Author’s response to reviews

Title: Characterizing the Transcutaneous Electrical Recruitment of Lower Leg Afferents in Healthy Adults: Implications for Non-Invasive Treatment of Overactive Bladder

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We thank both Reviewers for their very helpful comments and questions, all of which have helped to improve the clarity of our manuscript. We believe all questions were addressed in our responses to Reviewers and also by our edits to the revised manuscript.

Pankaj Wadhwa, MS, MCh (Reviewer 1): In this feasibility study, the authors investigate transcutaneous electrical activation of multiple neural targets in the lower limb and thus define the tolerable threshold level for simultaneous activation of all the targets. The reported results provide evidence for the same.

However the title of the manuscript is somewhat misleading.

It "suggests" that the study is being done in patients afflicted with OAB, which it clearly is not. I would strongly suggest re-framing the title to match the work elucidated. The rest of the manuscript is reasonably unambiguous with regards to potential use of this variation in TENS of the lower limb to possibly effect bladder -inhibitory reflex mechanisms.

Response:

We thank the Reviewer for the comments and have modified the title to the following:

“Characterizing the Transcutaneous Electrical Recruitment of Lower Leg Afferents in Healthy Adults: Implications for Non-Invasive Treatment of Overactive Bladder”
Sanjay Sinha (Reviewer 2): The authors present an interesting paper on transcutaneous stimulation of nerves in the leg that might be useful for the treatment of OAB.

The strength of this work lies in the methodical progress of the authors toward establishing the technique of transcutaneous nerve stimulation for OAB by studying the responses of normal subjects first. The concept of establishing the intensity of current needed for stimulation of the relevant nerve as a ratio of the maximum tolerable current is elegant and clinically relevant.

However, there are some important issues which need to be resolved:

1. From the methodology it is unclear whether the authors counted recordings from two limbs in one patient as two independent sets of information.

   Response: We agree with the Reviewer that the methodology was not fully explained in the original submission. In this study, we used data from both legs and treated them as independent measures from a single participant. Following each set of 3 stimulation trials for one nerve, we switched to the contralateral leg to test the next nerve target, and alternated until all 4 targets were tested in random order. The main reason for this was to avoid any potential carry-over effects, particularly due to prior electrical stimulation at Tlimit. For example, we wanted to avoid having TN stimulation affect the perceived recruitment of the subsequently tested MPN or LPN targets (and vice-versa). The Methods section (page 4, line 68-71) has been modified to better describe the experimental protocol.

2. What might have been the impact of potentially less stratified skin in the calf compared with that around the ankle and foot where friction with footwear would typically cause a thicker and potentially less sensitive skin? Could this be responsible for the higher Tnerve to Tskin ratio for the Saphenous nerve?

   Response: The Reviewer is absolutely correct in deducing the reason for the high Tnerve/Tskin ratio for the saphenous nerve. As indicated in Table 1, the more calloused skin of the plantar foot surface and ankle indeed yielded higher Tskin values than that for the saphenous nerve. We have added a sentence in the Results section (Page 6, line 115-116) that highlights this point.

3. The above could be resolved by examining the actual data for the stimulations. However, rather than give us the actual data the authors have merely given us graphical summations of the data. This reviewer could not find the actual data set in the manuscript provided by the editorial office.
Response: We apologize for the previous omission and have uploaded Table 1, which summarizes the mean ± SD (range) values of Tskin, Tnerve, and Tlimit obtained from all study participants. Please see our response to point #2 above.

4. For this relatively small number of subjects it should be feasible to provide the actual data sets for each patient. This would be more useful for readers and would enable them to verify the arguments made by the authors and confirm their statistical methodologies.

Response: We agree with the Reviewer on this point and have uploaded an excel copy of our raw data. The declaration has also been changed accordingly (Declaration, Page 10, Line 190-191) and (Addition Files, Page 14, Line 294-296).