Author's response to reviews

Title: Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study

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Author's response to reviews: see over
Dear Sir/Madam,

We thank you for reviewing our paper, entitled, “Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study”, for consideration for publication in *BMC Complementary and Alternative Medicine*.

Below is a point-by-point response to each point raised by each reviewer. The changes in the manuscript are highlighted in yellow. In addition the manuscript was reviewed and edited to comply fully with the journal guidelines. We believe that the changes made have greatly increased the quality of our submission.

We thank you in advance for the reconsideration of our work.

Sincerely yours,

Ronen Debi, MD
Reviewer 1:

Major Compulsory Revisions:

1. Your randomization seems strange. This may cause bias to the study.

   We agree that that the randomization for the study was unconventional in comparison to other, similar studies. The assumption was that the adjustments made to the original study results would compensate for any bias created by the imperfect randomization.

   An additional explanation for the adjustments made was added to the manuscript on page 10, line 21:

   “Additional nested variables were added to the analysis in order to adjust for any baseline differences in the distribution of certain variables (e.g. gender) between the groups. Results before and after adjustment are presented. The results of the ITT analysis were also adjusted for any baseline differences between groups.”

2. Do you calculate the sample size before enrollment?

   The sample size was calculated with the help of a statistician and a review of the literature on studies of methylsulfonylmethane and knee osteoarthritis.

3. How do you manage lost case in your ITT analysis? You did not mention about this.

   We added an explanation to this to the manuscript on page 10, line 13:

   “Intention to treat (ITT) analysis was carried out in order to include all the randomized patients within the analysis. In the case of any study drop-outs, the same values that were measured in the follow-up before drop-out were used for the follow-ups after drop-out.”

And on Page 11, line 18:
“These patients were still included within the ITT analysis.”

Figure 1 needed to be adjusted accordingly.

4. **You did not report compliance of drug between both groups.**

An additional explanation was added on Page 11, line 17:

“All patients in each group reported full compliance with the treatment protocol when questioned at each follow-up. In addition, pill bottles had the appropriate number of pills at each follow-up.”

5. **For the safety, how can you record the AE? Please describe in detail.**

   We recorded AE by asking the patients if they experienced any side effects due the medication that were not apparent before the study. This was described on page 9, line 18. We realize the study lacks a more robust examination of the AE, such as of liver function tests and others, as suggested by another reviewer. We hope to carry this out in future studies. This was added on Page 16, line 16:

   “Future studies should examine the adverse effects of MSM more thoroughly.”

6. **You had so many outcomes and only 2 in primary outcome and 1 in secondary outcomes were statistical significant, but not clinical significant. Therefore, you should be careful in your conclusion that MSM could be an additional therapy option for patients with knee OA. Usually we concern about drug’s efficacy, followed by its safety.**

   We understand that we should take better care in stating our conclusions. In addition, our measures of safety were lacking. For these reasons we have modified our conclusion:

   Removed: “Nevertheless, while the effects of MSM appear to be modest, due to the absence of
adverse side effects, MSM could be an additional therapy option for patients with knee OA.”

7. Are the methods appropriate and well described? I wonder about the randomization method, adverse event record, compliance and sample size calculation.

We hope these issues were adequately addressed above in questions 1, 2, 4 and 5.

8. Are the discussion and conclusions well balanced and adequately supported by the data?

Uncertain.

We hope this was adequately addressed above in question 6.

9. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Uncertain.

This was the first time we decided to examine an alternative/CAM therapy for knee osteoarthritis. We were surprised and excited with the results and the positive feedback from the patients. As such we hope to carry out further studies in the near future. We have no experiments, however, to declare at the moment.

10. Quality of written English: Needs some language corrections before being published

The English was reviewed by a native English speaker and research colleague prior to resubmission.
Reviewer 2:

Minor:

1. Who funded the study?

   The study was funded by the Assaf Harofeh Medical Center, Zerifin, Israel. The MSM and
placebo used in the study were donated by the manufacturer, Ta’am Teva.

   This was added to the manuscript on page 18, line 17:

   “This study was funded by the Assaf Harofeh Medical Center, Zerifin, Israel. The MSM
and placebo used in the study were generously donated by the manufacturer Ta’am Teva.

2. Perhaps you could elaborate on the effect size relative to several standard treatments.

   The following was added to the manuscript on Page 16, line 23:

   “A meta-analysis on NSAIDs for knee OA showed them to have an average effect size of
approximately 0.32 [32]. The effect size of MSM in the present study (0.28) falls slightly below
this number. Compared to topical NSAIDs, which have been shown to have an effect size of
approximately 0.4 [33], MSM also had a relatively smaller effect size in the present study. On
the other hand, MSM had a relatively greater efficacy than intra-articular hyaluronic acid
injections, which have been shown to decrease pain by only 4.3 mm [34]. These findings suggest
that the efficacy of MSM is modest in comparison to the standard care for knee OA pain and
falls below the efficacies of most standard therapies. These comparisons, however, should be
interpreted with care considering that these studies did not have identical methodologies.”

3. OA is not used consistently

   This was modified on Page 3, line 7 and Page 9, line 1.
Reviewer 3:

1. The primary limitations are the small size, limited duration, single site and limited power of the study, three of which are discussed by the authors.

The following addition was made on Page 15, line 25:

“The results of the study may have also been improved had a greater number of patients been enrolled to the study. These issues limit the power of the present study.”

2. Although multiple comparisons are tested, correction statistically is not discussed nor reported

Changes within the groups and differences between the groups in primary outcomes were calculated by repeated measures analysis, which produced three tests of significance: differences in changes over time between groups, total changes over time and differences between groups in general. These three tests are combined within one analysis that takes into account the multiple comparisons correction and adjusts the P values accordingly. The following was added to the manuscript on Page 11, line 6:

“The repeated measures analysis takes into account all three tests and a multiple comparisons correction.”

3. The trial also suffered some departure from randomization expectations as well, leading to the reporting of both adjusted and non-adjusted results. Unfortunately, no description of the approach to adjustment is included for review.

To adjust for baseline differences we entered the differing variables as another nested
variable within the repeated measures analysis in addition to the two groups themselves. An additional explanation for the adjustments made was added to the manuscript on page 10, line 21:

“Additional nested variables were added to the analysis in order to adjust for any baseline differences in the distribution of certain variables (e.g. gender) between the groups. Results before and after adjustment are presented. The results of the ITT analysis were also adjusted for any baseline differences between groups.”

4. Another concern is the lack of any reported ADRs, which seems unfathomable even in placebo trials and specifically lack of reporting on Blood pressure and liver function tests which they point out have previously been suggested as concerns of MSM use.

We recorded ADRs by asking the patients if they experienced any side effects due the medication that were not apparent before the study. This was described on page 9, line 18. We realize the study lacks a more robust examination of the ADRs, such as of liver function tests and others. We hope to carry this out in future studies. This was added on Page 16, lines 14&16: “Future studies should examine the adverse effects of MSM more thoroughly.”

5. Statistically, several things need to be considered. The number of comparisons, the time points and the use of adjustment. More description of why each of these is included, omitted or not important needs to be included.

We hope these issues were answered adequately above in questions 2 and 3.

Major compulsory revisions - None
Minor essential revisions -

1. Please add discussion of why multiple comparisons corrections were not used or conversely adapt the manuscript after applying them appropriately.

We hope these issues were answered adequately above in question 2.

Discretionary revisions -

1. I recommend that Table 2 be split into two tables, one with the primary outcome comparisons and non-adjusted statistical assessments at 12 weeks and a second showing the adjusted results and other secondary outcome results. This will keep the focus on the primary outcome at 12 weeks.

These changes were made as requested. Please see Tables.

2. Also figures 2 and 3 add very little and could be removed especially as confidence interval bars should be shown which then would be very overlapping.

We agree with this and have removed both figures.