Author's response to reviews

Title: Simultaneous transcutaneous electrical nerve stimulation mitigates simulator sickness symptoms in healthy adults: a crossover study.

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Version: 5 Date: 1 March 2013

Author's response to reviews: see over
February 28, 2013
Editor
BMC Complementary and Alternative Medicine,

Dear editor:

We submitted the manuscript “Simultaneous transcutaneous electrical nerve stimulation mitigates simulator sickness symptoms: a crossover study” for your consideration to be published as an original contribution in BMC Complementary and Alternative Medicine. This study evaluated the effects of an alternative remedy for simulator sickness symptoms developed after flight simulator exposure. Reviewers provided valuable suggestions. We have addressed the reviewers’ comments point by point in a question and answer pattern and revised the manuscript accordingly. A “marked copy” of the manuscript was also provided as supplemental file.

The manuscript is not being considered for publication, in whole or in part, in another journal, book, or government publication with a substantial circulation except in abstract form in connection with scientific meetings. Of all authors, there is no financial or other relationship that might be perceived as leading to a conflict of interest (i.e., affecting author objectivity). The manuscript has been read and approved by all signatories, all authors acknowledge that they have exercised due care in ensuring the integrity of the work.

The study complies with the Declaration of Helsinki, the protocol has been approved by the Institutional Review Board of the hospital, and all patients or their representatives gave a written informed consent. I attest to the fact that all authors listed on the title page have made substantial contributions to all of the following: 1) substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

Yours sincerely,

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The reviewers provided valuable recommendations. The manuscript was revised accordingly. Specifically, the revisions made are listed point-by-point as follows:

Reviewer: 1

Major Compulsory Revisions
Q1. How many subjects are recruited and excluded from the applicant? Please show the flowchart follow the CONSORT (consolidated standards of reporting trials) recommendation.
Ans: We appreciate and concur on the reviewer’s suggestion that the information of the passage of participants pertains to CONSORT flow diagram should be included in the manuscript. The CONSORT Flow diagram is intended to depict the passage of participants through the four phases (i.e., enrolment, intervention allocation, follow-up, and data analysis) of a parallel randomized trial of two groups. Our study adopted a within-group cross-over design in which a single group of participants go through the 4 sessions in a randomized order. For the current study, 20 participants were recruited and screened for eligibility and 18 were found to be eligible and enrolled in the study. All 18 subjects were assigned to each study condition. 3 subjects were not able to finish all sessions due to conflict between working and experimental schedule. The number of participants included in the main analysis was 15. With small sample size and relatively straight ford participants passage information, we decided to present such information in the Result section with text (page 15, line 264-267) rather than with flow chart.

Q2. There is no information about 4 cross-over sessions. There is information for stimulation session only. Please provide information about the 3 other sessions, especially focusing the non-stimulation period conditions (Same place or not, Same stimulator attached or not, Same position or not, etc.). Did the non SS (TENS) group was in the DISO trainer or not? Please clarify it. Did you use mock-TENS or not? As you know, there is high correlation between neck instability with MS. If you did not use mock-TENS, you should think about the tension induced attaching TENS-pad can affect the result, and give limitation on the interpretation of results.
Ans: Thanks for the great advice. We have tried to control for variables between different sessions. Some information was not included the in the original manuscript. The details of test sessions other than stimulation session were added to the manuscript as follows:
Place and position: (page 9, lines 145-148) "All the test sessions were conducted in the DISO trainer in Aviation Physiology Research Laboratory of Gangshan Armed Forces Hospital. In the non-stimulation period conditions (i.e., the Control and TENS
sessions), the participants sat quietly in the DISO trainer without activating the simulator while physiological recordings were made." 

Control for TENS treatment: (page 11, lines 175-177) "In SS session, placebo-TENS was applied in which the TENS electrodes were in place but no stimulation was given."

Q3. How do you think about the correlation of MSSQA and MSSQB in figure 2? If the value (36, 39) is outlier, still you would say there are correlated?

Ans: Thanks for the advice. With original data, the MSSQ-A and MSSQ-B had strong correlation (n=15; r=0.902, p=0.000). When the high leverage and high influential point[i.e., the “outlier”(36.34, 38.02)] is removed from the analysis, the correlation between MSSQ-A and MSSQ-B become fair but still significant (n=14; r=0.706, p=0.005). This information was presented in the inset in Figure 2 and also in figure legend of Table 2 (page 37, line 677-679; also see page 19-20, line 340-343).

Figure 2.

There are possible explanations for the existence of such data set: (1) the existence of significant inter-individual variation of motion sickness susceptibility and (2) small sample size. This is discussed in the Discussion section (page 20, Line 343-345).
Q4. The midline posterior nuchal region is not clear. TENS on the spine has different effect for the autonomic nervous system depending on the location of spinal segment. Please clarify the position and analysis should be consider the location of TENS position of nuchal region.
Ans: The locations of TENS electrodes were added to the methods section: (page 10, line 169-170). "The TENS electrodes were placed at the midline posterior nuchal region (1.5 cm lateral to the seventh cervical vertebra spinous process) and..."
In the discussion section, possible effects of TENS on spinal segment was discussed: (page 19, line 325-328) "Electrical stimulation to nuchal spinal segment had direct effects on central nervous system. For example, electrical stimulation of C2 increases activation of the dorsal cochlear nucleus through the somatosensory pathway. Whether other central mechanisms play a role awaits further study."

Minor essential revisions
Q5. In table 2
The group names, Baseline (Pre-20), Pre-10 min, are not consistent and confusing. I think it will be better to change the names like this; Phase 1(Pre-20 to Pre-10), Phase2(Pre-10 to 0), Phase3(30 to SS15), Phase4 (SS15 to SS30).
Ans: Thanks for this great suggestion. We have revised table 2 and changed group names to Phase 1 (Pre-20 to pre-10 min), Phase 2(Pre-10 min to 0 min), Early Post-test (30 min to SS15 min)and Late Post-test (SS15min to SS30 min). We did not use Phase 3 & Phase 4 as group names in table 2 to avoid confusion with original definition in study design. [please refer to Table 2 at page 39]

Discretionary revisions
Q6. Normally, “treatment” is done after symptoms appeared. In your protocol, you did TENS before symptoms appeared. In this case, you can say simultaneous TENS can mitigate the onset of SS symptoms only. It does not mean TENS treatment can mitigate SS symptoms. In my opinion, the expression should be changed like this “Simultaneous TENS stimulation seems to have preventive effect to the SS symptoms.”
Ans: To prevent the development of SS/MS, treatments are usually given before the onset of MS/SS. We therefore applied TENS prior to the beginning of simulator sessions. We decide not to describe the effect of TENS as “preventive” in the title as TENS treatment only partially alleviated MS symptoms. However, this concept was added to the manuscript. Whether TENS can delay the onset of MS symptoms was not tested in the current study. A time-series study would probably answer this question. The title and content of the manuscript were revised accordingly:
Title: Simultaneous transcutaneous electrical nerve stimulation mitigates simulator sickness symptoms in healthy adults: a crossover study.

Manuscript:

(page 18, line 323) “The preventive effects of TENS might involve……”
(page 22, line 390) “Simultaneous TENS treatment significantly ameliorated SS symptoms, as reflected by……”
(page 25, line 448) “We have identified a countermeasure to prevent the ill effects of SS.”
(page 26, line 463) “Preventive TENS was effective in reducing SS symptoms and alleviating cognitive impairment.”

Q7. Quality of written English: Needs some language corrections before being published.
Ans: The manuscript had been edited by native English speaking professional medical editor (from MedCom Asia, Inc). The certificate was enclosed for reference. [please see attachment document 1]
Reviewer 2

Q1. (Line 96)“……Most pharmacological agents that are recommended for the prevention of MS failed to show responses that were stronger than those of placebos [12]……”. This very strong assertion needs qualifying. There are some quite effective drugs, the main problem is side-effects. See ref Murdin et al for a recent review of effective anti-motion sickness medications. (Murdin L, Golding J, Bronstein A. Managing motion sickness. BMJ (2011) 343: 1213-1217.

Ans: We appreciate for the reviewer’s suggestion. The manuscript had been revised as follows: (page 7, line 97-98) "Although there are some quite effective pharmacological interventions for MS, most of the proven effective drugs have some side effects that may affect training efficiency [12]." The recent review of effective anti-motion sickness medications (by Murdin L, Golding J, Bronstein A. BMJ 2011) had been adopted as reference 12.

Q2. Please correct typo error (in line 504) the Ref 12 in the ref list…..the name of the author is JRR stott.

Ans: We replaced the paper by Stott JRR with more recent reference. Thanks for pointing out the typo.

Q3. (Line 105)-“….Cyclic manual pressure or electrical stimulation to the Neiguan (P6) acupuncture point suppressed MS symptoms of nausea and vomiting…..” Here, at the outset of this paper, it would be useful to mention to the reader of this Journal that some studies concluded these are ineffective, for example your refs 30, 31. Also other studies reported negative findings, here is an example: Miller KE, Muth ER. (2004) Efficacy of acupressure and acustimulation bands for the prevention of motion sickness. Aviat Space Environ Med. 75:227-34.

Ans: We agree with the reviewer that it is helpful for the readers to know that the effects of electrical stimulation to the Neiguan acupuncture point on MS symptoms had been inconsistent in different studies. We have revised the manuscript and included to Miller &Muth study as suggested. Please see page7, line105-109: "Stimulation of Neiguan (P6) acupoint had been evaluated as non-pharmacologic intervention for MS. Although some studies failed to demonstrate significant positive effects [15,16,17], however, cyclic manual pressure or electrical stimulation to the Neiguan (P6) acupuncture point suppressed MS symptoms of nausea and vomiting in a rotating optokinetic drum paradigm [18].".

Q4. (line 163)…”For the TENS and TENS+SS sessions…”
Please give some details as what happened in the Control condition.
Ans: We have added details about the Control session. Please refer to page 10, lines 146-148: In the Control and TENS sessions, the participants sat quietly in the DISO trainer without activating the simulator while physiological recordings were made.

Q5. (line 275) “...subcales, disorientation symptoms were predominant, followed by nausea symptoms...”.
Please give reader some idea of what proportion of subjects experienced actual nausea, by each condition. The scale scores do not give the reader a “feel” for how sick these subjects were. In addition, it would be useful to state if any subjects had to terminate early due to nausea. This could be given in text or added to one of the Tables in Results.
Ans:
The authors appreciate the suggestion by reviewer. We have added the following information to demonstrate the severity of SS in current study:
(1) (page 16, line 282): “Five participants suffered nausea.”
(2) (page 20, line 359-360): “The severity of SS in the current study can be evaluated by total SSQ scores. Scores greater than 20 indicate sufficient discomfort ([39]).”

(page 16, line 274-276) “All participants completed post-intervention measurements”
No participants terminated the study sessions due to nausea or vomiting.

Q6. (Line 307) “...The mechanisms of TENS is unclear. We simultaneously stimulated 2 sites in our TENS protocol with ...”.
This is interesting. It would be worth giving an opinion on why there are such great differences between studies in the effectiveness of TENS or acupuncture against motion sickness. Some studies such as this one find it is effective. By contrast others find this is completely ineffective. The readers of this paper would be interested in possible reasons for such differences between studies, eg, perhaps different stimulation methods, possible placebo or suggestion effects, maybe differences in the particular types of individual who will respond, genetic or racial differences, etc.
Ans: We agree with reviewer’s opinion. The manuscript was revised to address this issue (page 22, line 395-398): "Some other studies failed to demonstrate treatment effects of electrical or acupoint stimulation for MS symptoms. Possible explanations for such disparity include placebo effects, stimulation sites, experimental models, participants characteristics (for example, gender, ethnicity)."

Q7. (Line 333) “...MSSQ-B scores, ~20 [20,21].”
What is the 20? Is this an average value? This could be made clearer.
Ans: MSSQ is a subjective evaluation of propensity to MS according to previous life experience. The MSSQ scores in different groups of people might differ due to ethnicity, gender, socioeconomic status. The calculation of MSSQ subscores and total scores were explained in Method section (page 11, line 182-190). In two of the articles cited in the manuscript, mean MSSQ-A/-B scores varies but were around 20. Golding recruited 227 subjects in his study while 309 subjects participated in Klosterhalfen et al. study. Therefore, MSSQ-A and MSSQ-B scores (approximate 20) reported by Klosterhalfen et al. were comparable to that reported by Golding.

Q8. (Line 339) “…The severity of SS in the current study, as reflected by total SSQ score, was considered significant…”
I realize that these scales are useful, but see my comment above (about line 275) concerning the meaning of these scores for the understanding by an average reader. Does this mean that most subjects had definite nausea?
Ans:
(1) Nausea was not the most complained SS symptom in current study. Of 15 participants, 5 suffered nausea. This is explained in the manuscript (page 16, line 282; also please refer to our response to Q5.
(2) We also demonstrated the SS severity by presenting degree of severity in different reported symptoms (page 16, line 284-285): “In terms of the severity of SS, the most reported symptom severities were “slight,” with only 2 symptoms (eye strain and increased salivation) reported in the “moderate” range.”
(3) We further explained the severity of SS in this study relative to previous reports as follows (page 20, line 360-367): Another method to quantify SS severity is by comparing current data with values from calibration samples where original SSQ was derived [39]. Total SSQ score of 15 would represent 75th percentile point in a database of more than 1,100 SSQs from healthy subjects pooled from ten flight simulators [39]. The total SSQ score (26.4±5.7) in the current study would correspond to about 88th percentile points in the pooled samples. The scores of the disorientation subscale (32.5±7.2; >90th percentile) were the highest among all of the subscales, followed by nausea subscores (19.1±3.7; about 85th percentile) and oculomotor subscores (11.6±2.9; 69th percentile).

Q9. (Line 356) “… with previous reports, HR and sympathetic activity (low-frequency ratio) were evaluated while parasympathetic activity (high-frequency ratio) was suppressed….”
Reports vary as to whether motion sickness produces increased HR or decreased HR,
ie parasympathetic to sympathetic balance changes, etc. Eg see your ref Benson ref 51. Effects can vary even within an individual with an initial sympathetic effect shifting to a more prolonged parasympathetic effect. The nature of motion sickness is also important. If the nature of the stimulus is active and arousing (a stimulator is a good example) perhaps HR increases are more likely. Low frequency motion passively experienced often produces motion sickness with reduced HR. It would be useful to inform the reader that HR is not a consistent correlate of motion sickness.

Ans: The authors appreciate the suggestions from the reviewer that this information is important for readers. We have adjusted the manuscript accordingly. The following paragraph was added to page 22, lines 381-385: "Previous reports revealed conflicting observations about the HR responses to motion sickness. HR increases [46],[47], decreases [48] or not changed with MS [49]. Possible explanations for the discrepancy include individual variation and susceptibility [47], physical characteristics of the stimuli (different MS models; intensity, frequency and duration of motion) [50]."

Q10. Figures: please could it be made clear what the error bars are…..SE? SD? 95% CI?
Ans: The error bars in figure 3 indicate SD. This information is added to the figure legend (page 37, line 683).

PS: The PDF of the following reference is enclosed for your information.
Please see attachment 2.