Use of Beat-to-Beat Cardiovascular Variability Data to Determine the Validity of Sham Therapy as the Placebo Control in Osteopathic Manipulative Medicine Research

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Osteopathic manipulative medicine researchers often use sham therapy as the placebo control during clinical trials. Optimally, the sham therapy should be a hands-on procedure that is perceptually indistinguishable from osteopathic manipulative treatment, does not create an effect on its own, and is not a treatment intervention. However, the sham therapy itself may often influence the outcome. The use of cardiovascular variability (eg, beat-to-beat heart rate variability) as a surrogate for the autonomic nervous system is one objective method by which to identify such an effect. By monitoring cardiovascular variability, investigators can assess autonomic nervous system activity as a response to the sham therapy and quickly determine whether or not the selected sham therapy is a true placebo control. The authors provide evidence for assessment of beat-to-beat heart rate variability as one method for assuring objectivity of sham therapy as a placebo control in osteopathic manipulative medicine research.

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Research in osteopathic manipulative medicine (OMM) depends in large part on the ability to identify physiologic differences and improved clinical outcomes in treatment groups, compared with control groups and conditions. In clinical research, the reference standard is a double-blind, placebo-controlled, randomized clinical trial in which neither the investigator nor the study participant is certain whether the participant is receiving the treatment or the placebo. In OMM research, investigator blinding is very difficult to achieve because of the essential physical skills the investigator must use to provide osteopathic manipulative treatment (OMT); however, reliable and valid clinical outcomes can be obtained with participant blinding. In participant blinding, an OMT group is compared with a control or placebo group that optimally receives a sham therapy procedure involving positioning and physical contact similar to those used in the OMT group, except for the actual manipulation. An additional requirement for the design of sham therapy protocols is that they should be outcome neutral, plausible, unidentifiable, and reproducible.[1,2] Depending on the dependent variable measured, the difference between outcomes for the treatment and control groups may be quite small. In these cases, a measurable difference may depend on whether or not the sham therapy exerted any effect per se.

To illustrate this potential for a sham therapy effect, Balon et al[3] used chiropractic manipulation as an adjunctive treatment for children with asthma. The sham therapy procedure used in their clinical trial involved a combination of soft-tissue massage, multiple changes in position, and distraction maneuvers such as soft pushes to the gluteal region and massaging of the ankles and feet, in addition to low-amplitude, low-velocity impulses applied to nontherapeutic areas so that no joint opening or cavitation occurred. Treatment, on the other hand, consisted

of active spinal manipulation. No statistically significant difference was noted between the groups.[3]

It is difficult to determine whether the aggressive, multimodal sham therapy procedure used by Balon et al[3] might have affected the outcome measures in some way, thereby distorting a potential real difference, or type II error. These types of difficulties in interpreting outcomes resulted in Hondras et al[4] being unable to make definitive conclusions in their 2002 evidence-based review of the use of manual therapy for asthma. Instead, the investigators recommended that additional clinical trials be performed using appropriate sham protocols.[4]

Uncertainty surrounding the use of sham controls has led many investigators to adopt a methodology that only compares treatment with no treatment. Some investigators have gone so far as to suggest that outside of certain clinical trials, there is no justification for the use of placebos.[5] However, in OMM research, sham therapy procedures are a primary determinant of whether the measured effect is caused by the OMT or by another related or unrelated factor. For example, in a meta-analysis of randomized controlled trials assessing the use of OMT for low back pain, Licciardone et al[6] determined that OMT was associated with a positive outcome (ie, reduction of low back pain) both in the treatment vs sham therapy groups and in the treatment vs no-treatment control groups. In clinical trials, the necessary study population, personnel, and expenses often make it not feasible to include multiple study groups. Use of an optimal sham therapy protocol could alleviate the need for both a no-treatment control group and a sham therapy group and yet still allow detection of meaningful clinical outcomes. Accordingly, in the present article we focus on the design of sham therapy as a placebo control in OMM research, the use of beat-to-beat cardiovascular variability data to aid in evaluating the validity of sham therapy as a control, discussion of this approach in previous OMM studies using sham therapy, and ways that cardiovascular variability assessment can enhance sham therapy controls used in future OMM research.

Designing Sham Therapy as a Placebo Control in OMM Research

A number of types of sham protocols currently exist in manual therapy research[7]; however, which of these protocols is most appropriate for research on the effects of OMT on autonomic nervous system (ANS) activity remains to be determined. To answer this question, a number of points need to be addressed. First, the ability to demonstrate a causal relationship between OMT and the ANS has often been problematic because it is difficult to quantify sympathetic and parasympathetic activity noninvasively in a manner that does not affect nerve activity. For example, if a treatment increases the heart rate by 15 beats per minute, is this effect achieved through a sympathetic stimulation or through parasympathetic withdrawal? Second, autonomic reflexes, such as the baroreflex and the chemoreflex, may counteract treatment interventions, resulting in little or no absolute change in measurable parameters. For example, if a treatment results in no change in the heart rate, either the reflex may have "corrected" the change back to baseline or the reflex may have already been engaged, thus indicating that the baseline value was already being affected by the reflex. Assessment of beat-to-beat cardiovascular variability, such as heart rate variability (HRV), offers a potential solution because oscillatory techniques can give insight into sympathovagal balance, irrespective of an absolute change in heart rate[8] and if autonomic reflexes are engaged.[9] The assessment of beat-to-beat cardiovascular variability may also be a promising solution because it is reproducible and has a good degree of sensitivity with regard to the detection of subtle or pronounced autonomic changes induced by OMT. Thus, it appears that cardiovascular variability assessment may be robust enough to be used effectively as a method for determining whether a sham therapy procedure is a true placebo control in studies measuring ANS outcomes. Such a determination has the capacity not only to improve investigator confidence in treatment but also to provide the scientific rigor necessary for clinical trials research.

Beat-to-Beat Cardiovascular Variability: Theory and Methods

Beat-to-beat cardiovascular variability assessment can include a number of measurements, including blood pressure variability,[10,11] sympathetic-nerve activity variability,[12,13] and vascular variability, which is normally measured either in the skin[14] or in specific blood vessels, such as the middle cerebral artery.[15] However, the simplest and most widely adoptable measurement is HRV, because the investigator does not need to use indwelling catheters and expensive Doppler (ultrasound or laser) or photoplethysmography systems. Heart rate variability is based on the theory that the inherent variation in the R-R intervals noted during standard electrocardiography (ECG) are primarily based on changes in cardiac sympathetic and vagal nerve activity at the sinoatrial node.[16]

Heart rate variability assessment involves ECG (performed using 1 channel, with the precise lead used unimportant as long as a distinguishable R wave is present) and measurement of respiratory excursions (eg, using a piezoelectric chest transducer) with analog outputs. For data collection, an analog-to-digital converter (eg, from ADI Instruments, BioPac Systems Inc, iWorx Systems Inc, or Dataq Instruments) with a sampling frequency of 200 Hz or greater should be used to ensure appropriate spectral resolution of the signal interfaced with a personal computer. Digital records can be analyzed either post hoc, by using an R-wave peak detection algorithm to detect R-R intervals, or in nearly real time, by using a calculation channel located in the converter software. Alternately, the R-R interval can be streamed by routing the ECG signal through a cardiotachometer and then from the cardiotachometer to the analog-to-digital converter. Time-series data can then be converted to frequency data by use of a fast Fourier transform algorithm available as custom software (eg, from the Biomedical Signal Analysis Group in the Department of Physics at the University of Kuopio in Finland) or commercially available software (eg, AutoSignal [Systat Software], DADiSP [DSP Development Corp], or Matlab [MathWorks]). The duration of data recording can vary depending on the type of analysis, but it most often is within a 5- to 6-minute window. This time frame is long enough for low-frequency (LF) resolution to be obtained while still allowing for economy of measurement.

Spectral power analysis of HRV has been used to study balance of the ANS in humans. It is generally accepted that the high-frequency (HF) power spectra (0.15-0.4 Hz) in this type of analysis are a marker for cardiac vagal modulation, whereas the LF power spectra (0.04-0.15 Hz) are a marker for cardiac sympathetic modulation.[8] Because intrasubject variation in power spectra is considerable, especially in the LF range, data are often normalized to total power and thus are expressed in normalized units. In most circumstances, the LF:HF ratio provides a reasonable index of sympathovagal balance.[17,18]

Use of Sham Therapy in OMM and HRV Studies

We review 3 studies that used HRV assessment to investigate various OMM and sham therapy procedures with a primary ANS outcome.[9,19,20] Focusing on each study's sham therapy protocol and beat-to-beat cardiovascular variability data, we analyze whether the sham therapy used in each study met the requirements of being a true placebo control: that it was hands-on, that it was perceptually indistinguishable from the OMT, that it did not create an effect of its own, and that it was not an intervention in itself.

Henley et al[9] evaluated 17 healthy men and women using the following approaches: a treatment protocol during which cervical myofascial release technique was administered for 2 minutes; a time-controlled, hands-off, no-treatment control protocol; and a time-controlled, hands-on, but no-pressure sham therapy protocol. To engage the sympathetic nervous system and perturb the LF:HF ratio after treatment, patients in the control

and sham therapy groups underwent a 50° head-up tilt procedure for 10 minutes. The primary findings from this study were that the head-up tilt procedure increased LF:HF ratios in both the control and sham therapy groups and that these increases were significantly attenuated in the cervical myofascial release group ($P<.001$) (*Figure 1*). The findings were interpreted as denoting a shift in autonomic activity to a more parasympathetic or vagal tone when OMT was applied in a strongly sympathetic environment (ie, when the head-up tilt position was used). Treatment effect was not found to be influenced by the sham therapy, because the LF:HF ratios were not different from those noted for the control group when either the horizontal or head-up tilt position was used (*Figure 1* and *Figure 2A*). These data indicate that the sham therapy did not cause an effect of its own, as indexed by HRV. Because the sham therapy was hands on, and because the positioning was similar to that used for the cervical myofascial release technique, the sham therapy satisfies many requirements of being a true placebo control.

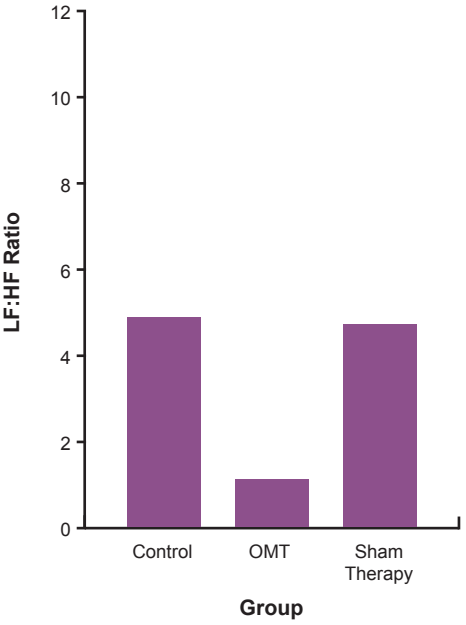

Figure 1.
Normalized low-frequency (LF) (0.04-0.15 Hz) and high-frequency (HF) (0.15-0.40 Hz) R-R interval spectral power to a sympathetic perturbation (a head-up tilt) after control, osteopathic manipulative treatment (OMT), or sham therapy. No statistically significant differences were identified when the control and sham therapy groups were compared, but significant decreases were noted when the OMT group was compared with the other 2 groups. Adapted from Henley et al[9] with permission from BioMed Central.

In a study of 21 men and women, Shi et al[19] used 2 osteopathic cranial manipulative medicine (OCMM) techniques—an augmentation technique and a cranial suppression technique (each of which was applied for 4 minutes)—in addition to a random, time-controlled, hands-on sham therapy maneuver that mimicked the suppression technique. Studies were completed with participants lying in a supine position, and no sympathetic or parasympathetic perturbations were performed. No hands-off time controls were used, but posttreatment measurements were compared with baseline measurements. In their study, Shi et al[19] focused on identifying differences in cerebral tissue oxygen saturation, but they also assessed HRV. The 2 OCMM procedures produced decreases in LF spectral power and increases in HF spectral power (*Figure 2B*). Unfortunately, the sham therapy produced identical effects on spectral power (*Figure 2B*). The finding that all conditions caused a decrease in the LF:HF ratio seems to denote that the manipulative techniques and sham therapy caused a shift in autonomic activity to a more parasympathetic or vagal tone. As indexed by HRV, the sham therapy caused an effect of its own, and although the procedure was hands on and mimicked the suppression technique, it was difficult to determine if OMT had an effect. Thus, the sham therapy did not satisfy all of the requirements that would make it a true placebo control.

In assessing a group of 19 men and women, Giles et al[20] performed suboccipital decompression for 2 to 3 minutes after 5 minutes of soft-tissue preparation; a time-controlled, hands-off, no-treatment control; and a

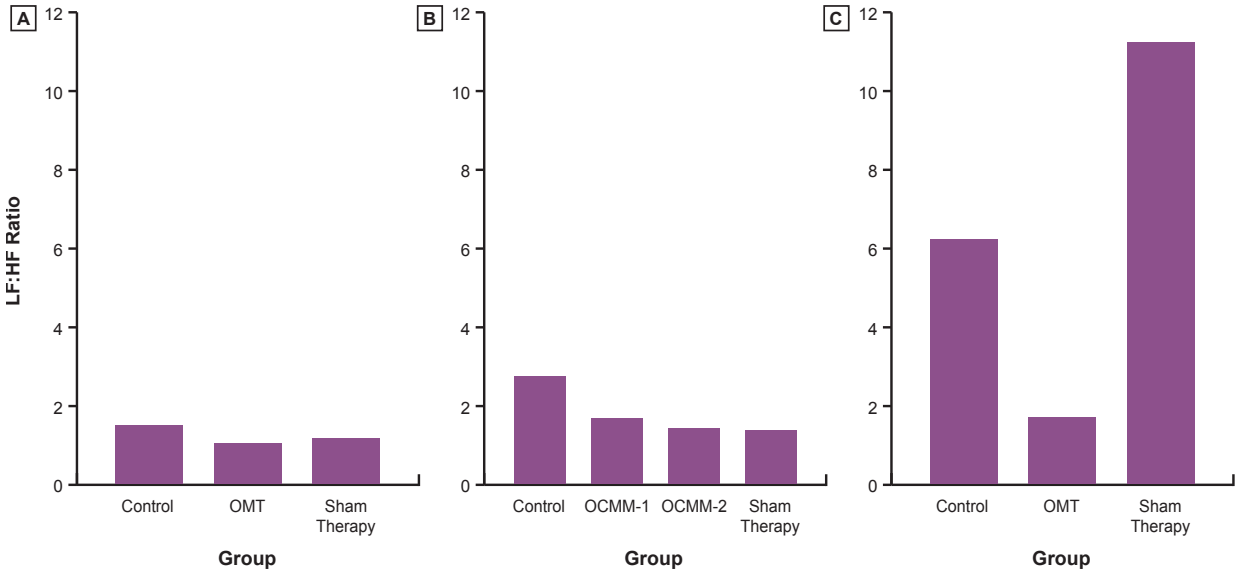

Figure 2.
(A) Normalized low-frequency (LF) (0.04-0.15 Hz) and high-frequency (HF) (0.15-0.40 Hz) R-R interval spectral power after no treatment (control), osteopathic manipulative treatment (OMT), or sham therapy. No statistically significant differences were identified between groups. Adapted from Henley et al[9] with permission from BioMed Central.
(B) Normalized LF (0.05-0.15 Hz) and HF (0.25-0.30 Hz) R-R interval spectral power during 2 osteopathic cranial manipulative medicine (OCMM) augmentation (OCMM-1) and suppression (OCMM-2) treatment and sham therapy protocols. Statistically significant decreases from baseline (control) were observed between the OCMM-1, OCMM-2, sham therapy, and control groups, but no statistically significant differences were identified between the noncontrol groups. Adapted from Shi et al.[19]
(C) Normalized LF (0.04-0.12 Hz) and HF (0.15-0.30 Hz) R-R interval spectral power during no treatment (control), OMT, or sham therapy. No statistically significant differences were identified between the control and sham therapy groups, but statistically significant decreases were observed between the OMT group and the other 2 groups. Adapted from Giles et al.[20]

time-controlled, hands-on but no-pressure sham therapy applied to the head. Studies were completed with participants in the supine position, and no sympathetic or parasympathetic perturbations were performed. The primary finding of this study was that suboccipital decompression decreased LF:HF ratios from baseline measurements and when compared with both the control intervention and the sham therapy measurements (*Figure 2C*). This finding was interpreted as denoting a shift in autonomic activity to a more parasympathetic or vagal tone when OMT was applied during a period of rest in the supine position. The LF:HF ratios noted for participants who received the sham therapy were not different from those noted for participants receiving the control intervention under study conditions. These data indicate that the sham therapy did not cause an effect of its own, as indexed by HRV. Thus, the sham therapy, which involved finger positioning similar to that used in application of the treatment but which did not include either soft-tissue kneading or application of tension, appears to satisfy the requirements of being a true placebo control.

Future Directions

The present article focuses on the use of sham therapy procedures mimicking hands-on treatment and the subsequent validation of these procedures as a placebo by use of HRV analysis. Observations that the sham

therapy group and the no-treatment control group consistently have the same effect under both baseline and sympathetic stimulated conditions[9] indicate both the consistency and the reliability of using HRV as a method for deciding whether a particular sham therapy could be used as an adequate control. In reviewing other OMM-related studies that have measured HRV, it appears that some,[20] but not all,[19] satisfied a lack of effect of the sham therapy as indicated by a lack of change in LF spectral power, HF spectral power, or the ratio of LF:HF spectral power.

Clinical trials that assess treatment outcomes from manipulation are needed, but these studies require stringent, realistic, and reliable controls. If a primary outcome or mechanism of action involves the ANS, a sham therapy procedure should have either no (or a small, consistent) measurable effect on the end organs of the ANS (eg, the heart and blood vessels) or autonomic control factors, as identified by beat-to-beat cardiovascular variability. An OMM clinical trials researcher could therefore be assured that the difference in outcomes was a truer measure of the treatment and was not caused by the sham therapy control.

Although our focus was on HRV as a representative measurement of beat-to-beat cardiovascular variability, as noted earlier, other methods of measurement are available, including those involving blood pressure, blood flow, and sympathetic nerve variability. These methods all have strengths and weaknesses. Nonetheless, whichever mode of beat-to-beat cardiovascular variability is selected for the experimental OMM paradigm, the investigator will have an accurate assessment of the sham therapy as a true placebo control if it can be assured that the sham therapy has no effect on ANS variability. We suggest that investigators performing HRV analysis adopt the normalization procedure to better compare those individuals with high and lower total spectral power. In addition, we suggest that these investigators adhere more strictly to the guidelines for LF (0.04-0.15 Hz) and HF (0.15-0.40 Hz) spectral power suggested by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[8] to allow for better direct comparisons between OMM studies.

Conclusion

Using the spectral analysis generated from HRV analysis, one can determine whether a sham therapy protocol is stable with regard to autonomic activity. If the sham therapy used in a protocol causes changes in the LF:HF ratio, then outcomes for the treatment group, compared with those for the control group, may be open to interpretation. If no change in autonomic activity is indicated by changes in the LF:HF ratio, then the sham therapy is a true ANS placebo and could be used as a reliable control. Overall, HRV is a safe, inexpensive, reliable, and sensitive method to characterize a sham therapy procedure and can substantially supplement our strategies for designing methodologies for OMM research, especially OMM clinical trials.

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