

17.02.2021

Dear Editor,

World Journal of Experimental Medicine

Thank you very much for reviewers' comments regarding our invited submission (Manuscript ID: 61885: Phase I Study on the Safety and Preliminary Efficacy of Allogeneic Mesenchymal Stem Cells in Hypoxic- Ischemic Encephalopathy). We therefore revised our paper related to reviewers' comments.

We hope that the impact and quality of the manuscript has been improved to merit publication in the World Journal of Experimental Medicine after the modifications and revisions made to the manuscript . We look forward to your reply.

Best regards.

Sincerely yours,

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Reviewer 1. 05410953 Conclusion: Accept (General priority)

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Authors present a new multiple route administration of MSC for HIE. The results in term of safety are good as well preliminary efficacy but with a short population (8 cases).

Authors present the manuscript as open label phase I study with the approval from the Turkish Ministry of Health. I Can not find the registration number and name of trial registry.

We thank the reviewer's comment. This study was performed with approval of Turkish Ministry of Health, General Directorate of Health Services, Department of Organ/Tissue Transplantation and Dialysis Services, and the Scientific Committee (Registry Number 56733164-203-E.2569). Therefore, this study has no any other registration to clinical trials database.

Reviewer 2. 03656580 Conclusion: Minor revision

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Cell therapies, particularly WJ-MSCs, have been paving the way for novel treatment protocols for preventing ischemic brain damage. However, (1) Clinical use of stem cell therapy remains conflicted and the root of its efficacy needs to be clarified ;

We thank the reviewer' s comment. In the manuscript, we already pointed that the optimal route of MSC administration still remains a question of significance in the introduction part.

(2) Several variables need to be elucidated, such as the mediators between cells, the optimal type and time of therapy, and the ideal patient characteristics :

We thank the reviewer' s comment. In the discussion section, we already defined that the findings are possibly influenced by other variables, such as growth factors and anti-inflammatory elements, perhaps even exosomes. Our aim in this open label Phase 1 study was to the safety and preliminary efficacy of WJ-MSC administrations in HIE patients for optimal type, optimal time of the therapy, and the ideal patient characteristics.

(3) Multi-center studies with larger populations are needed to verify the safety and efficacy outcomes obtained here, along with an optimization for the treatment protocol in question.

We thank the reviewer's comment. It is also clear that to need multicenter studies to confirm the safety and efficiency of stem cell treatment. We already pointed that future multi-center studies with larger populations are needed to verify the safety and efficacy outcomes obtained here, along with an optimization for the treatment protocol in question in the conclusion section.