

JOURNAL EDITORIAL BOARD'S REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 89203

Title: Effects of exosomes from mesenchymal stem cells on functional recovery of a patient with total radial nerve injury: A pilot study

Journal Editor-in-Chief/Associate Editor/Editorial Board Member: Shengwen Calvin Li

Country/Territory: United States

Editorial Director: Jia-Ping Yan

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	language polishing	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Major revision

JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

Comment: The revision did not sufficiently address the reviewers' comments, specifically regarding the product characteristics they put on the patient. Neither did they discuss the lack of controls, as it was a single-person clinical trial. Nor did they provide any quality control of their stem cell products, as any stem cell products could be either detrimental or beneficial; the balance should be weighed in on any medical procedure. Thus, they must re-address the reviewers' comments and the following specifics for clarity. EIC Specific comments: The title should be indicated as one patient, not controlled. The conclusion below is written like an introductory section, which is inappropriate for professional readers. A concise one-sentence summarizing the current study is preferred. "CONCLUSION The last century has significantly enhanced our comprehension of peripheral nerve pathology, while advancements in microsurgical techniques have contributed to improved outcomes in the repair of peripheral nerves. PNIs give rise to a complex cascade of processes within the

neuronal cell body and in adjacent cells. The phenomenon of nerve regeneration encompasses several biological processes, including the involvement of trophic factors, angiogenesis, stem cells, and inflammation. Enhanced comprehension of the neurobiological ramifications of PNI and the experimental and therapeutic approaches delineated in our investigation may potentially catalyze the forthcoming clinical progress. The integration of pharmacological and molecular treatment with innovative surgical procedures will be imperative in various clinical scenarios. The fundamental principles of surgical care continue to be centered around the processes of exploration, assessment, and nerve repair pertaining to the initial nerve injury. However, there is a growing trend towards the utilization of cell therapies and central reeducation in cases where primary nerve restoration was previously considered necessary, leading to an increase in their application. Potential future investigations might include the integration of exosomes sourced from stem cells, MSCs, or macrophages with nerve conduit technology or their direct injection into nerve stumps. This approach could potentially obviate the need for live cell transplantation. Moreover, it is possible to modify preexisting cells in order to enhance their ability to induce neuron regeneration by upregulating a specific miRNA within their exosomes. These multifactorial approaches have intriguing prospects for the treatment of PNI." "ARTICLE HIGHLIGHTS" should cover only the new findings in their study, not including "Research background, Research motivation, Research objectives, Research methods, Research results, Research conclusions, Research perspectives" - all those statements are duplicated. Page 29: "The nerve exhibited indications of nerve re-innervation as evidenced by control electromyography (EMG) at the 10th wk post-injury, and a significant electrophysiological enhancement was observed in the EMG conducted at the 6th-mo follow-up, indicating ongoing regeneration." How did they know nerve re-innervation morphologically? Page 25: "Multiple studies have demonstrated the efficacy of MSCs in enhancing the process of peripheral nerve regeneration. Nevertheless, some notable limitations, including as immunogenicity, retention, and neoplasticity, have also been documented in the literature[46]. Exosomes, which are a form of acellular treatment, has a reduced immunogenicity that allows them to alleviate the limitations associated with MSC transplantation while maintaining their biological functionality. Hence, exosomes has the potential to be utilized in the development of groundbreaking therapeutic interventions for the restoration and regeneration of peripheral nerves." The discussion did not tie into their data, but circumstantially drawing not related references. ". Safety evaluation of exosomes derived from human umbilical cord mesenchymal stromal cell" was not tightly associated with their studies, only remotely speculative. Pages 18-19: "The PNS possesses the ability to restore and regenerate by nature. PNIs elicit a substantial cellular and molecular reaction that involves not only the damaged neurons but also the supporting SCs. Antidromic electrical activity, which initiates kinase cascades and activates calcium channels, is the initial signal received by the neuronal cell body following axonal injury. This results in a substantial response in both protein and gene expression; the equilibrium of protein and gene expression determines whether the neuron survives and attempts to regenerate or undergoes apoptotic death. The degeneration of the axon and myelin in

the distal stump occurs within a very short timeframe, typically within a few hours. Subsequently, macrophages gather at the site of injury, playing a crucial role in the clearance of cellular debris. During the initial 24-h period, SCs undergo proliferation and transition from a myelinating state to a regenerative one. This transformation is accompanied by an increase in the expression of several molecules that play a role in both the degenerative and regenerative processes occurring simultaneously[33]. Following the clearance of debris by SCs and macrophages, SCs initiate the formation of Büngner bands, which create a trophic-rich environment that facilitates directed axonal regeneration. Similarly, the target organ that has been denervated experiences a depletion of trophic factors, resulting in the atrophy of muscle fibers and the death of satellite cells." These statements were not integrated into their data but pointed to a lack of control experiments in their study. So, they must point out the weakness of their study. Thus, as stated above, those 3 video clips were not supported by any alternative controls to show natural healing. Page 16: "Ten weeks subsequent to the injury, he demonstrated active wrist extension with a muscle strength rating of 3/5 (Video core tip). Electrodiagnostic testing revealed that although the extension of the finger and hand had commenced, rehabilitation and reinnervation were still in the early stages, characterized by severe axonal injury. During sensory evaluation, it was noted that the senses of contact and pain had been restored without any 14-excessive reactions. During the control examination conducted six months postoperatively, the strength of the muscles involved in extending the wrist, fingers, and thumb was assessed to be +4-5/5 (Video core tip). Additionally, the patient's sensory examination exhibited a near-complete improvement." The data did not show A) with a muscle strength rating of 3/5 (Video core tip) - How did they measure muscle strength? B) How did they measure "characterized by severe axonal injury?" C) "the senses of contact and pain" - As a single patient, they could not exclude the natural healing process." D) "electromyography (EMG)" Page 17: "Each assessment was conducted bilaterally on the upper limb." Table 1 Classification of sensory recovery according to the Mackinnon-Dellon scale. Table 2 The British Medical Research Council scale. Both tables show the scales: Where are their data? "Motor recovery grading following the recovery of radial nerve for a proximal forearm radial nerve lesion, extensor carpi radialis longus and brevis are the proximal muscles, and the extensor communis and extensor pollicis longus are the distal muscles." Are there scales specific to the patient in comparison to pre- and post-treatment? Page 16: "In order to facilitate neovascularization in the adjacent tissues, a minute quantity of exosomes administered via ubepineural route was permitted to traverse into the surrounding tissue." How did they assess "facilitate neovascularization in the adjacent tissues" - no adverse effects loci? Page 14: "Subsequently, the clarified supernatant underwent ultracentrifugation at a force of 100000 times the acceleration due to gravity for a duration of 70 min in order to achieve the concentration of exosomes." "at a force of 100000 times" by what ultracentrifuge? Page 13: "The WJ-MSC cells" - the source and nature of WJ-MSC? QC parameters? The data sets? Page 14: "A method where the isolated exosomes were tagged with well-established tetraspanin markers (CD81, CD9, and CD63)." Where are their data? Page 14: "Subsequently, flow cytometry was utilized to study these labeled exosomes." Where were



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their data? Page 14: ", the morphology and size of isolated exosomes were evaluated via transmission electron microscopy." Where were their data? Page 14: "Dynamic light scattering was also used to determine the size distribution of MSC-derived exosomes." How did they do that? By what device instrumentation? What was the profiling of their products besides protein concentrations? Any functional assays for their products? In the manuscript's current version, enhancing the clarity of figure titles and legend descriptions is essential. Figure titles should convey comprehensive information independently, ensuring readers can grasp their content without referring to the text. For each figure, it's advisable to provide a clear, overarching title followed by a detailed interpretation of the panel contents. Regrettably, the existing figure legends do not consistently adhere to this guideline. The same problems surfaced in those tables.