

April, 2022

Name of journal: *World Journal of Stem Cells (WJSC)*

Manuscript NO: 75819

Manuscript Type: MINIREVIEWS

Title: The role of stem cells-based in facial nerve reanimation: a meta-analysis of histological and neurophysiological outcomes.

Dear Editor of WJSC,

On behalf of the other authors and myself, I would like to extend my gratitude for the efforts and time spent reviewing our submission. The Reviewer makes excellent points and offer valuable suggestions to improve the manuscript. **Please find the responses in bold font under each of the comments made by the reviewer below, which can also be found in red font in the revised manuscript:**

**Reviewer #1 (number ID: 03448879)**

*Specific Comments to Authors: The manuscript focuses on the histological and neurophysiological outcomes of stem-cell based therapy in facial nerve reanimation. It is a thorough review of current studies on an interesting topic, although the lack of analysis on functional outcome is a drawback. Analytical methods are valid. Limitations are summarized and stated. Questions raised: 1. "Three studies included in the final analysis" in Figure 1 is inconsistent with the first paragraph of Results. 2. Authors should provide high resolution images.*

**Many thanks for the comments. The Reviewer raises a good point regarding the lack of analysis on functional outcomes, which has been reported in the last sentence of the Limitations section. We hope our paper can promote this type of assessment in future studies in this field to fill the missing gaps. The typing error in Figure 1 has been modified to read "5" instead of "3" as correctly pointed out by the Reviewer. High resolution images have been uploaded.**

**Reviewer #2 (number ID: 05532596)**

*Specific Comments to Authors: First i would like to compliment the authors, for the time and effort put on to the manuscript. Overall, the manuscript uses adequate statistics, has proper language and manage to communicate the purpose of the manuscript clearly. I recommend this article for publication.*

**We are grateful for the positive comments and compliments provided by the Reviewer.**

**Reviewer #3 (number ID: 02728252)**

*Specific Comments to Authors: 1. In the back ground section, the paragraph "A current frontier in facial nerve reanimation are potentially represented by stem cells (SC). 1. The role of SC in facilitating and accelerating nerve fibers spreading throughout grafts, ameliorating the myelinization, and reducing fibrotic degeneration have been recently reported in animal models" has been repeated at the end of the introduction section, please rephrase.*

**The sentence in the Background section has been rephrased to avoid repetition as follows:**

**"Treatments involving stem cell (SC) usage represent novel and potentially interesting alternatives in facial nerve reanimation. Current literature includes the use of SC in animal model studies to promote graft survival by enhancing nerve fiber growth, spreading, myelinization, in addition to limiting fibrotic degeneration after surgery."**

*2. In the abstract, please refer the abbreviation of CAMP to compound muscle action potential.*

**The abbreviation in the Abstract section has been replaced to read "compound muscle action potential".**

3. In the search strategy section, could you please change the statement "first round of review round" to the first review round?

**The sentence in the search strategy section has been changed, as suggested, to "first review round".**

4. In the result section what did you mean by "studies and patients selected".

**For better clarification, the subtitle in the Results section has been changed to: "Studies included in the analysis".**

5. In the Myelin thickness ( $\mu\text{m}$ ) section, could you please correct this sentence "meta-analysis analysis".

**The typing error has been modified to: "meta-analysis".**

#### **Reviewer #4 (number ID: 03372482)**

*Specific Comments to Authors: this study Aims To investigate the histological, neurophysiological, and functional outcomes in facial reanimation using SC, compared to autograft. Methods: This study is a systematic review of the literature, consistently conducted according to the PRISMA statement guidelines. The review question was: In facial nerve reanimation on rats, has the use of stem cells revealed as effective when compared to autograft, in terms of histological, neurophysiological, and functional outcomes? Random-effect meta-analysis was conducted on histological and neurophysiological data from the included comparative studies. Results: After screening 148 manuscript, five papers were included in our study. 43 subjects were included in the SC group, while 40 in the autograft group. The meta-analysis showed no significant differences between the two groups in terms of myelin thickness [CI -0.10 (-0.20, 0.00); I<sup>2</sup> = 29%; p = 0.06], nerve fibers diameter [CI 0.72 (-0.93, 3.36); I<sup>2</sup> = 72%; p = 0.6], CMAP amplitude [CI 1.59 (0.59, 3.77); I<sup>2</sup> = 89%; p = 0.15] and latency [CI 0.66 (-1.01, 2.32); I<sup>2</sup> = 67%; p = 0.44]. The mean axonal diameter was higher in the autograft group [CI 0.94 (0.60, 1.27); I<sup>2</sup> = 0%; p = <0.001]. Conclusion: the meta-analysis of studies comparing the use of autograft and stem cells for facial nerve reanimation in rats suggests that there appear to be no advantages in favor of stem cells, according to the evaluated histological and neurophysiological outcomes. A higher heterogeneity amongst the included studies, short follow-up periods, and the limitations of our investigation should be carefully considered for a proper data interpretation. Stem cell treatments have proven to be an interesting and viable option in many fields of surgery that have vast supporting scientific and clinically applicable literature. The role of stem cells in facial reanimation is still relatively new and poorly studied due to the limiting nature and number of studies carried out only in animal models. Future studies based on longer follow-up with homogenous criteria, preferably on human subjects, can pave the way to stem cell therapy in patients with nerve palsy. In General: it's a good paper and the subject of the manuscript is applicable and useful. Title: the title properly explain the purpose and objective of the article Abstract: abstract contains an appropriate summary for the article, language used in the abstract is easy to read and understand, there are no suggestions for improvement. Introduction: authors do provide adequate background on the topic and reason for this article and describe what the authors hoped to achieve. Results: the results are presented clearly, the authors provide accurate research results, there is sufficient evidence for each result. Conclusion: in general: Good and the research provides sample data for the authors to make their conclusion. Grammar: Need Some revision. (Check The Paper Comments). Finally, this was an appealing article, in its current state it adds much new insightful information to the field. Therefore, I accept that paper to be published in your journal*

**Many thanks for the detailed summary and comments regarding our study. Grammar and minor errors have been corrected throughout.**

#### **Science editor:**

*This is a good overview and the themes of the manuscript are applicable and useful. But lack of analysis of functional outcomes of stem cell therapy.*

**The Science Editor makes a good point here. As mentioned in the comments for Reviewer #1, the lack of analysis on functional outcomes is a problem with regards to the current literature in this field. This issue has been reported in the last sentence of the Limitations section. We hope this point can promote future studies based also on functional data.**

#### **Company editor-in-chief:**

*I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: <https://www.referencecitationanalysis.com/>. 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) 2022.*

**We extend our gratitude to the Company editor-in-chief. The figures have been formatted according to the journal guidelines. The phrase regarding the copyright information has been added the figures in the PowerPoint file, as requested.**

**The valuable comments and assistance with our paper is greatly appreciated. We look forward to your final decision regarding our modifications, with hopes that all concerns have been addressed in an appropriate manner.**

**Kind regards,**

**Luca Ricciardi, Marco Zeppieri, and the other coauthors.**