Reviewer’s report


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Reviewer: Kade Paterson

Reviewer’s report:

Thanks for the opportunity to review this paper which investigates the clinical effectiveness of HA based on obesity status and radiological severity. It uses a secondary analysis from a RCT which is a nice additional use of this data, and the findings suggest that HA is more effective in non-obese and people with less severe radiographic disease. These findings should be useful for clinicians and researchers alike.

I have a number of suggestions outlined below. The three main ones are (1) the discussion confuses the recommendations for those with more severe ROA - at one stage it says HA should still be used, but at other times says this group failed treatment, that HA should not be recommended for them and that it's not a viable solution in these people. This group still improved greater than the MCID, but the improvement was less than those with lower BMIs and less severe radiographic disease. The language regarding this needs to be improved throughout the manuscript. (2) I think the analyses do not reflect the aims of the paper. Quite often the study talks about identifying patient sub groups or risk factors. The type of analysis performed in this study are unable to determine these. I suggest preferably re-analysing the data using more appropriate statistical techniques, or as a last resort, removing all reference to these terms. (3) The analyses should be performed on mean change scores, or follow up adjusted scores.

Abstract
If space permits, a brief line on the stats would be helpful
Results - do these changes account for baseline levels? And the womac pain values at 6 months, are these the change in pain? I don't think reporting the raw 6 months score is necessary as the change will suffice (again, providing it accounts for baseline values)
I'm not sure the conclusion is supported by the results - see comments in the discussion/conclusion regarding true moderator analyses that is needed to identify subgroups. And other comments about not recommending HA for these people. Also "This trial confirms that obesity and advanced stage are independent predictors of a lower response to viscosupplementation" - the analyses are unable to determine predictors as such.

Introduction
The first sentence is quite long - perhaps break in to 2? And perhaps begin with a line or two about OA, symptoms, burden etc?
Does viscosupplementation need abbreviating?
Line 7 - what is viscosupplementation? A brief explanation for readers who are unfamiliar with the treatment would be helpful.
The EULAR recommendations are from 2003 and are out of date.
I agree their use is controversial, but there are variable recommendations given across clinical guidelines (Nelson, Allen, Golightly, Goode, & Jordan, 2014). Quoting only those positive recommendations doesn't tell the true picture. For example, an uncertain recommendation was given by OARSI due to inconsistent conclusions among meta-analyses and conflicting results regarding safety (McAlindon et al., 2014), while the UK National Institute for Health and Care Excellence recommended against their use (National Institute for Health and Care Excellence, 2014). It is important to acknowledge these uncertain/negative recommendations as well, and it may help strengthen the justification for your study - variable findings because of heterogenous samples of knee OA patients.

Line 19 should be "worse results"
Line 19-24 needs a reference
Line 24 - please explain this previous study of yours with a little more detail
It's not clear why you are comparing 2 HA groups. Why not saline as a control?
Overall the intro is quite brief but adding these changes above should help.

Methods
Page 5, lines 19-29: please break this sentence up
Line 34: spell out KOFUS first. Was knee or other surgery an exclusion?
Line 48: concomitant treatments are mentioned here but are not listed or compared between groups.
Page 6 line 17 - what/when is "each follow up visit"? This/these should be explained. Were these performed in the lab? Online or hardcopy at home?
Page 7 - did you control for anything in your analysis? Baseline score need to be accounted for at a minimum. And is the primary variable(s) change in pain (and function)? What data were the logistic regressions used on? And ANCOVA? The stats section would benefit from a little more explanation. Did you consider instead running a prognostic analysis, with ORs for predictors like the Altman study mentioned later? That would seem to be a stronger statistical approach than what was used - I would strongly recommend reanalysing the data using these techniques.

Results
Consider including a demographic characteristic table. What were the demographics of each group (e.g. BMI in the obese and non-obese groups)?
Please reference Table 1 in the opening results paragraph where you talk about the data from that table.
Please calculate and report (adjusted) mean difference and 95% CIs for your groups for change over time. These should be included in Table 1 and as appropriate also. This might look better by transposing the table so the column headings would be baseline to 6-month mean difference (SD) for each of your groups, with the values for pain and function in the rows. The more appropriate outcome would be this adjusted 6-month change in pain (and function) rather than simply the 6-month value. Then you could assess each group's change in pain relative to the minimal clinically important difference (MCID) values, as well as compare mean change between groups. You could then also remove Figures 1 and 2 which aren't very informative.
Discussion
Page 9 line: "...in subjects who combined THESE two risk factors."
Line 29 remove "an"
Line 34 "in the HAV-study". Perhaps amend to say in our previous study (HAV-2012) and add the reference
Line 41 maybe don't say the "FLEXX trial and the extension trial" and just say the Altman et al study (I think "Altman and al" should be Altman et al).
Your results showed that it was less effective in those with OARSI grade 3, and you mention that this is consistent with the Altman trial, and your other findings, but you spend just as much space (or more) justifying that it should be used in people with more advanced radiographic knee OA. Firstly, some explanation of why it was more effective in those with less advanced disease would be helpful (like in Altman's discussion). Same with non-obese later. Secondly, given your findings don't show less effect in people with more advanced disease, consider reducing some of the content justifying why it should still be used in these patients. I understand that advanced ROA shouldn't be a contraindication, but these findings show that it is less effective in these patients.
Page 10 lines 1-12 - this is a very long sentence. Are you able to break it up at all?
Lines 20-22 The findings don't really show a risk of failure in obese people, just less effective. Consider rewording this.
Lines 36-39 "the confirmation that the combination of obesity to an advanced radiographic stage is highly predictive of treatment failure" change to "the combination of obesity and advanced radiographic stage..." And again, it was not a treatment failure, just less effective - they still had a 28.6% reduction in pain which is greater than the MCID, as is pointed out in the next sentence.
Page 11, line 9 Change "Another interesting data to point out..." to "Also of interest, WOMAC function was...." Or something similar
Line 39 change "strictly identical" to "similar" or "the same"
Line 41—53 US guided injections have been found to be more accurate and lead to greater improvements in the knee than non-guided (Berkoff, Miller, & Block, 2012). These improvements with US guidance are likely to be even greater in obese patients given their greater amounts of adipose tissue around the injection site. Perhaps cite this, and remove the line that starts with "However, in daily clinical practice knee HA injections are usually achieved without imaging guidance".
Another limitation is the lack of a true control group. This means this study cannot perform a moderation analysis required to identify patient subgroups (e.g. see Kraemer, Wilson, Fairburn, & Agras, 2002). There was also not a prognostic analysis as mentioned earlier. This would be preferable.
Page 12 lines 1-2 - as mentioned this type of analysis doesn't identify a treatment subgroup of responders (a moderator analysis is needed). I suggest changing this language here, and in the abstract.
Line 5 I'm a little confused because in the discussion you argue that it should still be used in those with more advance ROA
Line 9 Likewise "VS is not a viable solution to alleviate their pain" is incorrect - this group achieved the MCID. Suggest rewording

References


**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published
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