Dear Editor,

Thank you for carefully reviewing our manuscript previously titled "**Effects of Exosomes from Mesenchymal Stem Cells on Functional Recovery of Total Radial Nerve Injury: A Pilot Study**" for possible publication in the ''World Journal of Stem Cells''. We are grateful to you and your reviewers for their constructive critique. We have revised the manuscript, highlighting our revisions in yellow. And have attached point-by-point responses detailing how we have revised the manuscript in response to the reviewers' comments below. Now we hope the revised paper will provide a more readable description on the study.

Thank you for your consideration and further review of our manuscript. Please do not hesitate to contact us with any further questions or recommendations.

Yours Sincerely,

Reviewer Comments

Reviewer 1:

1. Various types of cells can secrete exosomes, and exosomes derived from different cell sources may have different effects and mechanisms of action. In this study, the authors chose to experiment with exosomes derived from MSCs. The authors should explain why they selected exosomes derived from MSCs for their experiments and discuss the potential outcomes if exosomes from other cell sources were used.

Response: Thank you very much for the good comment. As an example, it can be expected that using exosome of Schwann cell origin in this study will give better results. To do this, it was necessary to obtain a peripheral nerve graft from the patient and produce Schwann cell-derived exosome. But, this is not an experimental study,

actually this is first clinical pilot study in the literature. There are articles in the literature indicating that mesenchymal stem cell-derived exosomes have the same effect. We have already touched on this issue In the 18 th paragraph of the discussion section. (*To improve nerve regeneration, patient-specific SC exosomes may be employed. However, to obtain SCs, a healthy nerve must be sacrificed. Evidence suggests that miRNA-containing exosomes from differentiated MSCs can either directly improve axonal regeneration or indirectly stimulate recovery by regulating the inflammation response to promote nerve repair*[46].)

2. Please provide the characterization and identification data of the exosomes in the article.

Response: Thank you very much for the good comment. We have revised the material and methods section of the manuscript, and we added much more detail regarding to characterization and identification of exosomes. We did not find it necessary to include numerical values of the data as it would unnecessarily lengthen the manuscript.

3. In the article, the authors mentioned that "1 ml MSC-derived exosome (containing 5 billion microvesicles) was divided into four equal amounts (0.25 ml) and applied microsurgically to both sides of the proximal and distal stumps by subepineural route." The basis for the amount of exosomes used in the experiment is not explicitly stated in the information provided. It is possible that the specific dosage was determined based on previous studies or preliminary experiments, where this particular amount of exosomes has shown desired effects or optimal results in promoting nerve regeneration. However, without further information, we cannot make a definitive conclusion regarding the exact reasoning behind the chosen dosage.

Response: First of all, thank you very much for touching on an important point. When we look at the literature, although there is a dose adjustment of 1 million cells per kg in clinical stem cell applications - unfortunately, there is still no consensus on the dose and method of administration of stem cells - In exosome applications, there are a small number of clinical studies in the literature with a dose of 5 billion microvesicles (ex: *Journal of Gastroenterology and Hepatology 38 (2023) 539–547*). Of course, randomized, controlled, double-blind clinical studies are needed to determine the effective dose to make definitive conclusion.

4. Extracellular vesicles contain a variety of substances, including proteins, nucleic acids, and small molecules. The composition of the vesicle membrane itself also varies. The author should describe or propose possible mechanisms for this. More references about the mechanism of exosomes should be cited, “Exosomes as mediators of intercellular crosstalk in metabolism”, “Exosomes Regulate the Epithelial-Mesenchymal Transition in Cancer”, for example, or any other similar references.

Response: Thank you very much for the good comment. We have revised the article in this respect and added to 16 th paragraph of the discussion section. We also cited the article that you mentioned in the manuscript.

Reviewer 2:

The pilot study authors show that a sural nerve graft and a mesenchymal stem

cell-derived exosome can be used to treat a left radial nerve injury caused by a sharp cut with very good results. The patient's nerve injury recovered almost perfectly in terms of both motor and sensory functions. The results speak for themselves. The pictures, figures, and tables are adequate. Although the authors of the article indicate three videos in the article, only one, the first video, has been uploaded. The two other videos should be replaced before the article is accepted. I suggest a minor revision.

Response: Thank you very much for the good comment. In fact, we tried to upload all three videos when the manuscript was first uploaded to the system, but the system did not allow it. That's why we sent email containing the remaining two videos directly to the editorial office. We will try to upload the videos again or contact the editorial office again.

Science editor: (also Reviewer 1)

Response: Thank you very much for the good comment. We revised the entire manuscript, taking into account the points you mentioned. (same as the answers given to the 1st reviewer comments)

Company editor-in-chief:

1. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

Response: Thank you very much for the good comment. We have revised the whole

manuscript with the assistance from a native English speaker. We also uploaded the certificate to the system.

2.Uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

Response: Thank you very much for the good comment. We checked all the pictures in the manuscript. Because all the images in the manuscript are original, we added copyright information to the bottom right-hand side of the picture in PowerPoint (PPT) as *Copyright ©The Author(s) 2023.*