Author’s response to reviews

Title: Gait analysis following single-shot hyaluronic acid supplementation: a pilot randomised double-blinded controlled trial

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Version: 1 Date: 26 Mar 2019

Author’s response to reviews:

To the reviewers – all revisions in the manuscript have been marked in bold.

Reviewer #1:

Thanks for giving me the opportunity to review this interesting work.

This manuscript reports the results of a pilot 3-arm RCT to examine the effect of (1) HA+mannitol (n=9), (2) HA+sorbitol (n=5), and (3) saline placebo.

Comments

1. In general, from the abstract, it looks like you aimed to test the effectiveness of the intervention. This is not the purpose of pilot trials, and I am not sure if you have the sample size to test effectiveness. Please make sure you make it clear in the results that the statistical significance is not conclusive and it was not the objective of the trial, as the main objective of
the trial is to determine which gait parameters are more sensitive following a single bolus injection of polyol-containing HA for knee osteoarthritis.

Thank you for these comments. We have rewritten the Objectives of the Abstract, to remove the concept of effectiveness of HA supplementation, and to clearly state that gait analysis is a complementary outcome measure for testing the effect of HA injection. We also state that the purpose of this study was to determine which gait parameters are more sensitive following a single bolus injection of polyol-containing HA for knee osteoarthritis. See lines 39-44. We have adjusted the final sentence of the Results to indicate that the observed increase in gait speed is clinically important, and thus gait speed is a sensitive gait parameter feasible for evaluation in a larger randomized clinical trial. See lines 58-59. We have also rewritten the Conclusions of the Abstract, to clearly state that this study demonstrated gait speed and stride length are the most relevant parameters for gait analysis investigation of the effect of polyol-containing HA viscosupplementation, and we have deleted the concept of testing the effectiveness of HA supplementation. See lines 60-65.

2. It would be great if you can report other feasibility outcomes, as suggested by Thabane et al 2010.

Thank you for bringing this publication to our attention. Thabane et al 2010 demonstrated that a pilot study is essentially a feasibility study. Feasibility outcomes can focus on a) the process and steps, such as recruitment rates and retention rates, b) the resources, i.e., time and budget, c) the management of the study, such as personnel and data management and optimization, and d) the scientific outcomes, i.e., assessment of treatment safety, dose levels, dose responses, and estimation of treatment effect. The primary feasibility outcome of our study was scientific, i.e., the determination of which gait parameters and clinical outcome measures were most relevant for assessment of polyol-containing HA injection in people with knee osteoarthritis. This is reported as the purpose of our study in the final paragraph of the Introduction (see lines 125-127), and it is the focus of the study. Although we did not specifically set out to determine other feasibility outcomes, a second feasibility outcome became apparent during the conduct of this pilot study, that of patient recruitment. Many patients were unwilling to participate in the pilot study for fear of being allocated to the placebo (control) group because they were in pain. This is a common concern in trials investigating osteoarthritis interventions. The present study did not introduce any rescue medication following the injection, to avoid additional confounding variables. The pain management protocol for this study will be reviewed, due to its limited feasibility with respect to patient recruitment, and may be revised for future trials, to perhaps compare outcomes of a single HA injection versus multiple injections, and thus avoid having a placebo group. We have added a new paragraph to the Discussion to discuss this feasibility outcome. See lines 275-286.
3. Abstract, Results, line 53, you need to clarify that mannitol containing viscosupplement effect is different than placebo.

Thank you for this suggestion. We have rewritten the second sentence of the Results section of the Abstract, which reports the results for the HA+sorbitol group and saline group, to better emphasize that these groups demonstrated no significant changes from baseline to 4W in any gait parameters or outcome measures, which is in contrast to the results for the mannitol-containing viscosupplement reported in the previous sentence. See lines 54-56.

4. Page 7 line 141, who did randomize the participants? Did you use a strategy to conceal your allocation?

Patients were randomized according to a previously developed, computer generated, online randomization key, through www.randomizer.org. We have added this citation to the text (see new Reference #23 and line 143 in the text). A researcher not participating in the trial (i.e., had no connection or relationship with the patient or with the person conducting the outcome assessment) performed the randomization and sent the notice to the secretary. Right before the patient’s appointment for injection, the secretary informed the physician performing the injection of the product to be injected, who therefore was not blinded to the injection, but was blinded to the subsequent outcome assessment. The physician performing the injection had contact with the patient only during the injection, but at no other times. We have clarified this in the Methods, see lines 146-149.

5. Page 7: did the 3 types of injections look/feel similar? Did you check if the physician or the participants can figure out the allocation group?

Yes, the 3 types of injections looked and felt similar. The injections were out of the packaging, so the participant could not identify the product. The volumes were similar and the needles were the same, so the participant could not feel any difference. The physician knew which product he was injecting, but the patients were blinded until after the end of the trial. The clinicians conducting the outcome assessment were also blinded until after the end of the trial. Additionally, the clinicians who conducted the 4W assessment had no information about the baseline scores, and therefore could not gauge if there was any change, either positive or negative. We have clarified this in the Methods, see line 141 and lines 150-151.

6. Page 7: line. 146 what was the physicians" training, what specialty?
Two physicians performed all of the injection – one is a senior physician with expertise in Sports Medicine, and the other is a senior orthopaedic surgeon.

7. Page 7, line 148, what was the assessors' training?

Assessments were performed by senior specialized clinical physiotherapists, according to an a priori established protocol, which we have cited as reference #27 in the Methods, see lines 165-166.

8. Page 8, line 160, more details about the gait analysis is needed, a brief description of the analysis protocol, the test setting.

Patients’ gait was assessed during two 30m walks along an indoor corridor of our institution, at each patient’s preferred speed. Patients were instructed to walk normally, and no verbal encouragement was given during the test. Miniature inertial sensors were mounted on the trunk (sacrum) and each thigh and shank to measure lower limb and trunk rotations, and these were linked to a portable data logger (Physilog, BioAGM, Switzerland). Temporal and spatial parameters were computed to determine four basic gait parameters: walking speed, stride length, cadence, and duration of the swing phase relative to the cycle duration. These parameters were measured over the 30m of the two trials according to a previously validated protocol, published by Dejnabadi et al (2006; Reference #27 in the manuscript). We have added these details to the Methods of the manuscript, see lines 157-166. The gait parameters measured in each cycle of the two walks were averaged during the steady part of the walks to provide a single measure of speed, stride length, cadence and swing duration for each patient at baseline and at 4W. The changes between baseline and 4W were calculated individually for each patient, for the four gait parameters and five clinical outcome measure scores. This is reported in the Methods under the subheading “Data collection and analysis”. See lines 171-175.

9. Page 8, line 168, how did you check for data normality? What test did you use?

No specific test was conducted for this study to check for data normality. However, our group has extensive experience conducting gait studies and gait analysis. We know that in previous gait analysis studies with larger sample sizes (i.e., n=25 per group), a strong non-Gaussian distribution was observed.

10. I would change table 2 heading into baseline, instead of visit 1 and 4 weeks, instead of visit 2.
We have changed the headings as requested. See Table 2.

11. Page 11, line 202, how often did you ask about adverse events? And who asked about that?
Patients were asked directly about adverse events by the outcomes assessor at one day, one week, and four weeks post-injection, and also by the physician who conducted the injection at five weeks post-injection. We have added this information to the Methods, see lines 166-167.

12. Was the data entry personal or the data analyst blinded?
Data was entered as blinded codes, such that the data analyst was completely blinded.

13. Page 11, line 206, how did you decide that gait speed and stride length are the most relevant gait parameters to investigate when assessing the effects of HA injection in people with knee OA? What was the success criteria? As it is a pilot study, you need to have a priori success criteria.
Change in walking speed and change in stride length were the only gait parameters that demonstrated sufficiently large changes from baseline to four weeks to be clinically meaningful. The increase in walking speed was 13% greater than the mean difference in walking speed between healthy subjects and those with knee osteoarthritis, based on data from a recent meta-analysis by Mills et al. (Arthritis Care Res 2013;65:1643-65), cited as reference #21 in our study. We used that publication to determine our success criteria a priori. This information is provided in the Discussion (see lines 234-240). For this reason, they were considered the most relevant gait parameters to investigate when assessing the effects of HA injection in people with knee osteoarthritis.

14. In page 13, line 260, you mentioned "Thus, a single HA injection appears to have a positive impact on pain and function up to six months following injection." Was this study powered to detect between group differences at 6 months? You may need to revise this statement.
This statement was made based on the results reported by Kotevoglu et al (reference #38) in the previous sentence (see lines 260-264). They reported on completed outcome measure data for 59 patients, at 1 month, 3 months, and 6 months following viscosupplementation with high molecular weight HA for the treatment of knee osteoarthritis, i.e., we state: “Kotevoglu et al reported improvements … at one month … that remained significant at 6 months”. In their power
analysis, for a significance level of $p=0.05$ and a power of $0.80$, the sample size was calculated as 26 patients.

15. Page 14, line 271, would you please explain what do you mean by "A sample size of 22 patients is suitable for a pilot study"? Was there a sample size calculation done based on the feasibility outcome? If not, this should be a limitation, even for pilot studies.

The reviewer is correct. We have revised this statement to indicate that the sample size of 22 patients, while informative for evaluating feasibility outcomes, is a limitation for statistical analysis, even in a pilot study. See lines 287-288.

16. In page 14 line 276, you mentioned the recruitment difficulty, is it possible to report the recruitment rate and retention rate? These are important feasibility outcomes as well.

Thank you for this suggestion. We agree with the reviewer that it would be helpful to have this information as a feasibility outcome. Unfortunately, formal records of recruitment attempts were not kept, as we did not anticipate any difficulties prior to initiating the study. Furthermore, the staff who were responsible for recruitment are no longer in the department, so we are unable to follow up with them. We have addressed recruitment difficulty as a feasibility outcome in the Discussion, see lines 278-282.

17. In the discussion, you may want to comment on that the HA+mannitol group was younger than the other two groups (table 1), also another limitation is including only 5 participants in the HA+sorbitol group, vs. 9 and 8 in the other 2 groups.

Thank you for these suggestions. We have added the following text to the paragraph on limitations within the Discussion: “The HA+sorbitol group included only 5 participants, compared to 9 and 8 participants in the other two groups, limiting comparisons. Also, the HA+mannitol group was, on average, 4 to 5 years younger than the other two groups, which may have contributed to the observed improvements in gait speed and stride length.” See lines 292-295.
Reviewer #2:

The authors investigated changes in four basic gait parameters of walking speed, stride length, cadence and swing duration from baseline to 4 weeks follow-up for each of three different treatment groups: hyaluronic acid (HA)+mannitol (n=9), HA+sorbitol (n=5) and saline placebo (n=8) in 22 patients with knee osteoarthritis. This was a 3-arm, prospective, randomised double-blinded controlled pilot trial. They found that only changes in walking speed and stride length with the HA+mannitol treatment group were statistically significant as tested with the Wilcoxon signed-rank tests. Overall, the paper is well written. I have the following comments.

1. This is a retrospectively registered study. The study started in May 2013 and completed in February 2015. Then the study was retrospectively registered on August 20, 2018. Explanation should be given why the study was registered a few years later after completing the study.

When we initiated this study, we were under the mistaken impression that only full-sized, randomized, clinical trials required registration in a clinical trial database. We did not realize that small pilot clinical trials, even though randomized, were also required to be registered in order to be considered for publication purposes. We welcome feedback from the journal’s Editor as to the most appropriate place in the manuscript to include this explanation, if necessary.

2. It is not clear what the primary outcome was in the study?

The purpose of this study was to determine the most relevant gait parameters and clinical outcome measures when assessing the effectiveness of polyol-containing HA injection in people with knee osteoarthritis. This is stated at the end of the Introduction (see lines 125-127). We have revised the opening sentences of the Abstract to improve clarity (see lines 39-44). The primary outcome was the four measured gait parameters, i.e., walking speed, stride length, cadence, and duration of the swing phase relative to the cycle duration. We have specified in the Methods that these were the primary outcomes for the study (see lines 162-165).

3. Randomization: on page 7, the authors indicated that patients were assigned to one of three groups according to the previously developed, computer generated, and randomization key. It may be better to provide the method in more details.

The computer generated randomization was completed using an online program, www.randomizer.org, in a way that blocks of patients were attributed equally to the three groups. We have added the citation for this website to the text (see line 143 and new Reference #23).
4. It is not clear why authors selected 22 patients in the study. Are there any evidence to support this?

For this pilot study, we did not perform a proper sample size calculation; however, one of the study's objectives was to provide a basis to calculate the size for a follow-up study. Thus, we did not know the to-be-expected effect, in terms of quantity of the treatment, or the within- and between-subject variation of the gait measurements. The number of 6 to 9 patients per group was a gross estimate based on the investigator's experience with gait analysis studies.

5. It seems that the study did not define clearly about the primary and secondary objectives for the main study and the outcome measures.

The primary feasibility outcome of our pilot study was the determination of which gait parameters and clinical outcome measures were most relevant for assessment of polyol-containing HA injection in people with knee osteoarthritis. This is reported as the purpose of our study in the final paragraph of the Introduction (see lines 125-127). The primary outcome was the four measured gait parameters, i.e., walking speed, stride length, cadence, and duration of the swing phase relative to the cycle duration. We have revised the Methods to clearly specify that these were the primary outcomes (see lines 162-165).