Author’s response to reviews

Title: The effect of Spinal Manipulative Therapy on Heart Rate Variability and pain in patients with chronic neck pain: A Randomized Controlled trial

Authors:

Anders Galaasen Bakken (Anders.galaasen.bakken@ki.se)
Andreas Eklund (andreas.eklund@ki.se)
Sören O'neill (Soeren.ONeill@rsyd.dk)
Iben Axén (iben.axen@ki.se)

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Author’s response to reviews:

We would like to thank the reviewers for valuable input and suggestions to clarify our protocol.

Below is a point-by-point response to the comments, and the revised protocol has visible changes in order to see where changes has been made.

Reviewer #1: This manuscript left me disappointed and somewhat confused. Despite the promise given by the title, I feel that the authors lacked clarity with their aims, objectives, research questions and methodology. There was also insufficient detail throughout. Thank you for this comment, we have provided extra detail and hope that this will serve to clarify the aims, objectives and research questions throughout. Please see our responses to your upcoming comments.

The idea of the study was good; the field of musculoskeletal healthcare sorely needs data that investigate mechanisms within interventions that have now been established as having a beneficial therapeutic effect (e.g. spinal manipulation). However, this requires explanatory trials of an intervention that contain nested measures (and possibly interruption) of mechanisms, such as those related to the autonomic nervous system. This is where the current study protocol begins to lose its way. The authors state (page 3, line 22) that "the aim of the study is to examine the effects of SMT on HRV and pain to test if a CPM test can be used to predict treatment response, in a population of patients with recurrent and persistent NP." In this quote, the word “and” is missing. We have changed the sentence in order to avoid this confusion.

- The aim of the study is to examine the effects of SMT on HRV and pain. Further to test if a CPM test can be used to predict treatment response, in a population of patients with recurrent and persistent NP.

The authors then describe how they will allow practitioners to choose from an array of treatments
(HVLAT or mobilisation) and additionally introduce another intervention across both groups of the study (stretching exercises) without any explanation or justification for this. Thank you for your comment, we have now described this in more detail, by adding this paragraph;

- A pure placebo trial is not indicated when either evidence-based treatment options exists or when the patients taking part in the study are actively seeking care (17). Due to this, all patients in this trial are given home stretching exercises to ensure that some care is provided. One previous study showed that SMT had a greater effect on pain in combination with home exercises (18). Using this design, the result will show if adding SMT to stretching will yield different HRV and pain responses. Using multiple interventions constitutes a pragmatic trial design, thus introducing multiple confounders that hinder any explanatory power for investigating mechanisms. Thank you for this comment. We have removed the phrase “a variety of techniques” as the clinicians are, in fact, rather limited in their choice of technique.

We can assume that the clinicians will use a similar approach, as they have the same educational background. However, we will collect data on the specific interventions used and, if possible, this will be controlled for in the analysis. As there are few options of SMT, we have changed the wording in the sentence, and added a paragraph;

- As the participating chiropractors have similar educational backgrounds and have received the same instructions concerning their limited choice of treatment techniques, we expect that they will have a similar approach to SMT. Data on the specific interventions will be collected.

The measure used to assess susceptibility for pain modulation, CPM, is by its very nature painful. It is therefore highly likely to affect the primary outcome, heart rate variability (HRV). It must therefore be used very carefully to avoid inadvertently changing outcome and conflating any effect of treatment. Insufficient detail was given in the text to make a judgement on this. Thank you for noticing this. As the object is measuring at night, we have changed the sentence to only include this;

- When patients leave, the HRV-equipment will still be attached to their chest, so that a measurement can be done the following night to record HRV at their deepest sleep (31). Data collected from the FirstBeat monitors are downloaded to a secure computer administered by Karolinska Institutet.

We have also attached the standardized protocol for the test procedures.

At no point could I find detail about when measures were taken; before, during or after treatment. This is not acceptable for a protocol paper, which should leave the reader in no doubt whatsoever, and should allow perfect replication of the study. In the text (Page 6, line 12) it is outlined that all measurements were done before treatment. We have included this in the test protocol to avoid any confusion.

Throughout the manuscript, I found myself having to search through the text for information relating to the chronology of screening, recruitment, assessment and intervention. The figures provided did not provide enough detail and the text did not make up for this lack of detail sufficiently. Thank you for this comment, we have attached the standardized protocol to provide sufficient details.

Arguably, the most concerning sentence of the manuscript was (page 5, lines 24-25) "Logistical details of this recruitment stage will be adapted to individual clinic routines." This introduces enormous potential bias; if unavoidable, much more detail is required so that the reader can assess the potential for bias. Thank you for this comment. This adaptation was mainly necessary regarding how information concerning the study was distributed locally to potential subjects. A sentence has been added to clarify this in the text;

- Patients in this study are self-referred after hearing about the study from another health care provider, or reading about the study in an advertisement or newsletter. A research assistant calls the
patient and assess eligibility using a standardized form. The patients are informed about the aim of the study and the study procedures. If eligible, the patient is scheduled for all study visits during this call. Logistical details of this recruitment stage will be adapted to individual clinics as some clinics have newsletters and some use social media to inform their patients about clinic news. Different local newspapers are also used to recruit patients, as the individual clinics are located in and around the Stockholm area.

I also could not find any detail of how potential participants were approached, screened for eligibility, recruited, etc. Thank you for noticing this. We have now added information about this in the procedure section;

- Patients in this study are self-referred after hearing about the study from another health care provider, or reading about the study in an advertisement or newsletter. A research assistant calls the patient and assess eligibility using a standardized form. The patients are informed about the aim of the study and the study procedures. If eligible, the patient is scheduled for all study visits during this call.

Nor was any detail of how data were collected (paper or electronic), transferred to database, and stored (data protection) prior to analysis. Thank you so much for this important comment. We have added specific information for each of the data collection points you now have mentioned;

- Data collected from the FirstBeat monitors are downloaded to a secure computer administered by Karolinska Institutet.
- This information is collected on paper on the first visit and transferred to a secure KI server by a research assistant. The follow up questionnaires are digital, administered through Karolinska Institutet, managed by Survey & Report by Artologic (https://www.artologik.com/en/SurveyAndReport.aspx).
- Reported pain measurements during the CPM test are noted in a paper form and transferred to a secure KI server by a research assistant.
- These data are automatically stored in a secure server at Karolinska Institutet, accessible only by authorized researchers.

One further concern is that data collection apparently began 6 months ago; hence, it may be too late to improve the methodological flaws highlighted above. These apparent deficiencies may be just due to poor reporting, but I fear this is unlikely to be the case. We do believe that some of the points you have raised are due to poor reporting. Due to the fact that the study is now on-going, we are confident that the protocol is a true reflection of the procedures. We have made the appropriate changes from your valuable input, and are now confident that the protocol reflects the true methodological quality of the study.

Reviewer #2

1. The primary outcome measure is not clearly defined. Thank you for your comment. It has now been clarified;

- The primary outcome is HRV, the variation in beat-to-beat heart rate, an indicator of parasympathetic and sympathetic modulation of the heart rhythm.

The website cited on page 5 is presented in lay language and does not go into detail on measures of heart rate variability, and the reference cited with the sample size justification (Hallman et al) presents a number of different measures - all leading to different required sample sizes (the proposed sample size of 60 makes me think you are planning to use the log of root mean squared successive differences in RR intervals, as measured by the firstbeat device). Thank you for your comment. You are absolutely right concerning this. Please see the following correction;

- Log root mean squared successive differences in RR intervals (RMSSD) is the primary
measurement of HRV. We will also explore other aspects of HRV according to Task Force Standards (35) to get an overall impression of the subjects’ HRV. In a recent study that examined the reliability of HRV measures, the sample size was estimated to 20 subjects in each group to detect a mean change of 20% in RMSSD, and 20-50 subjects in each group to detect a change of 10% (36). A difference of 10-20% has been considered to be clinically important (36). This value has also been used by other researchers investigating changes in HRV from manual treatment (37). With a significance level of 5%, it was estimated that 60 subjects were needed in each treatment arm to reach a power of 80%. This is also in line with the general recommendations to detect a medium effect size (38).

2. Randomisation is presumably stratified by clinic, since a separate sequence of opaque envelopes is presumably distributed to each clinic - this needs to be stated. Thank you for your comment. Randomization was done for 120 subjects, not stratified by clinic.

3. Some variation in the intervention delivered to different participants is allowed by the protocol. This is fine for a pragmatic trial, but I still find the detail of the intervention a little sparse (“a variety of techniques … which will be decided on and described by the participating clinicians”), and this would make replication of the trial difficult. Is any heterogeneity in the effect of the intervention anticipated between clinics (since clinicians at different clinics may use different approaches), and will this be addressed in the analysis? Thank you very much for this comment.

We have removed the phrase “a variety of techniques” as the clinicians are rather limited in their choice of technique.

We can assume that the clinicians will have a similar approach, as they have similar educational backgrounds. However, we will collect data on the specific interventions used and if possible this will be controlled for in the analysis. As the alternatives are few when it comes to the clinical application of SMT, we have changed the wording in the sentence, and added a paragraph;

- As the participating chiropractors have similar educational backgrounds and have received the same instructions concerning their limited choice of treatment techniques, we expect that they will have a similar approach to SMT. Data on the specific interventions will be collected.

4. The assessment of conditioned pain modification (CPM) is unclear. "CPM consists of the evaluation of a painful test stimulus followed by a second evaluation either at the same time as a distant, painful conditioning stimulus or in series after the painful conditioning stimulus has been withdrawn": which of these methods will be used, Thank you for your comment, we can see that this is not clear. The sentence has now been changed, to clarify precisely what we do in this study;

- In this study, CPM consists of the evaluation of a painful test stimulus followed by a second evaluation after the painful conditioning stimulus has been withdrawn (sequential stimuli and how will pain be evaluated? Thank you very much for this, we realize that we had a general description of the test. A more detailed description has now been added;

- Our study will use a structured CPM testing protocol with a standardized clamp pressing on the thumb nail for 10 seconds as the test stimulus, and cold water (0-2°C) as the conditioning stimulus (22). A NRS 11 point scale will record pain associated with both stimuli.

5. There is no description of how the secondary aim of the trial (to investigate whether CPM is a predictor of treatment outcome) will be addressed. I would expect this be analysed by looking at the statistical interaction between CPM and SMT. It is not sufficient just to say that "possible interaction
effects on the outcomes will be checked for". (The precise research questions addressed by the multiple regression analyses and path analyses are unclear.) Thank you for this comment. A section has been added to clarify this; CHANGE
- Possible interaction effects on the outcomes will be checked for. CPM and SMT are binary and if we estimate the model \( HRV = b_0 + b_1\text{SMT} + b_2\text{CPM} + b_3\text{SMT}\times\text{CPM} \) and if \( b_3 \) is statistically significant, we can either add \( b_3 \) to \( b_1 \) or stratify on SMT since both methods yield the same result. However, if \( b_3 \) is statistically significant in the model \( HRV = b_0 + b_1\text{SMT} + b_2\text{CPM} + b_3\text{SMT}\times\text{CPM} + b_4Z \), stratification and adding \( b_3 \) to \( b_1 \) will yield different results if the distribution of \( Z \) differs in \( \text{SMT} = 0 \) and \( \text{SMT} = 1 \). In this case we will not stratify on SMT and we will not use \( b_3\text{SMT}\times\text{CPM} \) if \( b_3 \) is non-statistically significant.

6. The discussion explains that a pilot study will be conducted prior to commencing the full-scale study. Presumably this has already happened - please make this clear: if there were any changes made as a result of this pilot work these should now be part of the protocol. Thank you for your comment, you are absolutely right. Changes has been made on page line ....;
- A pilot study was conducted prior to commencing the full-scale study. It resulted in changes to the recruitment strategy with regards to the use of newspapers and advertising. The responsibility of booking eligible patients was transferred to a research assistant from the local receptionist.