Peer Review File

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Reviewer A:

Comment 1: English editing is necessary.

Reply 1: We have done proof reading and tried our best to revise the grammartic mistakes and inappropriate descriptions in our article. All the changes in the manuscript have been marked by a red color.

Comment 2. The Tables need to be extensively re-edited, which should include font size, punctuation marks etc. But most importantly, more information, more clinical trials and their details should be included. So that the tables can become comprehensive and useful.

Reply 2: We have re-edited our tables extensively according to your valuable suggestions. More detailed information including cell dosage, delivery route and follow-up as well as outcomes are added in the manuscript which could make the tables more comprehensive and useful (see table 1 and table 2).

Comment 3: Probably the major problem is, in general, the manuscript did not provide a comprehensive and clear review of this topic.

Reply 3: We feel very sorry for the deficiency in our paper. To make our topic much comprehensive and clear, we reviewed a lot of the related literatures and re-write the manuscript extensively. We hope that the revised version could provide useful information about stem cell therapy for ischemic brain injury and all the changes have been marked by a red color.

Comment 4: The conclusion described in the perspective that, “Although the majority of pre-clinical and clinical trials about stem cells treatment for ischemic brain injury are

safe and effective….", are likely not a solid description and may be misleading at this moment.

Reply 4: We are sorry for the inappropriate description. We have re-written the sentence and the changes have been marked by a red color in the manuscript (see Page 10, line 1-3).

Comment 5: The abstract lacks a concise and precise conclusion about the current status of the stem cell therapy for ischemic brain.

Reply 5: We have re-written the abstract to make it much more concise and precise (Please see Page 2, line 2-10).

Comment 6. Figure 1 is not informative. The authors aimed to list the stem cell types for transplantation and the mechanisms of therapeutic actions. However, from this figure 1, we still do not understand which stem cell type use which mechanism(s).

Reply 6: We have re-drawn the figure 1 and we think the new figure is much clear and informative.

Minor

Comment 7. The title of table 2 is "finished clinical trial…". Actually, these studies have gone through only phase I or II and thus not finished. This is especially true since many trials have "no results published". This table also do not provide information about the current status of these unfinished clinical trials, which are very important.

Reply 7: Thanks for your valuable suggestions. We have re-edited our table 2. The title of table 2 have been changed into "Main clinical trials that have finished or currently being carried out". More detailed information including cell dosage, delivery route and follow-up as well as outcome measures are added in the paper which could make the table more comprehensive and useful.

Comment 8: The discussion about the therapeutic effects of stem cells in the context are not consistent with those listed in table 1, such as ESCs and iPSCs. For example, at

P5, the conclusion is ESCs/iPSCs can restore ischemic encephalopathy, but this is not supported by the description about ESCs/iPSCs effects in table 1.

Reply 8: We are sorry for the inconsistent results in our context. We have already changed the description in table 1.

Comment 9. P11: the authors listed the timing of transplantation published in literature for different kinds of stem cells. However, no brief description about the results were provided which make this paragraph, surely very important for the readers, not at all informative.

Reply 9: We are sorry for our uninformative description. Instead of re-writing, we have deleted this paragraph. Because the timing of cell transplantation varies greatly, and the optimal transplanted timing for different cell types has not been determined.

Reviewer B:

This study entitled “Stem Cell Therapy for Ischemic Brain Injury” intends to review studies that used different types of stem cells to treat ischemic brain injury and summarized the preclinical and clinical trials about stem cell therapy for ischemic brain injury.

The topic of this review is interesting, and the authors have done excellent works on data collection and perspectives statement. However, I have following concerns which need to be addressed before it can be published on ATM Journal.

Minor comments:

The language and grammar should be rechecked because of a number of errors. If the authors’ native language is not English, I strongly suggest the authors have their manuscript reviewed for clarity by colleagues or someone whose native language is English.

Reply to minor comments: We have done proof reading and tried our best to revise the grammartic mistakes and inappropriate descriptions in our article.

Major comments:

Comment 1. The authors need to review the biology of neural stem cells which are mentioned in this paper at the beginning and if they can, draw a schematic diagram to illustrate the generation and differentiation path of “ESCs/iPSC to NSC” on Fig1.

Reply 1: Thanks for your valuable suggestion. We described the biology of neural stem cells in detail in our paper (see Page 5, line 1-12). Besides, we have re-drawn the figure 1 in another informative way. While we are very sorry that we don’t add the illustration of the generation and differentiation path of “ESCs/iPSC to NSC” on figure 1 due to the integrity and concise of our new figure.

Comment 2. Although the majority of pre-clinical and clinical trials about stem cell treatment for ischemic brain injury are safe and effective. However, I think the authors need to dig more information about the limitations and potential adverse effects on stem cell therapy, such as tumor formation, and immune responses in cell transplantation therapy.

Reply 2: Thanks for your valuable suggestion. We have added more description about the limitations and potential adverse effects on stem cell therapy in the first section. Almost each cell source has its pros and cons for transplantation, and we discussed these limitations at the end of each part (see Page 3-6).

Reviewer C:

Comment 1: Ji et al presented an interesting review from the point of the stem cell angle in stroke. The paper could be further advanced by providing more details. For example, " Researchers considered the therapeutic effects of MSCs relying on cytokines secretion, immunoregulation, and promotion of endogenous NSCs proliferation ". The author should clearly show what cytokines, how to immune-regulate, mechanism, and signaling of promotion cell proliferation. Lots of statements were presented in such a broad way which significantly compromised the readibility and limited the useful information. All such statements must be represented in a detailed manner.

Reply 1: We have added the detailed description about the therapeutic mechanisms in our context. All the changes are marked by the red color in the manuscript (see Page 7, line 27-32; Page 8, line 9-14, line 17-22; Page 9, line 5-12).

Comment 2: In addition, lots of references were lost/lacking throughout the manuscript, such as " The low cell dosage is not beneficial for cell survival, while high cell dosage may oppress the intracranial tissue."
Reply 2: We have added the relevant references in the corresponding description.

Comment 3: For figure 1, the author should also include a form to indicate the details, such as the summary of detailed factors, cytokines et al.
Reply 3: Thanks for your valuable suggestion. We have re-drawn and added the detailed anti-inflammatory and trophic factors in figure 1.

Comment 4: The mechanism of Stem Cell in different studies should also be summarized in one form and presented in a graph in detail, but not be presented broadly like the right part of Figure 1.
Reply 4: Thanks for your valuable suggestion. We have re-drawn figure 1 and summarized the therapeutic mechanisms and effect in a much clear and precise manner.

Comment 5: For table 2, the exact size of each clinical trials should be provided.
Reply 5: We have added the exact size (number of patients exact recruited) of each clinical trial in table 2.

Comment 6: In table 1, the stroke should be clearly noted "ischemic stroke"
Reply 6: We have added the “ischemic stroke” in the title of table 2.