The Effect of Combining Spinal Manipulation and Dry Needling in Individuals with Non-specific Low Back Pain

Study Protocol and Statistical Analysis Plan

Approved until 12/10/2023

This study will use a randomized comparative design with three intervention groups in individuals with nonspecific LBP. The first patient-reported outcome to be assessed is disability, assessed with the LBP Oswestry Disability Index Questionnaire (ODI). The ODI score is derived from the Oswestry Disability Questionnaire, resulting in a score ranging from 0-100 with higher numbers indicating a greater level of disability [84]. Patient-centered outcome measures represent the majority of clinical nonmechanistic measures from the view and disability outlook of the patient. They are an effective way for the patient to explain the degree of pain and disability being experienced from LBP.

The second patient-reported outcome will utilize the pain rating score derived from the numeric pain rating scale (NPRS) to evaluate pain intensity throughout the trial. Participants will be asked to make separate ratings of current pain intensity and the best and worst intensity over the past 24 hours on a 0-10 scale (“0” no pain and “10” worst imaginable pain). The mean of the three ratings will be used to represent pain intensity.

The mechanistic outcome measures include LMM, ES, and GM muscle activation measured by changes in contraction thickness at rest and sub-maximal isometric contraction. The primary comparison will consist of the combination group compared against each single treatment group of SMT or DN in order to evaluate the advantage of utilizing both modalities together. This study will further perform a secondary exploratory comparison of the SMT and DN only groups. The primary comparison time-point will evaluate these outcome measures at 4-weeks (late effect) compared to baseline and a secondary comparison (early effect) at 2-weeks with comparison being controlled for baseline value. A third comparison time-point will be evaluated at 1-week consisting of

only patient-reported outcomes to assess initial effects of treatment on reported pain. All patient-reported outcomes will be assessed 48 hours following the second and fourth treatment sessions. The duration of the trial intervention for a participant will be four weeks from initial baseline assessment. Participants will be randomly assigned to one of three intervention groups for the first 2 weeks of treatment: combination of SMT and DN, DN only, and SMT only. Each treatment group will receive two treatment sessions per week for the first two weeks with NPRS and ODI measures assessed at baseline, 1-week, and 2-weeks. The third and fourth weeks will consist of an at home exercise program with NPRS and ODI measures taken at the final assessment at the end of the fourth week. Diagnostic ultrasound measures of the LMM, ES, and GM muscles will be taken at baseline and post-treatment following the fourth and final assessment sessions.

Randomization and data collection

Randomization will be conducted utilizing REDCap in order to conceal sequence from participants and researchers. Participants will be randomized into one of three treatment groups. The use of standard protocols and compliance audits throughout the study will be utilized to minimize potential bias. Study data will be collected and managed using REDCap electronic data capture tools hosted at the University of Utah.

Outcome measures

After attaining informed consent, participants will complete a baseline assessment. Participant demographics, age, gender, race/ethnicity, body mass index, marital status, employment status, highest education level, current and past LBP

interventions, and a physical examination will be collected and performed. The physical examination will include various tests designed to ensure proper study inclusion and to identify the most symptomatic side (right or left) and most symptomatic levels (L3, L4, or L5) for treatment and outcome assessment.

LMM, ES, and GM muscle activation will be measured with brightness-mode ultrasound images using a Sonosite MicroMaxx (Sonosite Inc. Bothell, WA, USA) and a 60-mm, 2–5 MHz curvilinear array or a Butterfly iQ+ (2020 Butterfly Network Inc., Burlington, Massachusetts) with both using a validated protocol. Measures for the LM will be taken with the participant in the prone position. The ultrasound transducer will be placed just lateral to the spinal midline and angled medially until a parasagittal view of the multifidus muscle is obtained. Images will be obtained at the most symptomatic side and level with the muscles at rest and during submaximal contraction in response to the participant raising the contralateral arm about two inches while holding a weight proportional to body weight, resulting in approximately 30% maximum voluntary isometric LMM contraction. Measurements at rest and contracted will be taken three times at the treatment sites. Offline measures of the multifidus muscle activation will be obtained for both the resting and contracted states from determining the distance between the posterior-most aspect of the facet joint inferiorly and the plane between the multifidus and throacolumbar fascia superior. Images of the GM muscle will be obtained with the transducer positioned midway between the posterior iliac spine (PSIS) and the greater trochanter. Thickness measurements will be taken between the ischium and the fascial plane between the GM and gluteus maximus muscles along the mid-axillary line and the middle of the muscle belly centered within the field of view. The ES muscle will

be imaged following techniques used with the transducer positioned on the bulk of the muscle immediately above the iliac crest centered on the symptomatic side and spinal level. The transducer will be oriented in the sagittal plane so that it is roughly parallel to the muscle fibers and angled slightly medially to optimize image clarity. Muscle activation will be calculated as the change in thickness at rest and submaximal contraction ($Thickness_{contracted}$-$Thickness_{rest}$) /($Thickness_{rest}$). The average of the three measures will be calculated at each treated symptomatic spinal level. All muscle thickness measures will be downloaded and performed offline on a different date from when the images are obtained utilizing Image J software (V1.38t, National Institutes of Health, Bethesda, Maryland) [85]. The researcher performing the offline muscle thickness measures will be blinded to participant treatment group allocation and measurement timepoint in order to control for any potential measurement bias.

Intervention groups

This study will involve three intervention components provided in different sequences and combinations for four weeks. Following baseline assessment, each study participant will be randomized to a treatment group to receive SMT, DN, or a combination of DN and SMT. Each treatment session will begin with a brief assessment by the clinician to assure the participant has remained appropriate to receive treatment.

All SMT treatment sessions will be provided using protocols applied in previous studies investigating clinical outcomes and mechanism of effect. The preferred SMT technique will be performed with the participant supine. The clinician will stand opposite the side to be manipulated and side-bend the participant. The side to be manipulated will be the side identified as more painful. The participant will then interlock their fingers

behind the head. The clinician will then rotate the participant and deliver a high-velocity, low-amplitude (HVLA) thrust to the anterior superior iliac spine with a posterior/inferior direction. The clinician will note if a cavitation (i.e. a “pop”) occurs and record which attempt and side that it occurred. Each participant receiving SMT will have two attempts per side performed regardless of when a cavitation occurred. If no cavitation occurs on any attempt this will also be noted. The substitution of the supine position for the side-lying technique will be permitted based on participant preference or comfort. Once participant preference is determined at the baseline examination the chosen technique will be used for the duration of the trial for that respective participant.

DN treatment will be performed in the ES, GM, and LM at the most symptomatic side and spinal levels determined at baseline examination. If the clinician is unable to determine the most symptomatic levels or areas, treatment will be performed to the middle of the ES and LM bellies at the L4 and L5 levels and the ipsilateral GM. General needle technique utilized for all muscles will include insertion of a sterile, disposable, solid filament steel needle (Seirin Corp., Shizuoka, Japan) into the desired muscle. The size of the needle will be either 0.25 x 50mm or 0.30 x 60mm based on the size of the participant. “Clean needle technique” will be used throughout the treatment procedures which included hand washing, clean latex-free nitrile exam gloves, and cleaning the participants skin with an alcohol swab prior to treatment. The needle technique that will be utilized for the LM is to start at approximately 1.5 cm lateral to the spinous process angling approximately 15-20 degrees medially and slightly inferior inserting the needle into the depth of the muscle until the lumbar lamina was reached. For the ES muscles, the needle will be inserted just lateral to the paraspinal muscle bulk (approximately 5-10

cm lateral to the spinous process) in the lateral to medial direction towards the spinous process. The GM will be needled in the upper lateral quadrant of the buttock between the region proximal to the greater trochanter and inferior to the iliac crest. The needles will remain in the muscle for 10 minutes with needle manipulations being delivered every 2 minutes to elicit a local twitch response.

Exercise sessions will consist of a series of LM exercises targeting isometric muscle contraction and activation. Specific exercises were selected that not only activated the LM, but also the GM and ES muscles. Following the fourth treatment session, the participant will be assigned a home exercise program consisting of isometric multifidus contractions in different positions with initial clinician feedback and exercises to isometrically co-contract the multifidus and deep abdominal muscles. Participants will also perform lumbar extensor strengthening exercises shown to produce 20-50% multifidus maximum voluntary contraction. Participants will continue to perform the assigned exercises through the third and fourth weeks at home up until the final assessment. The prescribed exercises and participant compliance with assigned exercises will be recorded at the final assessment session.

There is little to no research on which therapy should precede the other in the combination SMT and DN group, and instead of leaving it up to clinician preference and to maintain consistency in treatment, SMT was designated to be performed first with DN following manipulation therapy. Following the two-week intervention period of SMT and DN, DN, or SMT the participants will begin the second phase of treatment consisting of two weeks of at home activation/strengthening exercises for two weeks.

Statistical methods

The study treatments will include spinal manipulation therapy (SMT), dry needling (DN), and exercise (EXER). Participants will be block randomized in sizes of 3 and 6 into three study groups: (SMT+EXER), (DN+EXER), and (SMT+DN+EXER). Repeated measurements of the outcomes will be collected at baseline, two weeks post-treatment, and four weeks post-treatment. The first primary outcome is the continuous variable Oswestry Disability Index (ODI). The second primary outcome is the continuous variable 0-10 numeric pain rating scale (NPRS). The primary time point is at four weeks (late effect) and the secondary time point is at two weeks (early effect). To determine if (SMT+DN+EXER) is superior to (SMT+EXER) on the ODI outcome, a linear regression model will be fitted using the 2-week ODI as the outcome variable, group as the primary predictor [(SMT+DN+EXER) vs (SMT+EXER)], and baseline ODI as a covariate, in an analysis of covariance (ANCOVA) fashion. In a similar model, (SMT+DN+EXER) will be compared to (DN+EXER). All comparisons will be made at the alpha 0.05 level.

Exercise compliance will be measured by participants self-reporting adherence to the program by selecting average number of days per week the exercises were completed. Self-reporting will take place during the final visit at the end of the fourth week. Participants will be informed of this method of self-reporting compliance in order to aid in tracking adherence over the two-week period.

Sample size justification

For a simple comparison of a post (week 2) standardized (z-score) outcome variable, which is the standardized outcome variable in the ANCOVA model, mean +/- SD: 0 +/- 1 versus 0.64 +/- 1 (that is, a 0.64 SD difference), we required n= 41 per group to achieve 80% power using a two-sided alpha 0.05 comparison. We assumed a

correlation of r = .50 between the baseline and post-treatment outcomes, which was a reasonable assumption given that changes over two weeks would mostly be in the improvement direction, with minimal patients changing in the opposite direction. The n=40 per group sample size was next adjusted to account for the increased power achieved by the ANCOVA approach [180]. In doing this, the n = 40 was multiplied by the factor $(1 - r^2) = (1-0.50^2) = 0.75$, so we only required n = 40 × .75 = 30 per group to achieve the same effect size. Based on prior work of 92% retention to a four-week trial, a sample size of n=99, 33 per group, accounts for potential participant drop-out [20,168]. This planned sample size works if a 0.64 SD difference is likely or represents at least a minimal clinically meaning difference. In a DN study, baseline ODI was mean +/- SD 31.5 +/- 11.5 which decreased to 23.4 +/- 13.5 one-week post-treatment, a mean difference divided by pooled SD, while assuming r=0.50, of (23.4 - 31.5)/12.6 = -0.64 SD difference. In the same study, although a difference in NPRS was not reported, baseline NPRS mean +/- SD was 5.0 +/- 1.7. A 0.64 SD improvement would be (5.0/1.7) x 0.64 =1.9 point change. This reduction in pain would be noticeable and beneficial to the patient, and so is at least a minimally, clinically relevant effect size [181]. In a SMT study [51,182], reported baseline ODI mean +/- SD 32.2 +/- 11.9 which decreased to 23.9±11.4 post-treatment, a (23.9-32.2)/11.7 = -0.71 SD difference. So, both DN and SMT achieve a 0.64 SD effect size by themselves. However, our study specifically tested if DN+SMT is superior to DN and is superior to SMT. Individual participant response to only DN or only SMT could vary, with some level of synergy of DN+SMT being more effective than the sum of the individual effects. Therefore, we used the 0.64

SD effect size for this test as our minimally clinically relevant effect, consistent with the individual treatment effects.