Author's response to reviews

Title: Effect of acustimulation on morning sickness or hyperemesis in pregnancy: a systematic review of Western and Chinese literature.

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Author's response to reviews: see over
Leuven, 2nd Sept 2015

Dear BMC Complementary and Alternative Editorial team,

We would like to submit revision revised version of our manuscript MS: 1320894860174702
Effect of acustimulation on morning sickness or hyperemesis in pregnancy: a systematic review of Western and Chinese literature.

We are very thankful to the reviewers for the thorough analysis of the manuscript allowing us to improve the paper. We have adapted the manuscript taking into account all comments. In the following paragraphs you can find a point-by-point response to each of the concerns of the two reviewers dr. Caroline A Smith and dr. Hyangsook Lee.

Answers to the first reviewer and changes to the format of the paper:

1) Referencing.
Statements have been supported to secondary data supporting the statements made. Suggest the authors need to go back and include primary sources when citing statements to the following.
Line 56 ref 4 is a meta-analysis suggest source study that demonstrates the effect of N&V on qol.
Line 54 ref 3.
Line 57 ref 5
Line 67 ref 8 would the latest Cochrane review be a more appropriate reference?
Line 72 ref 10.
Line 77 ref 5.
Line 178 and 180 ref 14 is not the most appropriate reference to include here.
Please include other appropriate sources

Other comments on references
Line 59 ref 6, line 69 ref 9 why do these statements need a reference?

Answer:
In some cases the references we used were secondary sources, while some primary sources were books which are not readily available for the average reader. However, we did this only if all necessary data were available. We carefully reassessed every reference and concluded that we used the appropriate references.

2) Types of studies
Line 28: The rationale for including trials with at least 20 participants per arm needs to be stated, and why include only normal pregnancy, and how was this defined.

Answer:
Trials (and other study designs) with a low sample size are always very vulnerable for selection bias and should therefore be avoided. The exact cut-point with respect to sample size is, however, arbitrary. For the last 15 years, after carefull study and deliberation, and in agreement with many others, our group has always used 20, which we consider very conservative (one could also use 50). For a short discussion of this issue see chapter 10 in Knottnerus JA & Buntinx F. The evidence of clinical diagnosis 2nd ed. Wiley Blackwell BMJ Books 2009.

Hyperemesis during normal pregnancy was defined as not having nausea and vomiting as a result of pregnancy complications or other diseases not related to the pregnancy (e.g. cholecystitis or appendicitis). These would be a totally different problem, for which a specific treatment may be more or less helpful. See line 131-133.
3) Type of control

Line 181: The distinction between sham and placebo acupuncture is not well supported by appropriate references.

Answer:
We adapted the text line 183-188.
“Sham acupressure involves needling or pressure in a minimal way such as needling real or wrong points or non-points shallowly with minimal stimulation. Critics of sham needling suggest that even minimal needling produces some physiological effects and is not a truly physiologically inert procedure. Placebo acupuncture uses a noninserted needle with a telescopic function or a needle encased in a cartridge so that the patient can not tell whether the needle has been inserted or not. Unlike sham acupuncture, placebo acupuncture offers a presumably almost physiologically inert placebo.”

4) Outcomes

Primary and secondary outcomes are not well stated and defined. Why is the analysis limited to an unspecified primary outcome?

Answer:
In this review, we limited our analyses to the primary outcomes: (cure or improvement of) nausea and vomiting or ketones in case of HG, because they are our main topic of concern, the measure is straightforward, and they were reported in all articles. Primary outcomes were reported as the Rhodes index or Vas score as defined in types of outcome measures, line 195-214.
Secondary outcomes as e.g. rate of food intake, length of inpatient stay, weight gain, inpatient parenteral drug and fluid use, were not included in the study because of a wide variation in outcome measures between different studies. We added this to the manuscript line 194 and 211-214.

5) Statistical analysis

What were the pre-specified sub group analyse?

We added: “Besides the main analyses we performed subgroup analyses per acustimulation technique and per outcome measure (cure and improvement of nausea and vomiting).”

Line 236: What heterogeneity test was performed and how was this interpreted.

Both the bull-eye test (carefully studying the forest plots) and the $I^2$ test were used to test for heterogeneity. An $I^2$ test > 50% was considered to indicate a moderate or high level of heterogeneity (http://www-users.york.ac.uk/~mb55/msc/systrev/week7/het_text.pdf). We added this in line 257-260.

6) Discussion

Line 239: exclusion of data from studies with multiple arms results is a potential bias, please reflect on this in the discussion. The control groups are controlling for different aspects; ie regression to the mean and for specific aspects of the intervention.

Answer:
For an individual study, studies with multiple arms can be a good research strategy. For a meta-analysis it is not appropriate to deal with multiple comparisons, because every patient would be counted multiple times while trying to compare them to each other. This is obviously a bias especially in a meta-analysis, which is something that we always try to avoid.
We reflected on this in the discussion line 441-446.

7) What did you do with the blinded studies with multiple treatment groups, which data was entered?

Answer:
If there were more arms in a study, we used the control group which provided the most optimal degree of blinding. E.g. if one of the control groups was sham acupuncture we have opted to choose this control group for comparison to acupuncture because that was the most blinded one.

8) Results
a) Figure 1 can you please clarify the reasons for exclusion for the 50 trials described as not an inclusion criteria.
b) 6 duplicate studies are they not part of 311 identical citations.
c) 9 studies not included for pooling was this insufficient data or insufficient information or both?

Answer:
a) We excluded the studies of which the inclusion criteria were insufficiently reported. Possible reasons for exclusion were e.g. acupoint injection, less then 20 participants in each arm, cross-over study, acupuncture on top of the use of medication. All studies that not met the inclusion criteria.
b) Six studies were different publications of the same papers.
c) Table 6 shows more detailed information about the reasons for excluding. We adjusted the text in line 368.

9) Please include a summary of studies by country setting.

Answer:
We added the country of each article in table 1. We refer to description of included studies, Line 275-279 and to Fig 1 for the exact numbers of studies in English and in Chinese.

10) Table 2 studies may need cross checking for accuracy.

Answer:
The studies have been cross checked by the people who assessed the risk of bias. We initially did not report this. We added this to the text line 237.

11) Lines 334-340 suggest these definitions are moved to the methods under the outcomes.

Answer:
We do agree this part belongs to the method section. We have moved the sentence from effects of interventions to the methods, types of outcome measures. Line 195-202.

12) Discussion
a) Line 399 suggest this data on sensitivity analysis is reported in results.
b) Line 415 statistical heterogeneity can be reduced by combining trials with different controls, agree, so why do it?
c) Line 440 I think it is worth highlighting other differences between your review and the Cochrane review ie inclusion of Chinese literature and reflecting the strength of this

Answer:
a) We moved the data on sensitivity analyses from the discussion to the results section. See line 398-405.
b) I’m sorry, but we do not understand this question.
c) In our view there are two big differences between the reviews. First we included the Chinese studies, and secondly we opted to choose the last day of the intervention for outcome measurement in contrast with the latest Cochrane review that tried to present findings for a time point approximately three days after the start of treatment, This is mentioned in the discussion in line 415-416 and 476-480.

13) There are some limitations associated with this review would the authors like to reflect on this and include for completeness?

Answer:
The limitations of the study have been extensively discussed in the discussion Line 447-473.

Answers to the second reviewer and changes to the format of the paper:

1) Apart from the high risk of bias and poor reporting in most of Chinese studies, my main concern is that the authors pooled the studies with various control interventions. Effect sizes may change among studies with heterogeneous control interventions and the authors pooled studies comparing, for instance, acupuncture alone with conventional treatment and those testing acupuncture as an adjunct to conventional treatment. Acupuncture or acupressure can be used as an adjunct to conventional treatment or possibly as an alternative. Although I don't think this will reverse the direction of the conclusion a lot, I find that the present approach can be problematic.

Answer:
We appreciate the problem of the reviewer. We have discussed this as a major limitation in the discussion. Line 447-461.

2) Another concern is that there should be interpretation on why there emerged difference between dichotomous and continuous outcomes. Although not perfect, it would be helpful if the authors can provide the explanation on this finding based on current knowledge in statistics and clinical research.

Answer:
We do not have a full explanation for this finding. However, dichotomising continuous variables always results in loss of information.
Dichotomous answers are yes or no, there is nothing in between, while continuous data have all variations, Regression to the mean is also much more nuanced in continuous data.

3) Last essential suggestion is that Tables 1, 3, 4 and 5 should be included in the manuscript, not as supplementary files so that the readers can fully understand this review. If revisions are done, the corresponding tables also should be revised accordingly.

Answer:
The editors require that figures and additional files must be submitted as separate files, not as part of the main manuscript file. We revised the corresponding tables according to the remarks of the reviewers.

4) Based on the WHO standard acupuncture nomenclature, We changed PC6 instead of P6.

Answer:

5) Artemisia vulgaris in italic.

Answer: We have written Artemisia vulgaris, L. in italic.

6) There are some trials where Chinese herbal medicine was used as a control group. I'm not sure whether these controls are valid and acceptable for testing the effectiveness of acupressure or acupuncture.

Answer:
We agree with the statement of the reviewer that it may indeed not be a good control group for testing the effectiveness of acupressure or acupuncture. We performed a sensitivity analysis (line 399-401 and 425) excluding control groups with Chinese herbal medicine. We would leave it to the readers to draw their own conclusions.

We hope the editor and reviewers will agree with our revisions and find the revised manuscript now acceptable for publication.

We look forward to your response.

On behalf of all co-authors,

Sincerely Yours,

Els Van den Heuvel, MD