Author's response to reviews

Title: The Effect of Long vs. Short Duration of Electroacupuncture on Analgesia and Sensory Thresholds: A randomized study for acupuncture analgesic mechanisms

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Author's response to reviews: see over
Dear Editor,

I thank you and the reviewers for the recent comment in regards to the revised submission. I am delighted that we have addressed most of the concern related to the manuscript. I think that Dr. Zheng’s (reviewer #2) additional comment and suggestion are well considered. This has led to the following response and modifications to the manuscript (italic, bold and underlined):

**Reviewer's report:**
The authors have addressed the comments adequately. I note that the introduction and discussion sections have been revised and additional information has been provided. I accept the authors’ choice of the methods of statistical analysis and data presentation. The aims, the results and discussion are now coherently presented. Overall this study has addressed an important and clinically relevant issue. The finding that EA of long stimulation produced a prolonged and expanded area of analgesia on hot pain is significant and requires further exploration. I agree with the authors’ view that the mechanisms of EA with long stimulation are different from EA of short stimulation.

I am however not entirely satisfied with the hypothesis “a shifting of A-delta mediated C-fibre modulation to a more centrally mediated modulatory mechanisms of thermal pain” and “the shifting from peripheral afferent induced inhibitory mechanisms to a centrally mediated modulatory mechanism was supported by the fact that the duration of the analgesic effect outlasted the de qi sensation of the EA stimulation and observed analgesic effect was in bilateral lower extremities” (page 16 para 1). I do not understand the argument here. Acupuncture analgesia is often centrally mediated but induced by peripheral stimulation, such as needling. I assume that the authors tried to say that A-delta mediated inhibition on C-fibre was via the peripheral neural mechanisms so that the analgesia was localized and short-lasting. I am however not aware of such inhibition at the peripheral site. Did the authors refer to the gate control theory, in which activation of myelinated afferents, in particular, A-beta fibres, inhibits the inputs from C-fibres. If so, then this action is not exactly a peripheral phenomenon. I wonder whether the authors meant to say that A-delta mediated inhibition on C-fibres is a spinal phenomenon, whereas with prolonged EA stimulation, other action centres involving supraspinal mechanisms have been recruited. It is important that the authors clarify this. – Compulsory changes

**Response:** We appreciate the reviewer for pointing out the ambiguity and confusion related to the statement in the discussion section of the manuscript that “the shifting from peripheral afferent induced inhibitory mechanisms to a more centrally mediated modulatory
mechanisms of thermal pain.” This statement was revised to indicate that we primarily referred the “peripheral afferent” to the initial peripheral stimulation effect of EA on pain inhibition.

In addition to the modulatory effect of A-beta afferent fibers as suggested in the Gate Theory, the potential modulatory effect of A-delta afferent activation (as with punctate nature of the stimulation) on C-fiber mediated pain sensation has been documented by several studies as indicated in reference #27-29. We thank the reviewer for pointing out that one of the possible early mechanistic linkages EA and analgesia may occur in the spinal cord because in a previous study with a short burst of unilateral EA stimulation we have observed bilateral dermatomally correlated analgesic effect. Relevant statements in the Discussion and Conclusion sections of the manuscript have been revised based on the reviewer’s suggestion in regards to the corresponding neuronal mechanisms that may mediate short vs. long durations of EA analgesic effect.

On the same page, the sentence starting with “This postulation was supported by ….” is incomplete. – Minor changes

Response: The sentence was completed in relevance to the remaining paragraph.

In the addition, please check the initials of the authors of references 7 – 10. – Minor changes

Response: Formatting error has been corrected in the Reference section of the manuscript.

In addition, I have expanded the background section of the abstract to place the study in the context of the current knowledge.

I hope the above revision has adequately addressed all the concern in regards to the manuscript.

I thank you and the reviewers for the consideration.

Sincerely,

Albert Leung, MD