April 26, 2022

Manuscript NO: 75827

Title: How mesenchymal stem cells co-transplantation in hematopoietic stem cells can improve the engraftment in animal models

Editors-in-Chief: Lian-Sheng Ma
The World Journal of Stem Cells

Dear Editor

We would like to thank the reviewers for their careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve considerably the quality of this manuscript.

We are sending the revised version of the manuscript entitled***: How mesenchymal stem cells co-transplantation in hematopoietic stem cells can improve the engraftment in animal models***, Manuscript NO: 75827, with point-by-point corrections (see below) suggested by you and the reviewers.

Thank you again for your time and consideration. We hope the paper is now suitable for publication in *The World Journal of Stem Cells.* We are looking forward to hearing your decision.

Sincerely,
Lionel Gamarra and collaborators

Reviewer #1 (code: 05684808)

1) *Please add the results of ongoing clinical trials in the prospective section;*

Answer: Thank you for your suggestion. We added one paragraph about the prospective in clinical trials[1] in the end of the discussion section of this manuscript.

References

1. **Liu Z**, Wu X, Wang S, Xia L, Xiao H, Li Y, Li H, Zhang Y, Xu D, Nie D, Lai Y, Wu B, Lin D, Du X, Jiang Z, Gao Y, Gu X, Xiao Y. Co-transplantation of mesenchymal stem cells makes haploidentical HSCT a potential comparable therapy with matched sibling donor HSCT for patients with severe aplastic anemia. *Ther Adv Hematol* **2020**, *11*, 2040620720965411-2040620720965411, doi:10.1177/2040620720965411.

2) *Please included the limitation of this study.*

Answer: Thank you for your suggestion. We improved the limitations description of this study in the end of the discussion section of this manuscript.

Reviewer #2 (code: 02524651)

The manuscript "How mesenchymal stem cells co-transplantation in hematopoietic stem cells can improve the engraftment in animal models" analyzes the hematopoietic and mesenchymal stem cells characteristics and the several interactions through the co-transplantation in murine models. A total of 18 original studies have been included. The chimerism, hematopoietic reconstitution, survival, homing and cellularity were evaluated. An improvement was concluded in the graft when HSC and MSC were administered concurrently. This review is designed well and provides valuable information for co-transplantation of HSC and MSC.

1) *In discussion, the authors mentioned that "After searching original articles published between January 2011 and December 2021……The majority of the papers were produced by Asian researchers and published between 2013 and 2016". Why did the trend of the related papers publication decrease in the period of 2016-2021?*

Answer: Thank you for your observation and dedication to this review. In this more recent period, there has been a significant increase in evidence on this topic focusing primarily on models of hematological diseases, particularly GVHD, and using clinical trials, which suggests that the therapeutic translation from the bench to the bedside is taking place. That's why our study extended the time interval to 10 years. This information was added in the discussion section of the manuscript.

2) *The authors mentioned "The recent study by Huang and collaborators was inconsistent with previous reports showing that UCB HSC are a source effective for HSC compared with other sources." Please give explanation on the "inconsistent".*

Answer: Thank you for your comment. We would want to point out that the term inconsistent was misused, as the right message would be inconclusive as to the best source of HSC for co-transplantation with MSC.

3) *Please compare more information on the routes of IV versus IB.*

Answer: Thank you for your suggestion. We improved of the information about the route comparison in the discussion section of the manuscript.

4) *Regarding the limitation of this review, the authors mentioned "the mechanisms by which MSC perform their roles have not been explained clearly in the studies included in this review". I think more mechanism information is necessary to enrich this review.*

Answer: Thank you for your suggestion. Only some studies reported more specifically the MSC mechanisms to enhance the HSC graft, and this information was added in the manuscript in the discussion section and also in the paragraph about the study limitations.

Reviewer #3 (code: 04861666)

The bone marrow transplantation is a standard procedure for the treatment of hematopoietic and non-hematopoietic diseases but still has several difficulties and obstacles in the failure of treatment. Keeping it in the mind, in the current review Garrigós et have systemically reviewed the preclinical studies of MSCs and HCS co-transplantation and demonstrated several aspects of the MSCs and HSCs transplantation process and showed the molecular and/or structural synergism aspects of co-transplantation which result in complete successful engraftment. Finally they have concluded that these preclinical findings validate the MSCs potential to enable HSCs engraftment in vivo in both xenogeneic and allogeneic HSCs animal models in the absence of toxicity. Approaches used by author is nice, presentation of the experimental outline is very clear. In my opinion it is nice screening of the works for the supporting the co-transplantation of MSCs along with HSCs for it better efficacy. As for the language of the manuscript is concern it is not easy to understand. Authors should use simple language to make manuscript more clear to the reader. I think it will be beneficial to the reader of World Journal of Stem cells and should be accepted for publication after minor language corrections.

Answer: Thank you for your observation and dedication to this review. We reviewed the manuscript and send it to a professional English language to polish the text, turning it into clearer and more understandable.

Reviewer # 4 (code: 02446101)

The manuscript was designed to analyze the hematopoietic and mesenchymal stem cells characteristics and the several interactions through the co-transplantation in murine models. This is a very hot research area and there are a lot of research reports in recent years. It is clear that the authors had done a great deal of careful analysis of the researches in this field. Unfortunately, these analyses mostly confirm that there're still a lot of contradictory and ill-founded speculations on this topic. It is difficult to draw any meaningful conclusions from these studies. In addition, the authors focused the simply descriptions the studies and there's few necessary summaries and suggestions in this manuscirpt. To sum up, this manuscript cannot provide meaningful ideas for readers.

Answer: Thank you for your comment and consideration. We agree that lacked appoint some conclusions from the results found in our systematic, and after reviewing the manuscript, we improve the discussion section of the manuscript to try to highlight some important aspects that contributed to improving even more in the HSC graft with the co-transplantation, as also some MSC functions that influenced in the hematopoietic recovery in the co-transplantation. Furthermore, we added similar findings in clinical trials and the perspective future for this approach. So, the manuscript review allowed improving the message about the trend in the characteristics of HSC and MSC cells used in co-transplantations to achieve the HSC engraftment enhancement.

Reviewer # 5 (code: 05935626)

I would like to congratulate the authors for this manuscript. The study is interesting. I have some comments about the manuscript: In the abstract and introduction, the authors should clearly present the reason of conducting this study. The importance of this study, and what differs this study with previously done studies.

1) *The research question of this review is missing.*

Answer: Thank you for your suggestion and observation. We added the research question in the introduction section of the manuscript.

2) *Please add the clinical PICO question to be answered.*

Answer: Thank you for your suggestion and observation. We added the PICO description in materials and methods section of the manuscript.

3) *Systematic Review articles summarize the recent and comprehensive published material on a particular subject, without bias. To avoid the susceptibility of bias, what did the authors do? please clarify. To assure the study won't give misleading results, do you use a tool or bias table? If so please clarify. Please explain briefly how do you determine the evidence level and state which guideline. In the discussion, please address the most important potential source of bias on your methodology and study limitations.*

Answer: Thank you for your observation. We highlighted and improved the description about bias in the materials and methods and discussion sections of the manuscript, addressing the most important potential sources of bias in both methodology and study limitations.

4) *Please give recommendation for future studies.*

Answer: Thank you for your suggestion. We added the perspectives future of this approach at the end of the discussion section of the manuscript.

5) *Please provide biostatistics review certificate from external / independent biomedical statistician.*

Answer: Thank you for your observation, however our systematic review did not perform a conventional statistics analysis, only the percentual distribution of data and besides that, the group has a huge experience in statistics analysis.

Science editor:

The manuscript summarizes comprehensively that most studies can visualize the improvement of homing when hematopoietic stem cells and mesenchymal stem cells are administered together. Interesting study with accurate methodology. Nevertheless, there are a number points that may deserve some revisions.

1. The format of the table should be a three line table.

Answer: Thank you for your observation. We fixed the table format for the "three-line table" and added it to the end of the manuscript.

2. The authors can add some mechanisms by which MSC plays a therapeutic role.

Answer: Thank you for your suggestion. We improved the MSC mechanism described in the introduction section of the manuscript and added the MSC mechanism evaluated in some of the selected studies include in this review in the discussion sections of the manuscript.