Peer Review File

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Reviewer A

Well written.

Sound methodology.

The authors would like to appreciate this comment.

Reviewer B

Comment 1: Rows 51-52: potentially efficacious is any treatment before being tested. Has efficiency been proved or not?

Response 1: Thank you for the great suggestion. The study showed improvement in mean spontaneous bowel movements (SBM) however no improvement in mean CSBM (SBM with a sense of complete evacuation). We changed the text to the following as suggested:

Changes in the text: "The systematic review and meta-analysis suggest that VC is safe and efficacious in some outcomes, however, larger RCTs and real-world data are needed to establish this."

(page 4, paragraph 1, lines 1-2).

Comment 2: Rows 61-62: trans-anal irrigation is missing. Add it.

Response 2: Thank you for the great observation. We add trans-anal irrigation to the text to the following:

Changes in the text: "Treatment for constipation is mainly dietary therapy, lifestyle interventions, pharmacological therapy, trans-anal irrigation, and rarely surgery."

(page 5, paragraph 1, line 6-7).

Comment 3: Rows 68-70: hypothesized mechanism of action based on CSBM. However, the reviewed papers failed to demonstrate a significant increase in CSBM, so, either the VC mechanism of action is not the hypothesized or the VC has failed to demonstrate efficacy.

Response 3: Thank you for the excellent comment. Per the comment we modified the text as following:

Changes in the text: “The mechanism is thought to be via mechanical stimulation of the colon wall and augmenting the circadian rhythm of colonic peristaltic activity resulting in an increase of bowel movements.”

(page 5, paragraph 2, line 2-4).

Comment 4: 70-71: multiple studies? and you only review 3? how many studies are there evaluating safety and efficacy in human beings? why your search only retrieve 3 of them? It's been a biased search?

Response 4: Thank you for the good observation. To be grammatically accurate and eliminate any notion of bias, we deleted the word multiple. As we will mention in the upcoming sections only 3 papers passed our inclusion and exclusion criteria. We accordingly changed the text as follows:

Changes in the text: “Recent studies evaluated the efficacy and safety of VC in patients with CIC with variable results.”

(page 5, paragraph 2, line 5).

Comment 5: 71-72: you can't reference here, in the objective of the study, the 3 papers that have resulted from the systematic review, unless your initial aim was to review only the results of these previously known papers with the aim to pool their results to conclude the benefits of VC. It seems a bias.

Response 5: Thank you for the detailed comment. We modified the reference citations in this sentence to eliminate any false sense of bias:

Changes in the text: “We aimed to perform a systematic review and meta-analysis of available studies to assess the impact of VC on patients with CIC.”

(page 5, paragraph 2, line 6-7).

Comment 6: 90-91: CSBM1 and CSBM3 very specific. Why not others, i.e: CSBM2 or CSBM4?

Response 6: Thank you for the good comment. We were not able to measure CSBM 2 as it was reported in only one study (Rao 2023). Neither were we able to report CSBM4 as it was not reported in any studies.

Comment 7: 93-94: subjects with constipation includes constipation causes other than CIC, i.e. NBD or OIC. why do you only search for patients with CIC? Are there other VC studies on patients with other constipation causes? If yes, why do you exclude them? If not, why do you narrowed the search criteria to CIC?

Response 7: Thank you for the great comment. The following was the librarian search criteria (supplementary table 1):

"constipat* OR obstipat* OR defecat* OR dyschezia* OR 'colonic inertia*' OR 'bowel movement*' OR 'bowel function*' OR 'defecation'/syn OR 'constipation'/syn."

Therefore, to be accurate we should change CIC to constipation per your comment. We corrected the text per your suggestion.

Changes in the text:

"All studies addressing the following were selected: (1) Patients: patients with constipation.

(page 7, paragraph 1, line 2-3).

Comment 8: 94-99: why do you used as inclusion criteria the outcomes CSM1 and CSBM3?

Response 8: Thank you for the great observation. Per the methods section, authors manually searched for SBM and CSBM in the articles. Mentioning CSBM 1 or 3 in the manuscript was a typo. We corrected the text per your comment.

Changes in the text: "(2) Outcomes: SBM, CSBM"

(page 7, paragraph 1, line 3).

Comment 9: why do you limited the search to only the placebo/VC? Why not other comparators?

Response 9: Thank you for the excellent comment. In order to pool data in a meta-analysis, we require same groups in multiple studies. VC is a novel modality; therefore, full text RCTs are limited, and thus far placebo is the main control group that is published.

Comment 10: I don't find RCT within the inclusion criteria. Why?

Response 10: Thank you for the good comment. We have mentioned RCT in the inclusion and exclusion criteria of methods in the following sentence. Please see below:

We included only full texts of RCTs assessing efficacy and safety of VC in subjects with constipation.

(page 7, paragraph 1, line 1).

Comment 11: Why do you exclude case series, observational and cohort studies?

Response 11: We appreciate the great comment. Observational studies, case series, and cohort studies are not randomized and have their inherent biases. To improve the quality of this meta-analysis we only chose RCTs.

Comment 12: 121: the age range is surprisingly narrow. Include in the discussion the fact that VC has only shown to be potentially effective increasing SBM in CIC people in their 40's.

Response 12: The authors greatly appreciate the excellent suggestion. We have included the following sentences in the discussion:

This systematic review and meta-analysis showed an improvement in CSBM 3 and mean SBM in adult CIC patients receiving VC compared with placebo.

(page 11, paragraph 1, line 1-2).

Fourth, the age range of studied population is narrow which limits generalizability of the data to patients far from their forties.

(page 13, paragraph 1, line 8-9).

Comment 13: 164-165: you talk about the clinical improvement of VC in first person (we). Why? Are you involved in the clinical studies of VC? Have you discussed the VC exposure threshold theory with the authors of the reviewed 10-12 papers? Which kind of relationship do you have with them or with the VC owners? If any, it should be stated under the disclosure section.

Response 13: The authors greatly appreciate the excellent suggestion. The authors have no relationship, communication, or conflicts of interest to disclose. We have corrected the grammar to mirror that:

Since the most recent study used the same VC type, it is possible that the key to clinical efficacy was the higher exposure protocol of two vibration sessions, an intensity not achieved by prior studies.

(page 11, paragraph 1, line 10).

Response 14: 167-169: is it said in any of the papers that vibration sensation is a trigger for taking rescue medications? If so, add the reference here.

Response 14: The authors appreciate the good comment. Our theory was not mentioned in any of the three papers. We have added to the sentence to emphasize that this is not a proven fact:

This may be due to the subjective nature of opting for rescue medications, for instance vibration sensation being a trigger to do so. Validity of this claim needs to be further studied.

(page 11, paragraph 1, line 19-21).

Comment 15: 170 and 177: Did the studies reviewed include IBS-C patients? Weren't they just CIC? Explain it.

Response 15: The authors appreciate the astute observation of this typo. The patients were CIC and not IBS-C. We have removed IBS and corrected the sentence as follows:

The implications of this finding are in subjective aspect and patient satisfaction with VC.

(page 11, paragraph 1, line 21-22).

Comment 16: 178-188: add the narrow age range as a limitation of the reviewed studies.

Response 16: We appreciate the great comment. We added the narrow range as a limitation in the following sentence:

Fourth, the age range of studied population is narrow which limits generalizability of the data to patients far from their forties.

(page 13, paragraph 1, line 8-9).

Comment 17: 188-191: why do you discuss about possible solutions to overcome the limitations of VC capsule? Do you have any interest in finding a solution?

Response 17: The authors greatly appreciate the good observation. The authors suggestions are in order to encourage and improve further research in the field of treatment of CIC. Authors have no conflicts of interest.

Comment 18: 193: why your search only retrieved 3 papers? Discuss the possible reasons (restrictive inc and exc ctriteria?

Response 18: We appreciate the great comment. Per this comment we have discussed the possible reasons and added the following in the manuscript:

First, only four RCTs were available that assessed the efficacy and safety of VC in CIC patients. This limitation was likely due to novelty of VC, limited availability, and our search criteria limiting the results to high-quality multicenter double blinded RCTs with strong methodologies.

(page 12, paragraph 2, line 1).

Comment 19: 194: CIC patients? What about the IBS you mentioned in the discussion??

Response 19: We appreciate the great comment. We have removed IBS per comment 15 from the discussion and corrected the sentence as follows:

The implications of this finding are in subjective aspect and patient satisfaction with VC.

(page 11, paragraph 1, line 21).

Comment 20: 196-198: The fact that the studies were run in US and China does not demonstrate anything about the mechanisms of action. Maybe it would the heterogenicity of the sample if there was any

heterogenicity (age range too narrow, very restrictive inclusion and exclusion criteria that "homogneneizes" the sample…).

Response 20: We appreciate the excellent suggestion. We have removed the sentence with US and China and replaced it with the following sentence as suggested:

Nevertheless, restrictive inclusion criteria and narrow age range make the study population more homogenous.

(page 13, paragraph 1, line 3).

Comment 21: 198-199 & 205: the title and aim of this review was safety and efficacy, not cost-effectiveness. Change title and aim or delete cost-effectiveness here.

Response 21: We appreciate the great comment. We have deleted cost effectiveness as suggested.

Comment 22: 213: delete NR here, there is no NR in the table

Response 22: We appreciate the good suggestion. We have deleted the NR.

Comment 23: Table 2: it seems as if you make this table before designing the criteria to retrieve these 4 studies (CSBM1 and CSBM3).

Response 23: We appreciate the good comment. Per response 8, we manually searched for SBM and CSBM in the articles and we deleted CSBM 1 and 3 in the inclusion criteria. This should resolve the current issue.

Changes in the text: "(2) Outcomes: SBM, CSBM"

(page 7, paragraph 1, line 3).

Comment 24: Fig1 (40 papers excluded by title/abstract screening + 18 papers excluded because of irrelevant …): what do you mean by irrelevant? Give examples. What did you find or did you find not in title/abstract to exclude the paper? Explain.

Response 24: We appreciate the good comment. There are studies generated by librarian electronic search criteria (supplementary material) that were excluded based on title and abstracts. An example include:

Chey WD, Lembo AJ, Phillips JA, Rosenbaum DP. Efficacy and safety of tenapanor in patients with constipation predominant irritable bowel syndrome: a 12-week, double-blind, placebo-controlled, randomized phase 2b trial. Gastroenterology. 2015 Apr 1;148(4):S191-2.

This example can be excluded as it is investigating tenapanor and there is no mention of VC in the title.

Comment 25: Fig.2.C and D (results CSM3 and SMB): how many patients in total are they in these 2 studies? Detail in the text. Since your conclusion about the effectiveness of VC is based on significant differences in SBM, you should detail the sample size.

Response 25: The authors appreciate the great comment. We have mentioned the sample size of the following studies in the text as suggested. Please see the changes as following:

On closer inspection, two studies with sample sizes of 349 and 106 were noted to show positive results that resulted in statistically significant results when mean SBM and CSBM 3 were compared.

(page 11, paragraph 1, line 4).

Comment 26: PRISMA checklist: it's difficult to locate the different points because the manuscript is not numbered. Please, number the pages, and add the rows in the checklist where the different points are located in the text.

Response 26: The authors appreciate the comment. We have updated the PRISMA checklist and added the rows as instructed.

Comment 27: Yours is not a systematic review but a post-hoc analysis of 4 pooled previous RCT studies. State it like this in the title and all along the paper.

Response 27: The authors appreciate the comment. We used the guidelines in the PRISMA checklist and performed a systematic review. Per our response to comment 4, there was no bias in this systematic search. Please see the following paragraph and the supplementary material from the librarian search protocol.

We used the guidelines in the Preferred Reporting items for Systematic Review and Meta-Analysis (PRISMA). A systematic search of the literature was performed through June 14th, 2023, in databases including Embase (Embase.com, Elsevier), MEDLINE (Ovid), Cochrane Central Register of Controlled Trials (CochraneLibrary.com, Wiley), Web of Science Core Collection (Clarivate), Global Index Medicus (World Health Organization) and Google Scholar via the Publish or Perish software. The author M.A. formulated the initial search that was refined by librarian (W.L-S.).

(page 6, paragraph 1, line 1).