

Response to Review Comments

We would like to thank the reviewers for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We are pleased to resubmit for publication the revised version of manuscript #33245 “Stem Cell Therapy for Nerve Injury.” We have addressed each of their concerns as outlined below. (the reviewer’s comments are in *italics*, also in the revised manuscript we add new paragraphs in **Red** and highlighted existing paragraphs by turning them into **Green**).

Response to Reviewer # 00397384 Comments

Comment 1: The author made a good review on the implication of three types of mesenchymal stem cells in neural injury repair. However, there are plenty of grammar errors. For example, although...but.... A language editing service should be sought.

Response: Thank you, the paper is checked again to improve its grammatical errors.

Response to Reviewer # 02446025 Comments

Comment 1: Describe the PNIs and all therapeutic options.

Response: We have divided the introduction into smaller sections with headings and as suggested, a paragraph describing the PNIs was added and the existing paragraph describing the therapeutic options was also entitled as: “Therapeutic Strategies”. As we mentioned in the revised manuscript that we are focusing mainly on the transection injuries, we described the main strategies targeting this type of PNI.

Comment 2: List what challenges and problems of all therapeutic options.

Response: We made it clear in the revised manuscript that this paper concerns the transection injuries, and we described the complications of gold standard therapeutic strategy. We also described advantages and disadvantages of other kinds of interventions such as using different sources of stem cells.

Comment 3: Concisely introduce stem cells and focus what are mesenchymal stem cells.

Response: The correction has been made.

Comment 4: *Why can mesenchymal stem cells can improve PNIs.*

Response: Just like it is stated in the text, the main reason by which MSCs can improve PNIs is their ability to transform into Schwann cell like cells and produce tropic and trophic factors. We also stated the fact that they can affect the native Schwann cells activity.

Comment 5: *It's good to describe 3 types of MSCs to treat PNIs, but need to have points, such as mechanism, research or clinical benefit, potential problems, instead of compiling all references.*

Response: We think, as we mentioned before, the potential mechanism and the advantages/disadvantages are stated in different sections of the paper.

Comment 6: *Need to give your opinion on potential of MSCs to treat PNIs and future directions to readers.*

Response: The correction has been made.

Response to Reviewer # 02445329 Comments

Comment 1: *The authors have evaluated the MSC tx in PNI in this MN. This MN is well written and designed. In addition, it would be better that the authors mention about MSC may also be one of new therapeutic option for neurodegenerative disease. (for example; Neurological Research, 2016 Apr;38(4):364-72.)*

Response: Authors are grateful to the reviewer for his positive and encouraging comment. As this paper is addressing the beneficial effects of stem cells on peripheral nerve regeneration, this (regardless of how amazing the results are), we think, could be a little irrelevant to talk about neurodegenerative diseases.

Response to Review Comments

We would like to thank you again for the careful reading of this manuscript. We have addressed each of comments and provided you with further information on author's initials and headings/sub-headings orders.

Response to Comments

Comments: Ref 112 repeat with ref 111; ref 41 repeat with ref 27, please correct them. Thank you. Please mark the location of ref 113 in the text also. Thank you.

Response: All corrections have been made.

Further Information

-Author's Initials

Please notice that "Sayad" is not the middle name of the first author. Two words "Sayad Fathi" together make the last name of the first author. We have corrected it in the revised manuscript we have sent. Just to be sure, here are the examples:

"Sayad Fathi S *et al.* Stem cell therapy for nerve injury"

"Sayad Fathi S, Zaminy A. Stem cell therapy for nerve injury."

-Formatting of Headings and Subheadings

Please make sure that headings and subheadings are going to be written in order. We have corrected it in the revised manuscript we have sent. Just to be sure, here is the example:

1. INTRODUCTION

- a. What is PNI?
- b. What happens in cellular and molecular level?
- c. Therapeutic strategies
- d. Use of stem cells
- e. Mesenchymal stem cells

2. SURGICAL TECHNIQUES

3. THE IMPORTANT ROLE OF NEUROTROPHIC FACTORS

4. SCs IN NERVE REGENERATION

5. STEM CELLS USED IN PNIs

- a. Bone marrow mesenchymal stem cells
- b. Adipose-derived mesenchymal stem cells
- c. Umbilical cord mesenchymal stem cells

6. CONCLUSION