Reviewer’s report

Title: Manual therapy followed by specific active exercises versus a placebo followed by specific active exercises on the improvement of functional disability in patients with chronic non specific low back pain: a randomized controlled trial

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Reviewer: Mitchell Haas

Reviewer’s report:

This is an interesting pilot randomized trial looking at instantaneous pain improvement following manual therapy for low back pain, as well as longer-term efficacy outcomes. There are some issues with the analysis that could completely change the authors’ conclusions about instantaneous pain changes in subjects receiving manual therapy and sham therapy.

Major Compulsory Revisions:
1. Abstract:
   a. The study actually has mixed results in terms of efficacy: positive Oswestry and negative pain findings. This need to be clear in the conclusion.
   b. In the results, I think you mean “immediate” rather than “short-term.”
2. Explain the randomization process (e.g., computer-generated or coin flip, and who did this) and how concealment before randomization was maintained.
3. Include a sample size calculation (a priori power analysis).
4. An adjusted alpha level is required when there are more than one primary outcomes. The usual conservative adjustment for two primary outcomes is alpha = .05/2 = .025.
5. The term “time effect” is confusing because it is used in two different ways in the manuscript. For the pain outcome, just call it average 48-hour pain. Clarify that this variable is used in Table 2. The term “time effect” should be reserved for the main effect of time in the longitudinal analyses.
6. Longitudinal analysis: Repeated-measures ANOVA is no longer recommended because it does not generally treat correlated errors in the repeated measures properly. Linear mixed models or generalized estimating equations can address the clustering effects (correlated error) within subjects.
7. Instantaneous pain analysis: The 3-way instantaneous pain analysis for the 8 treatment sessions is too complicated and difficult to follow because of all the interaction effects. There is also a subtle flaw. The analysis corrects for baseline differences between groups but does not correct for regression to the mean. This is important here because of the very large imbalance at baseline across treatment groups for pain. In fact this imbalance may explain all the findings. There is a clearer way to do the analysis that also can address the potentially
fatal flaw associated with regression to the mean.

a. One factor can be eliminated by computing the after – before pain change for each subject at each time point (instantaneous pain change). The new analysis is a two-way treatment x time analysis with instantaneous change as the dependent variable. The treatment main effect compares the groups directly and the interaction effect looks at differences in treatment effects across time points. This is much easier for the reader to understand.

b. Regression to the mean: The baseline value (before score at the first treatment) must be included in the analysis as a covariate to correct for baseline differences between groups.

c. The same problem can arise at each of the other treatment visits. Therefore, a meaningful comparison between treatments appears to require correction at all time points. This can be done by using the “before” pain score at all eight time points in a time-dependent covariate. You should consult with a statistician on performing analysis with a time-dependent covariate.

8. Reporting the instantaneous pain change analysis. Figure two is fine, but it will be clearer if you include a table like Table 2.

9. Table 2 is well done and very informative.

a. However, the reader is likely to be confused by the “treatment effect,” especially for the pain outcome. In your analysis the interaction effect is the test of differences between groups (because baseline is included in the repeated-measures vector for the dependent variable). The main effect of treatment has no useful interpretation, and is significant only because there is such a large imbalance across treatment groups at baseline.

b. Include an explanation in the table/text that efficacy is tested by the treatment x time interaction.

b. Alternatively, you could do the efficacy analysis with the baseline value as a covariate instead of including it in the repeated-measures factor. This has the advantage of being more powerful. It would also make it easier for the reader, because the meaning of the main and interaction effects will be the same as under comment 7. (Of course, in this analysis you do not need a time-dependent covariate).

10. Results: Clearly present the efficacy results separately for the primary and secondary outcomes. This is important because the conclusions should be based principally on the two primary outcomes.

11. Discussion:

a. Changes will be required based on the new analysis.

b. Limitation: It is not heterogeneity alone that is of importance here. The small sample size produces a statistical power problem.

c. Limitation: The therapist providing the sham ultrasound should have been blinded to the sham. This could have easily been accomplished.

d. Limitation: The specific effects of the manual therapy regimen may not be
isolated because the nonspecific effects of the sham ultrasound may be different from the nonspecific effects of the manipulation regimen.

12. Conclusion:
   a. The immediate analgesic effects will need to be confirmed in a new analysis recommended above.
   b. The mixed positive and negative efficacy results from the primary outcomes must be emphasized.
   c. The results are preliminary, because of the small sample size (pilot study).

Minor Essential Revisions:
1. Three and six-month outcomes are short-term effects not long-term effects.

Discretionary Revisions:
1. None.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.