed to apply our measurement tools to participants with LBP using a cross-over design with an immediate and delayed treatment group to examine the effects of OMT on postural control of the trunk (Figure 1). At each test session, study participants will undergo an assessment of postural control using unstable sitting tasks. In addition to postural balance performance, patient-oriented outcome measures (e.g., self-reported pain, disability, fear avoidance, etc.) will be collected.

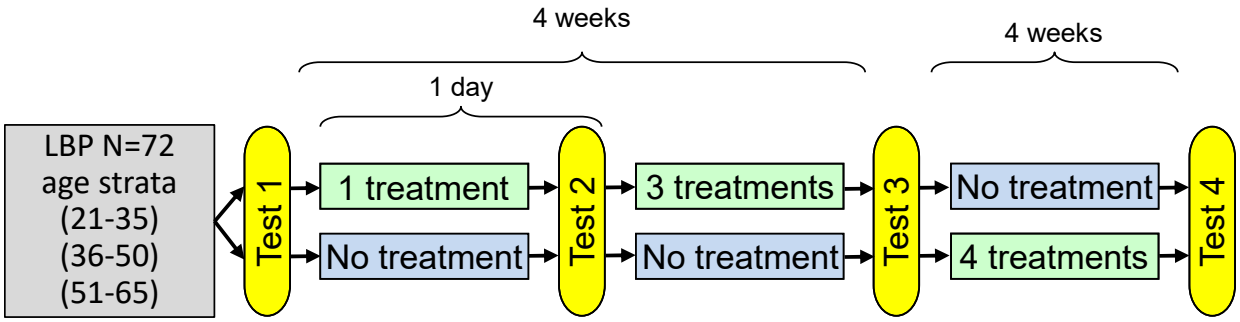


Figure 1. *Experimental design implementing a cross-over design with a delayed treatment group.*

Interventions and Duration

LBP participants will undergo four sessions of OMT over a 4 week period. Each LBP participant will receive high velocity low amplitude (HVLA) technique. 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 of this study, LBP participants will be tested at multiple time points (Figure 1) and will be in the study for approximately 8 weeks.

Sample Size and Population

A total of 72 participants with LBP, between the ages of 21-65, will be recruited. LBP 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).

STATISTICAL CONSIDERATIONS

General Design Issues

Primary Hypotheses:

Hypothesis 1: Postural control of the trunk will improve in participants with LBP after a single treatment (balance performance measures will improve). This improvement will be greater than any learning effect.

Hypothesis 2: Postural control of the trunk will improve in participants with LBP after 4 weeks of treatment (balance 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 LBP after 4 weeks of treatment. There will be a correlation between the change in clinical outcomes and the change in postural control in participants with LBP 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 postural control performance measures taken during balancing tasks. The secondary outcome measures will be patient-oriented outcome measures such as level of pain (NPRS), disability (Oswestry Disability Questionnaire), and medications use.

We have previously demonstrated excellent reliability of the unstable sitting task (Cholewicki et al., 2000, Radebold et al., 2001b).

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. In order to compare postural control before and after OMT, we calculated the minimum sample size needed for Type 1 error at alpha of 0.05 and a power of 0.80. In one of our previous studies investigating trunk muscle responses to perturbations (Reeves et al., 2005), we found that latencies of muscles shutting-off and switching-on were significantly longer in the LBP group as compared to the healthy group (mean LBP response time for shutting-off = 65 msec, sd=14; mean healthy response time for shutting-off=44

msec, sd=11; mean LBP response time for switching-on = 82 msec, sd=15; mean healthy response time for switching-on=62 msec, sd=10). Using a conservative estimate to predict the effect size of d=1.16, it would require 20 subjects per group. In terms of improvement in postural control with OMT treatment, a preliminary study of postural control before and after a single strain-counter-strain treatment showed a 22% and 26% greater improvement as compared to sham and control (no treatment), respectively. An overall standard deviation of this measure was 19% giving the effect size between1.2 and 1.4. To identify these differences statistically at the power level of 0.80 requires between 10 and 12 subjects in each group. To be conservative, we will enroll 36 subjects to each group, thus allowing us to detect an effect size of 0.67 at alpha = 0.05, power = 0.80.

Treatment Assignment Procedures

LBP 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.

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 two groups:

1) Immediate Treatment – This group will consist of individuals with LBP and will be treated soon after being enrolled in the study.
2) Delayed Treatment – This group will consist of individuals with LBP and will be treated approximately 4 weeks after being enrolled in the study.

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 postural control performance measures. Postural 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 LBP 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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