Author’s response to reviews

Title: Magnetic Resonance Tracking of Transplanted Autologous Bone Marrow-Derived Mesenchymal Stem Cell in Chronic Spinal Cord Injury at Upper Cervical Level: Case Report

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Author’s response to reviews:

Dear Journal of Medical case report,

The authors would like to thank you for reviewing our paper titled “Magnetic Resonance Tracking of Transplanted Autologous Bone Marrow-Derived Mesenchymal Stem Cell in Chronic Spinal Cord Injury at Upper Cervical Level: Case Report”. We have looked through each comment and to the best of our ability addressed these issues in our manuscript. We feel that this revision has significantly improved the paper. Again, thank you for taking the time and effort to evaluate our submission.

Reviewer#1

- In my opinion, you should focus the paper entirely on the use of SPIO as tracker of the stem cell migration in a human being. It does not make sense discussing the feasibility and secondary effects as you could not split up those referred to the stem cells and those related with the labelling particles. What it can be concluded is just the fact the patient did not significantly change the previous clinical state. You can not raise any conclusion regarding the feasibility; you would need a larger sample.

Thank you very much for reviewing our paper, we appreciate your comments. We agree with your suggestion that this paper should not discussing about feasibility and secondary effects. This version manuscript was revised to focus on SPIO tracking. We also agree that the conclusion should not have the feasibility from single patient study.
The introduction and discussion should then be shifted to the use of SPIO and significantly less to the stem cells, there are other papers reporting on samples of injected patients but not with labelled cells.

Again, we revised this version in both introduction and discussion to focus on tracking with SPIO as your suggestion.

- Why is important tracking the stem cells from a clinical point of view? It seems to me it is important from a research point of view. Clinically, if the intrathecal injection is successful, you might not need tracking the cells.

We think the stem cell tracking is very important for clinical use in our point of view especially early state of clinical translation. It is important to confirm the effectiveness of each stem cell transplantation technique. The clinical response of patient is various from many uncontrollable factors. We believe the benefit of tracking stem cell with MRI will be closely related to its ability to identify sites of transplanted stem cells which could help us to evaluate the correlation of clinical outcomes and stem cell treatment accurately.

- One of the main problems of the paper is that histological confirmation is lacking. Therefore, we cannot definitely assume that we are seeing the labeled stem cells at the cervical spinal cord. That is not clear in my opinion

We agree that the stem cell tracking with serial MRI is indirectly observation of SPIO signal at the injured spinal cord; however, we could not confirm histology from ethical issue. Nevertheless, we think that our result showed some important data in human that labeled stem cell could reach the injured cervical spinal cord even the chronic spinal cord patient.

- Even if we accepted that the low signal focus is related to the labeled stem cells, again we cannot assume they grafted. The low signal is on the cord surface, not within. Moreover, more than “fading” at two weeks, it is not clear you are visualizing that low signal anymore after the second day. So, I don’t feel the paper could be focused on “migration” and “grafting”. Discussion should be focused on the problems of imaging with labeled stem cells, why labeled cells could fade, what the problems of visualization.

We have changed discussion from your excellent point; the discussion focused more on tracking and imaging as your suggestion.

- There are statements in the introduction and discussion that need references' support

Thank you for point out this important issue. We added more references in the sentences that we thought they need reference to support.
Reviewer#2

- First the authors should clearly state what is really new in this manuscript

Thank you very much for reviewing our paper. This study was an attempt to track BMCSs from intrathecal transplantation in a chronic cervical spinal cord injury patient by SPIONS labeling. To the best of our knowledge, this is the first clinical human study to show positive evidence of tracking stem cell migration from intrathecal transplantation at lumbar region to cervical region in chronic spinal cord injury.

- Second, it would be worth to add a table with previously published papers using the same method of spinal stem cell transplantation.

Thank you for your suggestion. The same tracking method has not been done in human before. There is one paper, Callera et al. study, focused on tracking in intrathecal stem cell transplantation; however, they use extracellular labeling with magnetic beads.

- Third, in such a setting molecular Imaging is essential. At least the authors should mention this method in the discussion and cite the corner-stone articles (Methods Mol Biol. 2013;1052:195-201// Stem Cell Rev. 2012 Dec;8(4):1265-6)

Thank you for pointing out our oversight on this issue. We added more detailed about molecular imaging and newer technique for tracking cells in discussion as your excellent suggestion.

Reviewer#3

Thank you very much for reviewing our paper.

Thank you again to all the reviewers for reading our study.