Journal of Clinical and Translational Research
Peer review process file 08.202202.006

Human stem cells prevent flap necrosis in preclinical animal models: A systematic review

Francisco R. Avila, Ricardo A. Torres-Guzman, María T. Huayllani, Gunel Guliyeva, Abba C. Zubair, Alfredo Quiñones-Hinojosa, Antonio J. Forte, Rachel Sarabia-Estrada

Corresponding author
Antonio J. Forte
Mayo Clinic Florida, 4500 San Pablo Rd, Jacksonville, FL 32224

Handling editor:
Michal Heger
Department of Pharmaceutics, Utrecht University, the Netherlands
Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

Review timeline:

Received: December 7, 2021
Editorial decision: January 7, 2022
Revision received: February 6, 2022
Editorial decision: February 10, 2022
Published online: March 1, 2022

1st Editorial decision
07-Jan-2022

Ref.: Ms. No. JCTRes-D-21-00196
Human Stem Cells Prevent Flap Necrosis in Preclinical Animal Models: A Systematic Review
Journal of Clinical and Translational Research

Dear Dr Forte,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Feb 06, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Thanks for your submission.
We have been searching for a solution of flap necrosis for decades. Stem cells definitely brings hope. Regarding this topic, a few key questions could be since the versatility of stem cells is known, what's the specific mechanism of stem cells prevent flap necrosis? What's the quantitative relation between the volume/ concentration/ patients' age of the ADSC and the flap necrosis it can prevent? Will the conclusion changes according to flap category, area, thickness, location, length-width ratio, surgical technique, single flap or multiple flap in a subject or the ADSCs donation area?
From a different point of view, why only the articles tested human ADSCs used on animal models included? Are those articles only have human ADSCs involved? It's hard to distinguish the interference factors across species, even only the nude mouse/rat/rabbit were used. However, it's not clear in this article. It's better to have articles investigated homologous ADSCs on those animal models included at the same time. I believe there must be some articles reported both human and animal resourced ADSCs in one study.
The outcome evaluation criteria were not clear. It also lacks quality assessment of enrolled studies.

Authors' response

Numbered lines were added to the document to assist the reviewer with tracking our modifications. The modifications are in red in the revised manuscript.

Reviewer #1: Thanks for your submission.

We have been searching for a solution of flap necrosis for decades. Stem cells definitely brings hope. Regarding this topic, a few key questions could be:

1. Since the versatility of stem cells is known, what's the specific mechanism of stem cells prevent flap necrosis?

Thank you for your comment. We briefly describe the most likely mechanism of action of ADSCs to prevent flap necrosis, which is secretion of proangiogenic factors (e.g., VEGF) to enhance neovascularization, in lines 45 – 49 and lines 197 – 199. Also, throughout section 4 of the systematic review, we highlight that the conclusions observed in other studies should be corroborated in more rigorous studies.

2. What's the quantitative relation between the volume/ concentration/ patients' age of the ADSC and the flap necrosis it can prevent?

This is a fantastic question in which we are very interested. However, the heterogeneity of cells administered, dilutions, vehicles, and patient's characteristics preclude a proper analysis of

these variables. Additionally, only three studies (Gao et al, Gong et al, and Feng et al) provide information on the patients from which cells were obtained. We believe that these variables cannot be analyzed until more studies using a standardized technique and cell number are developed.

3. Will the conclusion changes according to flap category, area, thickness, location, length-width ratio, surgical technique, single flap or multiple flap in a subject or the ADSCs donation area?

Thank you for this observation, we agree that the results can definitely be influenced by those variables. We added one line in section 6 of the systematic review (Limitations, lines 294 – 295) stating that these data is mostly obtained from studies using McFarlane flaps and should therefore be interpreted with caution, since this may pose a substantial risk of bias.

4. From a different point of view, why only the articles tested human ADSCs used on animal models included? Are those articles only have human ADSCs involved? It's hard to distinguish the interference factors across species, even only the nude mouse/rat/rabbit were used. However, it's not clear in this article. It's better to have articles investigated homologous ADSCs on those animal models included at the same time. I believe there must be some articles reported both human and animal resourced ADSCs in one study.

The article focuses on the use of adipose-derived stem cells of human origin in preclinical animal models because we believe that the study of these cells should increase. Furthermore, most of the studies included only used cells of human origin. When planning the study, we also wanted to include the immunologic reaction towards the xenogeneic cells. However, we realized that this is seldom studied. We expressed this concern in Sections 4 and 6. Additionally, lines 213 – 226 were added to section 4 to highlight that three studies did measure the immunologic reaction in different ways. We also reviewed the studies using autologous ADSCs in animal models and performed a simple statistical analysis to see if cells of human origin were as good as cells of animal origin in these preclinical animal models (Section 3.5 from lines 146 – 159, Figure 4 line 157). We went over our included studies again and confirmed that only one study used autologous stromal vascular fraction (SVF) (Toyserkani et al). However, they did not compare the results of this groups with those obtained from groups using human stem cells.

5. The outcome evaluation criteria were not clear. It also lacks quality assessment of enrolled studies.

Thank you for your comments. The primary endpoint was rephrased to increased readability in line 85 and lines 87 – 88. Assessment of enrolled studies is detailed in Figures 2 and 3, as stated in lines 97 – 101.

2nd Editorial decision
10-Feb-2022

Ref.: Ms. No. JCTRes-D-21-00196R1
Human Stem Cells Prevent Flap Necrosis in Preclinical Animal Models: A Systematic Review
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: