

April 30, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7646-edited.doc)

Title (Revised): Efficacy of therapeutic ultrasound versus sham ultrasound on pain and physical function in people with knee osteoarthritis: A meta-analysis of randomized controlled trials.

Authors: Norma J MacIntyre, Ahmed Negm, Adalberto Loyola-Sánchez, Mohit Bhandari

Name of Journal: world Journal of Meta-Analysis

ESPS Manuscript NO: 7647

The manuscript has been improved according to the suggestions of reviewers as described below.

Authors' Responses to Reviewer 1's Comments:

Reviewer 1's Comment: An interesting meta-analysis

Authors' Response: We thank you for your review of and interest in our manuscript.

Authors' Responses to Reviewer 2's Comments:

Reviewer 2's Comment: This meta-analysis was used to determine the efficacy of therapeutic ultrasound versus sham for improving pain and physical function immediately post-intervention in people with knee osteoarthritis (OA). The five trials eligible for 276 meta-analysis reported data for a total of 281 participants and OA knees. The meta-analyzed provide that therapeutic ultrasound decreases knee OA pain but it does not improve physical function. The manuscript is quite well written and documented, and the data provide a high level evidence to further study of ultrasound therapy for knee OA. So I suggest it is better to revise this manuscript again as the following suggestion.

Reviewer 2's Comment #1. The paper title can be modified as efficacy of therapeutic ultrasound versus sham ultrasound on pain and physical function in people with knee osteoarthritis: A meta-analysis of randomized controlled trials.

Authors' Response: We have revised the title as suggested.

Reviewer 2's Comment #2. The previous systematic (2009) on this topic do not agree with this paper research content as well as search strategy, so the meta-analysis depended on the previous retrieve articles plus 2009-2013 retrieved articles maybe have something to explain.

Authors' Response: AL Loyola Sánchez reviewed all references resulting from the search strategy published in our systematic review published in 2010 and AL Loyola Sánchez and NJ MacIntyre reviewed all potentially eligible fulltext articles in duplicate. Despite the broader research question being addressed in our review, we included the same published articles included in the Cochrane Systematic Review completed at the same time as our review. We are certain we have screened all potentially eligible papers published prior to 2009 and have included all studies that fit the inclusion/exclusion criteria for our current systematic review published prior to our updated search. For the updated systematic review, we narrowed our research question and included only those articles that exposed the control group to sham ultrasound and were published in peer reviewed journals. Therefore, we replicated the search strategy published in the Cochrane Systematic Review. As reflected in the title, the purpose of the current review was to synthesis the effectiveness literature that included sham ultrasound. We chose this focus for the current review so all participants were blinded to the intervention and the impact of expectation bias on the self-reported measures of pain and physical function would be similar for both the experimental and the control groups. We focused on the important clinical outcomes of pain and physical function since our previous review demonstrated a lack of literature addressing biological effects in humans with knee osteoarthritis and patient-perception of disease severity. Therefore, we did not include the search terms we used previously to find trials investigating the effect of ultrasound on cartilage which was of interest for our previous systematic review (Loyola-Sánchez A et al 2010).

The focus on clinically important outcomes in the current review is the same as the focus of the Cochrane review published in 2010 (Rutjes AW, et al 2010). The Cochrane review by Rutjes et al (2010) included the same published articles as those included in our previous review (Loyola-Sánchez A et al 2010). Therefore, we replicated the search strategy published in the Cochrane review to identify those studies published since 2009 that incorporated a study design in which participants were blinded with respect to receiving active or sham ultrasound. We included this search strategy in the appendix as recommended in the PRISMA statement. The current review includes the studies with the best design for determining the effect of ultrasound on self-reported knee OA pain and physical function. Syntheses of these date provide results that agree with and strengthen the confidence in the findings of the previous systematic reviews that included groups who received similar treatments with the exception of ultrasound and two trials that administered sham ultrasound to the control arm (Loyola-Sánchez A et al 2010; Rutjes AW et al 2010). The current review includes the studies designed to answer the question regarding clinical efficacy and confirm the findings of the systematic reviews published in 2010 - which included study designs less suited to answer the clinical question regarding the efficacy of therapeutic ultrasound for reducing pain and increasing physical function. As the current review points out, the quality of the included studies provides limited evidence. Nevertheless, the evidence suggests that ultrasound may be beneficial in the treatment of knee OA and this is interpretation is reflected in the recently published 'OARSI guidelines for the non-surgical management of knee osteoarthritis' published in *Osteoarthritis and Cartilage* journal by McAlindon TE et al (2014) In the text (lines 434 to 437) we say "Nevertheless, our results confirm the findings of previous meta-analyses^[8-10] reporting that therapeutic ultrasound reduces knee OA pain and further research will clarify if there is a beneficial treatment effect with respect to physical function outcomes." Given that we draw conclusions consistent with our previous review (Loyola-Sánchez A et al 2010) and those of others (Rutjes et al 2010; McAlindon TE et al 2014)., we have made no changes to the manuscript.

Reviewer 2's Comment #3. No language limit was placed on the search in the text, but English was limited in the abstract.

Authors' Response: Despite the fact that English language was an *a priori* exclusion criterion for abstract review, no abstracts or titles retrieved were excluded on the basis of language as shown in Figure 1.

Reviewer 2's Comment #4. Cohen's unweighted kappa (κ) was used to interrater reliability in Risk of bias and quality assessment, but the result was linear weighted kappa (κ).

Authors' Response: This is correct. As stated in the methods, we reported Cohen's unweighted kappa (κ , line 157) in the case where the choice was dichotomous - include or exclude, and when judging the risk of bias - yes, unclear, or no, we assessed agreement using the linear weighted kappa (line 198). Reviewers screening the citations judged the articles as being eligible or ineligible for inclusion. In the case of risk of bias assessment, unclear was closer to yes and no than those two categories were to each other. We have also calculated the agreement regarding risk of bias using the unweighted kappa where $\kappa(95\%CI) = 0.73(0.54, 0.91)$. The ratio for agreement and disagreement were 36/42 and 6/42, respectively, prior to correcting for chance agreement. We leave it to the editor's discretion regarding whether we report the linear weighted or linear unweighted kappa statistics for risk of bias agreement for which the judgement fell into one of three categories not equally spaced from each other.

Reviewer 2's Comment #5. Where is the basis for Chi-square values with $p \geq 0.1$ and $I^2 < 60\%$ were considered to be acceptable homogeneity for pooling the data?

Authors' Response: We thank you for pointing out our omission in referencing our source for setting these criteria. We have added reference 16 to the text on line 228. We selected these criterion on the basis of the Cochrane Handbook (most specifically section 9.5.2 Identifying and measuring heterogeneity). These decisions are open to debate. Since the studies in our meta-analysis were few in number and had small samples, the chi-squared test has low power. The Cochrane Handbook states: "while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity. This is also why a P value of 0.10...is sometimes used to determine statistical significance." We followed the Cochrane Handbook recommendation to set the statistical significance for Chi-square values at $p \geq 0.1$. Similarly, we set $I^2 < 60\%$ based on Chapter 9 of the Cochrane Handbook's where the rough guide for interpretation suggests that values less than 40% 'might not be important' and those falling between 40% and 60% "may represent moderate heterogeneity". It is recommended that these two methods be incorporated in the assessment of heterogeneity.

Reviewer 2's Comment #6. What is the basis of random effects model? Why did not put forward fixed effects model?

Authors' Response: As is the case for most Cochrane reviews, we have few studies which prevent reliable investigation of the reasons for heterogeneity across studies. As shown in Table 1, the application sites, protocols for administering ultrasound (duration, mode, number of visits), and concurrent interventions varied across the studies. Therefore, we opted to use a random effects model which allows for heterogeneity based on the assumption that the underlying effects are normally distributed. We have revised the text to better explain the rationale for using the random effects model. Lines 220-224 now read: "We used inverse-variance random-effects models to pool results to account for the inevitable variation in patient populations, concomitant treatments, and specific components of the physical therapy intervention as recommended when the number of studies is small and the reasons for heterogeneity across the studies cannot be reliably evaluated^[16]."

Reviewer 2's Comment #7. Why do you set much stricter inclusion and exclusion criteria? In the result only 5 articles was carried out to meta-analysis.

Authors' Response: We wanted to include only those trials using the study design best suited for answering the clinical question of ultrasound efficacy for improving pain and physical function given that these outcomes are determined most commonly by patient report. In studies where the comparison group did not receive ultrasound, the self-reported pain and physical function may be influenced by expectation bias. The use of sham ultrasound versus active ultrasound results in less variation in terms of treatment exposure. Although it is difficult to know the sources of heterogeneity, the 5 studies included in this review were more homogeneous (and therefore, better suited for pooling) than in our previous review. For example, for the pain outcome homogeneity among the 6 trials included in our 2010 review was $I^2 = 51\%$ and $\text{Chi}^2 = 10.28$ ($p = 0.07$). This compares with $I^2 = 36\%$ and $\text{Chi}^2 = 6.26$ ($p = 0.18$) for the 5 studies pooled in the current review. The heterogeneity dropped from 'moderate' to 'might not be important'. (See response to Reviewer 1's Comment #5 for interpretation of the I^2 value.) In the previously published review, we were unable to reduce the heterogeneity among the studies with respect to the self-reported physical function outcome ($I^2 = 86\%$ and $\text{Chi}^2 = 29.11$ ($p < 0.00001$)) and walking performance ($I^2 = 92\%$ and $\text{Chi}^2 = 52.20$ ($p < 0.00001$)). In the current review, heterogeneity among the studies was 'unlikely to be important' and 'moderate' for self-reported physical function outcome ($I^2 = 0\%$ and $\text{Chi}^2 = 1.92$ ($p = 0.238$)) and walking performance ($I^2 = 64\%$ and $\text{Chi}^2 = 8.37$ ($p = 0.04$)), respectively. We believe this supports our decision to restrict the inclusion/exclusion criteria in order to obtain the best answer to our clinical question regarding the efficacy of ultrasound for knee OA pain and physical function.

Reviewer 2's Comment #8. Confidence interval can be removed in the line 322.

Authors' Response: We have removed the 95% confidence interval for the point estimate of the kappa agreement (0.81) from the text. We thought the readers may want to know that 95% of replicate judgements would yield a kappa value above 0.67 and below 0.96.

Reviewer 2's Comment #9. This sentence that pooling the three studies administering high dose ultrasound versus sham ultrasound yielded an insignificant decrease in pain may be incorrect, as P value was 0.06 in the line 348-351.

Authors' Response: On line 240 we state that "Statistical significance was considered at $p \leq 0.05$." Therefore, we have revised lines 350-351 to read "yielded a statistically insignificant decrease in pain and, although still acceptable, the heterogeneity increased (3 trials, $\text{SMD} = -0.46$ (-0.94, 0.03); $p = 0.06$; $\chi^2 = 4.49$, $P = 0.11$; $I^2 = 55\%$)." The pooled data from the 3 trials (149 participants/OA knees) comparing low dose ultrasound and sham ultrasound revealed a statistically significant benefit of ultrasound ($p = 0.03$). The pooled data from 3 trials (159 participants/OA knees) comparing high dose ultrasound and sham ultrasound revealed a statistically insignificant benefit of ultrasound ($p = 0.06$). The heterogeneity among the latter trials was higher compared to the 3 trials in which low dose and sham ultrasound were administered. The source(s) of the moderate heterogeneity among these trials may factor into these results and further research is required.

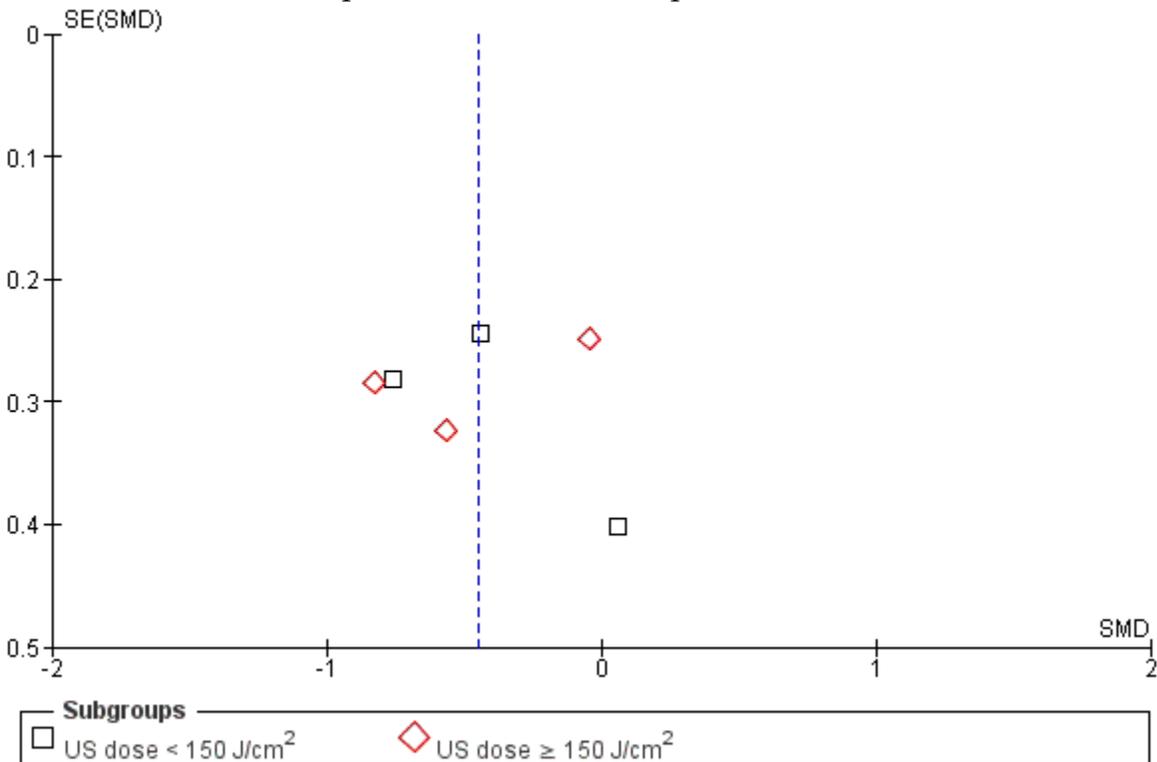
Reviewer 2's Comment #10. The three wire table also has some problems in drawing.

Authors' Response: We have fewer than 10 trials and that precludes conducting statistical analyses to evaluate publication bias according to The Cochrane Collaboration (as described in lines 477-479) therefore the pseudo 95% confidence intervals are not generated. To clarify this, we have revised the figure legend as follows. "Figure 2. Funnel plot illustrating the statistical precision plotted as

a function of the standardized mean difference for the effect of therapeutic ultrasound on patient-reported knee pain. Statistical inferences are not possible when fewer than 10 trials are available; therefore the pseudo 95% confidence limits around the summary treatment effect are not shown."

We can remove Figure 2 if this is preferred or we can show the funnel plot for the trials as a function of therapeutic ultrasound dose. (See alternative figure 2 below.) However, there are still fewer than 10 trials and the pseudo 95% confidence limits are not generated for this figure either.

Alternative Figure 2. Funnel plot for effects on knee pain.



Reviewer 2's Comment #11. The above nine articles to do funnel have practical significance, but only five papers included in the study in figure 2.

Authors' Response: Because the purpose of this systematic review was to determine the efficacy of therapeutic ultrasound versus sham ultrasound on knee OA pain and physical function, we have included only the 5 studies which meet the eligibility criteria for this review.

Reviewer 2's Comment #12. Analysis software better using Stata.

Authors' Response: We understand that meta-regression may be performed using the 'metareg' macro available for the Stata statistical package. We use STATA for a variety of statistical analyses. We used both Review Manager version 5 and Comprehensive Meta Analysis version 2 software packages to conduct this meta-analysis. Both packages yielded the same results but we preferred the graphics generated using The Cochrane Collaboration's Review Manager version 5 software available for download at <http://tech.cochrane.org/revman/download>.

In response to the editor's comments: We have added the COMMENTS section, including 1) Background, 2) Research frontiers, 3) Innovations and breakthroughs, 4) Applications, and 5) Terminology. We anticipate that the editorial team will determine the content to be included in the final section, 6) Peer review.

Thank you for considering our manuscript for publication in the World Journal of Meta-Analysis.

Sincerely,

A handwritten signature in blue ink that reads "Norma MacIntyre".

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