

Reviewer's report

Title: Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint(R)) on pain relief and quality of life in subjects with knee osteoarthritis: a pilot randomized double-blind placebo-controlled trial

Version: 1 **Date:** 12 November 2007

Reviewer: Luke Bucci

Reviewer's report:

General

This submission appears to be the first human clinical study on OA utilizing oral, high molecular weight hyaluronan (HA) without other ingredients added. Since the use of HA is found in a wide variety of dietary supplements for years, the question of efficacy of oral HA is timely, practical and of interest.

Points to consider:

1. Is the question posed by the authors new and well-defined?

Yes

2. Are the methods appropriate and well described, and are sufficient details presented to replicate the work?

Yes, Yes

3. Are the data sound and well controlled?

Yes, Yes

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

Yes

5. Are the discussion and conclusion well balanced and adequately supported by the data?

Yes, Yes

6. Do the title and abstract accurately convey what has been found?

Yes

7. Is the writing acceptable?

Yes

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Page 6: Add Rescue Medication instructions to subjects in Materials & Methods. With a low subject number per group, and the nature of rescue

medication being to increase variability for pain and function scores on questionnaires, the actual instructions given to subjects needs to be known. Rescue medication usage has been acknowledged as causing large placebo responses, especially in North American osteoarthritis trials (see NIH GAIT study for but one example). Large “placebo” responses due to self-medication to low pain levels can easily prevent finding an effect from the active group. Also, the use of rescue medication is another important indicator of a difference between groups when pain is a variable. Instructions to subjects were not given, and thus, it is not possible to determine if rescue medication usage was an influence on results. This is a key point.

2. On pages 7-8, the description of Per Protocol (PP) is actually Intention-To-Treat (ITT). It should be made clear if analysis was ITT or PP (as defined by finishers only), or change PP to ITT.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. In the abstract and throughout the text, the WOMAC Activities of Daily Living scores (ADL) were presented as “physical functioning.” This appellation is inaccurate and confusing, as the investigators also measured Physical Function by SF-36. This score was reported as “Physical Function” – virtually identical to the WOMAC ADL results, since whether the score was from WOMAC or SF-36 was usually not indicated clearly. Need to change all descriptions of WOMAC ADL to another descriptor (WOMAC ADL is commonly used in the literature) to prevent confusion among readers with the SF-36 Physical Functioning results.
2. Figures have no legend to describe which group is open or solid symbols.
3. Page 6, line 3 – please change ‘nutraceuticals’ to the more accurate ‘dietary supplements.’
4. Page 8: Initial (baseline) use of acetaminophen was not mentioned. Any information on this variable is vital for proper interpretation of results. The baseline acetaminophen use can easily be added to Table 1.

Discretionary Revisions (which the author can choose to ignore)

1. In the abstract, numerical results for the primary variables were not presented since they were not statistically significant, but similarly nonsignificant changes for other measurements were presented. If room allows, it would be fair to also list the same numerical results for the primary variables, since room was taken to accentuate the positive.
2. Page 9: Rescue medication results – it would be helpful to analyze the rescue medication effects on the study if the percent of subjects using rescue medications were presented (or a distribution of average or total dose in each group).
3. Page 11, 2nd paragraph: The authors state that the rescue medication usage

was held constant throughout the study or was “kept to a minimum”, but their results argue otherwise – placebo group usage was close to 2000 mg daily whereas active group usage was around 1000 mg daily. This is a large practical difference, regardless of statistical difference. Also, this is a large effect, not minimal, as 1-2 g/d acetaminophen can easily control and reduce pain in persons with mild-moderate pain, as these subjects exhibited. Rescue medication usage is very important for interpreting results of this study since the primary variables (WOMAC Pain and SF-36 Bodily Pain) were not always significantly different between groups, while other measures were. Thus, an effect of the active agent might have been missed due to rescue medication usage differences. One suggestion is to plot rescue medication usage in a new Figure 3 to better illustrate the differences between groups, and perhaps further explain the results.

4. Page 12, line 1: “This...effects” – grammar needs to be corrected.

5. Reference 30 – perhaps replace this reference with the review by Dougados on structure-modifying effects of intraarticular HA on knee cartilage and synovial, which would better fit the discussion.

What next?: Accept after minor essential revisions

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.