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Systemic anti-inflammatory effects of mesenchymal stem cells in burn: A systematic review of animal studies

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Ref.: Ms. No. JCTRes-D-22-00021
Systemic Anti-inflammatory Effects of Mesenchymal Stem Cells in Burn: A Systematic Review of Animal Studies.
Journal of Clinical and Translational Research

Dear Dr Eldaly,

Reviewers have now commented on your paper, yielding a full spectrum of recommendations: 1 reviewer recommended to accept, one recommended a minor revision, two a major revision, and one a reject and resubmit. The editorial board has weighed all the commentary and decided to give you a chance to revise your draft accordingly, paying extra attention to reviewer 3 who recommended a reject. 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 and attached to this decision letter.

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 May 20, 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: Overall, this is a clear, concise, and well-written manuscript. The manuscript is relevant and
is practically based. Sufficient information about the previous study findings is presented for readers to follow the present study rationale. This is a very excellent a systematic review you have done here.

Reviewer #2: 1、Improve the quality of citations and make them more representative
2、A more reasonable explanation should be given for the contradictions of IL-10 ,suggested to increase the discussion about heterogeneity
3、Literature demonstrating elevated IL-10 should be strongly representative
二、Suggestions for the modification of details in the article:
1、On page 6
METHODS
1）Study Selection and Data Collection Process
① Please indicate whether the two researchers had different views in determining inclusion
2、On page 8
RESULTS
1）Description of the Intervention
Increase the dosing cycle or medication interval

3、On page 16
1) Therefore, the exosomes should have mediated their effect
① post-translational (i.e., after the protein was produced). ②"after the protein was produced"
① post-translational or post-transcription?
②after or before?
2)On the other hand, the serum levels of IL-6 and CINC-1 were significantly higher in the MSC-treated animals on post-burn day 30 ($P<0.05$ and 0.02, respectively).
Please add references

Reviewer #3: Systemic Anti-inflammatory Effects of Mesenchymal Stem Cells in Burn: A Systematic Review of Animal Studies

General comments:
Authors conducted a systematic literature review to evaluate the efficacy of Mesenchymal Stem Cells (MSCs) in modulating burn-induced systemic inflammation and organ damage in animal models. Two authors independently surveyed the published citations in four major databases (PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Scopus, and Web of Science) according to specified selection criteria. Out of 2353 initial search results, 40 underwent full-text reading and only 8 were included in this review.
In general, the review is well written and appropriately organized sections. While the inclusion and exclusion criteria are clearly identified, the review lacks consistency in actually following these criteria for selection of papers they reviewed. Further, certain points affect its overall importance and quality. While some of these points were acknowledged by the authors, they still pose limitation and compromise the quality of the review.
Major Comments:
1. The number of included studies is low compared to the broad aspect of this study "the systemic anti-inflammatory effect of MSCs in burn". This may be attributed to the selection criteria set by authors (specially the full text availability) and/or the database searched. As a result, no sound conclusion could be driven out of this review. More papers should be added to this review. Searching another search engine might be helpful.
2. Systemic inflammation or inflammation should be a keyword to search for as well

3. Moreover, the wide heterogeneity among these few included studies regarding;
a) Type of MSCs (Human BMMSCs X1 paper, Hu UCMSCs X 2 papers, Hu UCMSCs exosomes X 2, Mouse BMMSCs X 1, Mouse UCMSCs X 1 and Rat UCMSCs X1) and
b) Route of administration (IV X 5, IM X 1, SC X 1 and ID X 1)
c) Animal model (rat X6 and Mice X 2)
d) Cell dosage (ranging from 5x105 to 2x106)
Such heterogeneity further divides the studies into groups for sound comparison and weakens any driven conclusion which may explain the seemingly contradicting results of these studies as pointed out by the authors. It would be helpful if authors can add extra papers to this review. Nevertheless, authors could also address these concerns in their discussion. The authors need to clearly identify how each of these variables (type of MSC, route of administration and cell dose) affect the outcome, i.e systemic anti-inflammatory effects of MSCs. Which route is better, which dose is more effective, are there any differences due to the chosen model (mouse or rat), which MSC source is more efficacious in its anti-inflammatory effects.
4. It worth mentioning that only 3 out of the 8 selected studies have reported their sample size. Absence of sample size reporting affects any meaningful differences and statistical relevance. Authors must address this when reporting the findings.
5. While the authors conducted analysis of risk of bias in the selected papers, interestingly, all the included studies showed high risk of selection and performance bias which again pose many questions about the selection criteria of these papers.
6. Due to the aforementioned limitations, authors primarily describe the findings without performing statistical or meta-analysis (descriptive report).
7. It's also noteworthy that all the included studies are from rodents. As an expected result for the primary selection criteria set by authors. However, it would be anticipated to include other animal models (i.e. pig) for more sound results. Authors should have at least discussed it in their discussion part.
8. A concluding section is required that discusses clinical trials on systemic administration of MSCs. This is required to demonstrate whether animal models appropriately reflect the

clinical relevance of this therapy.
9. Authors did not discuss or comment on how TBSA affects systemic inflammation in the reviewed studies. Three out of the 8 papers (almost 50%) did report the TBSA. Such an important parameter in burn treatment should be discussed adequately.
10. The authors discuss MSCs and MSC-exosome in the same context and do not differentiate between the two modes of this therapy; cellular vs acellular or cell-derived. The authors need to discuss the efficacy of these therapies in the paper reviewed? Are they different in their outcomes? Which one is better or worse?
Figures and tables:
* It is difficult to understand why the toll-like receptor pathway was chosen for the graphical abstract. This needs to be justified.
* Table 1; Reporting the outcome variable was confusing and repetitive in some parts. Though summarized in table 1, however, authors chose to arrange papers chronologically which is not justified by the authors let alone it's confusing to jump from one outcome with different variables (cell source, number and animal model) to another set of variables with different outcome. Authors should either justify their choice of chronological order or try another order to make closely related papers in sequence.
* Figure 1; it's mentioned that after a 1st round of selection authors had 40 articles left. On each, they performed a full length reading review and excluded another 32. However, it's confusing why they did not exclude these 32 articles from the first round since all reported reasons are (being reviews, conference papers or editorials) already fall in their Inclusion/Exclusion criteria as mentioned in Methods.
* Figure 2 and table 2; both are representing same information. One of which could be removed for more clarity. Figure 2 especially is confusing as (+) and (-) marks were not explained in figure 2 legend as signs of bias presence or absence. Only by comparing table 2 and figure 2 reader can understand that (High) bias in table 2 is represented as (-) in figure 2. Figure 2 legend should be modified to with appropriate description.
* Figure 4; the UC MSCs effect is produced by MSCs exosomes as mentioned in page 6. However, in figure 4 and in figure 4 legends there is no mention for exosomes which might be misleading. Figure 4 and figure legend should be modified accordingly.
* Figure 5; fig. 5 is an illustration of the results published in paper (Yagi et al. 2010) as reviewed by authors. The figure is adequately illustrated and explained.

Reviewer #4: Comments and suggestions
1. Preface: There are too little details about the concept, characteristics, mechanism of SIRS and how the SIRS occurs in the process of burns. It is also recommended to discuss this part in the discussion section.
2. Results section: authors summarize the research conclusions of the 8 experiments, the structure is not clear, the segmentation is unreasonable, and all the experimental conclusions are not summarized;
3. Discussion section: There are too many details about the experimental research. You can consider putting it in the results section. Some paragraphs are unclear, for example:
① It is recommended to discuss the prognosis of burn-induced SIRS and prognostic factors together;
② The immune regulation and anti-inflammatory effects of MSCs are suggested to be discussed together;
③ Burn-induced liver, kidney, and lung injury are recommended to be discussed together

with blood-brain barrier damage, and the role of MSCs and exosomes in reducing organ damage is recommended to be discussed together;
4. This paper deals with the therapeutic effects of exosomes secreted by MSCs on SIRS and organ damage after burns, but it does not systematically introduce exosomes before the preface or paragraph, but only when citing a literature. A brief introduction to the concept of exosomes is given. Its characteristics, advantages, and connection with MSCs are not mentioned, and it is suggested to supplement.

Reviewer #5: - Interesting systematic review of MSC effects on burns
- Authors are transparent in the potential biases and limitations
- Did the authors account for possible variations that can affect derived conclusions if there is heterogeneity in the types of MSCs, source etc.?
- although 2 separate tables/figures dedicated to comparing the various biases in the included studies, very little discussed within the manuscript

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors' response

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Jacksonville, 20 April 2022

Re: Ms. No. JCTRes-D-22-00021

Dear Dr. Heger,

Thank you for giving us an opportunity to resubmit a revised version of our manuscript entitled "Systemic Anti-inflammatory Effects of Mesenchymal Stem Cells in Burn: A Systematic Review of Animal Studies."

We have addressed all comments of the reviewer using the track changes function in Word. Moreover, every modification or rebuttal of the reviewer's comments is detailed per comment below in red italics. Regarding reviewer #3 comments which we were asked to pay special attention to, we have invested a lot of time and effort to address all the comment appropriately. We are grateful for the useful comments of the reviewer, as a result of which the paper has been considerably improved.

On behalf of the authors, kindest regards,

Abdullah S. Eldaly, MD.

REVIEWER'S COMMENTS

Reviewer #1

Overall, this is a clear, concise, and well-written manuscript. The manuscript is relevant and is practically based. Sufficient information about the previous study findings is presented for readers to follow the present study rationale. This is a very excellent a systematic review you have done here.

We would like to thank the reviewer fo this comment. We are glad and humbled by the reviewer's comment and we hope this review will be useful for both physicians and scientists.

Reviewer #2

1. Improve the quality of citations and make them more representative
   We thank the reviewer for this important comment. We have revised all our references to ensure their quality and remove any low quality papers.All the references used are from peer-reviewed PubMed indexed journals. We have also expanded our references to strenghten our point of view.We have also changed the reference style to the JCTRES style.
2. A more reasonable explanation should be given for the contradictions of IL-10 ,suggested to increase the discussion about heterogeneity
   We thank the reviewer for this essential comment. Only one study showed lower levels of IL-10 in the treated animals. We have mentioned two possible explanations for this phenomenon. We have conducted an extensive search in literature to find a more convencing explanation about this variability in IL-10 between studies. In one study investigating the effects of intravenous UC-MSC therapy, it was reported that stem cell therapy induced IL-10 production on day 3 but lead to mild reduction in IL-10

levels on day 14 compared to controls[1].These findings suggest that stem cells might have different effects on IL-10 at different time points. We have also searched for any published literature discussing the heterogeneity regarding IL-10 expression in animals, but we could not find strong evidence in literature.

3. Literature demonstrating elevated IL-10 should be strongly representative
We thank the reviewer for this important comment. We have added references demonstrating that stem cell therapy indusces IL-10 levels.We have included four more references to suppport this statement.

Suggestions for the modification of details in the article：

1. On page 6
METHODS: Please indicate whether the two researchers had different views in determining inclusion.
We thank the reviewer for this important comment. There was one major conflict between the first two authors regarding including the studies investigating the use of stem cells exosomes. The third author determined to include these studies. We have added this statement to the methods section: " one major conflict between the first two authors was regarding including studies evaluating the use of exosomes, and it was decided by the third author to include these studies."
2. On page 8
RESULTS**:** Increase the dosing cycle or medication interval.
We thank the reviewer for this comment. Unfortunately, we have screened the results section searching for this statement but we could not find it. We are willing to undertake the required correction if the reviewer could specify the statement that needs correction.
3. On page 16
Therefore, the exosomes should have mediated their effect① post-translational (i.e., after the protein was produced). ②"after the protein was produced"
① post-translational or post-transcription?
②after or before？
We thank the reviewer for this essential comment. We have revised this statement and the reviewer is correct about his/her concern. Therefore, we have corrected it to be "post-transcriptional", "before the protein was poduced".
4. On the other hand, the serum levels of IL-6 and CINC-1 were significantly higher in the MSC-treated animals on post-burn day 30 ($P<0.05$ and 0.02, respectively). Please add references
We thank the reviewer for this important comment. We have added the reference.

Reviewer #3

Major Comments:

1. The number of included studies is low compared to the broad aspect of this study "the systemic anti-inflammatory effect of MSCs in burn". This may be attributed to the

selection criteria set by authors (specially the full text availability) and/or the database searched. As a result, no sound conclusion could be driven out of this review. More papers should be added to this review. Searching another search engine might be helpful.

We thank the reviewer for this critical comment. When we conducted our search, we tried to make it as broad as possible. Therefore, we did not include search terms such as "Anti-inflammatory" or "Immunomodulatory" which could have narrowed our search significantly.Instead, we used only three search terms: "Burn", "Animal model", and "Mesenchymal stem cells". In one data base (CINAHL), we only used "Burn" AND "Mesenchymal stem cells" to further expand the search results. Moreover, we have not applied any filters for our search to avoid missing any potential studies. In addition, we have not excluded any study based on full-text availability as the authors come from different institution which provided us with multiple institutional accesses to all the full-texts we needed to screen. Unfortunately, we were surprised by the rarity of the studies discussing the use of MSCs to modulate burn-induced inflammation. Most of the studies retreived from the data base search discussed the use of stem cells for wound healind and corneal alkali burn.

We have followed the reviewer's advice and conducted a new search in another data base (EMBASE) using the following search terms: ("Burn" AND "Stem cells" AND "Animal model"). Unfortunately, after title screening, we were left with only one study for full-text screening and we ended up by excluding it as it was discussing the anti-inflammatory effects of stem cells in a sepsis model.

The aim of this systematic review is to shed the light on animal models utilized for this purpose and whether or not these therapies are promising enough to start more preclinical trials.We were aware that the number of the included studies is not enough to reach a final conclusion regerding the effectiveness of MSCs in modulating burn-induced inflamation. However, we do believe that this review is important to draw attention to this potential use of MSCs and to guide researchers to choose a model that can fit their research purposes.

2. Systemic inflammation or inflammation should be a keyword to search for as well

We thank the reviewer for this important comment. We have followed the reviewer's advice and added these term "Systemic inflammation" to the keywords.

3. Moreover, the wide heterogeneity among these few included studies regarding;
   a) Type of MSCs (Human BMMSCs X1 paper, Hu UCMSCs X 2 papers, Hu UCMSCs exosomes X 2, Mouse BMMSCs X 1, Mouse UCMSCs X 1 and Rat UCMSCs X1) and
   b) Route of administration (IV X 5, IM X 1, SC X 1 and ID X 1)
   c) Animal model (rat X6 and Mice X 2)
   d) Cell dosage (ranging from 5x105 to 2x106)
   Such heterogeneity further divides the studies into groups for sound comparison and weakens any driven conclusion which may explain the seemingly contradicting results of these studies as pointed out by the authors. It would be helpful if authors can add extra papers to this review. Nevertheless, authors could also address these concerns in

their discussion. The authors need to clearly identify how each of these variables (type of MSC, route of administration and cell dose) affect the outcome, i.e systemic anti-inflammatory effects of MSCs. Which route is better, which dose is more effective, are there any differences due to the chosen model (mouse or rat), which MSC source is more efficacious in its anti-inflammatory effects.
We thank the reviewer for this crucial comment. We agree with the reviewer that the heterogeniety of the included studies precluded the possibility of conducting any sound statistical analysis and therefore, limited our ability to drive definite conclusions about the effect of MSCs in these models. We agree with the reviewer on the importance of discussing these issues. Therefore, we expanded our discussion to clarify that the variability in the dose, animal model, and route of administration may significantly affect the outcomes. Unfortunately, we cannot state which route, dose, or stem cell type is better in modulating burn-induced inflammation as such conclsuions cannot be drive without metaanalysis.

4. It worth mentioning that only 3 out of the 8 selected studies have reported their sample size. Absence of sample size reporting affects any meaningful differences and statistical relevance. Authors must address this when reporting the findings.
We thank the reviewer for this important comment. We have reported in the results section as well as table1 that 5 studies are missing sample size. This is one of the major limitations to conducting a meta-analysis in this review. However, we do not believe that not reporting the sample size precludes any statistical relevance or meaningful differences among different groups in the same study. We made sure that all the included studies reported a (P value) to report differences between groups. Therefore, not reporting the sample size does not preclude the ability to detect meaningful differences among groups. In addition, although some studies did not report the total sample size, they reported a range number for each group (for example 7-12 animals per group).

5. While the authors conducted analysis of risk of bias in the selected papers, interestingly, all the included studies showed high risk of selection and performance bias which again pose many questions about the selection criteria of these papers.
We thank the reviewer for this important comment. We have utilized SYRCLE's tool for assessment RoB in animal studies. It is true that all the included studies showed selection bias (sequence generation domain) and performance bias (bliniding).However, we have to calrify that SYRCLE's tool is strict especially regarding selection and performance bias. For selection bias (sequence generation), the tool evaluates whether the animals were randomized to the groups and whether or not the randomization method was clearly described in the manuscript. However, this practice is not common in animal studies and based on our experience with previous systematic reviews of animal studies, most animal studies either do not randomize or clearly mention the method of randomization.This was also acknowledged by the creators of the tool in their foundational paper[2].It is worth mentioning that four studies reported randomization but not the method and therefore tested positive for selection bias based on the tool's criteria. Regarding the performance bias (blinding), this is also still not a common practice in animal studies. Therefore, we believe that

the studies included in this review are not of low quality compared to most animal studies.

6. Due to the aforementioned limitations, authors primarily describe the findings without performing statistical or meta-analysis (descriptive report).
We thank the reviewer for this important comment. This is true, we could not perform a statistcal analysis for variable reasons including the marked heterogeneity of the studies and missing sample sizes in many studies and we have clearly mentioned that in the limitation section.
7. It's also noteworthy that all the included studies are from rodents. As an expected result for the primary selection criteria set by authors. However, it would be anticipated to include other animal models (i.e. pig) for more sound results. Authors should have at least discussed it in their discussion part.
We thank the reviewer for this important comment. We do not believe that the primary selection criteria precluded any other animal models from the search results. The search term we was used was "Animal models" not rodents or small animal models. We did not exclude any study reporting another animal model such as pigs or sheep. In general, rodents are the most commonly used animal models in burn research as they are affordable, easy to handle, house,and breed, and provide multiple options of knockout strains.
8. A concluding section is required that discusses clinical trials on systemic administration of MSCs. This is required to demonstrate whether animal models appropriately reflect the clinical relevance of this therapy.
We thank the reviewer for this critical comment. We have conducted a PubMed search to find the clinical trials that utilized systemic use of MSCs in sepsis or burn patients. We found few studies that fullfil these criteria. We have discussed them in a separate section as recommended and summarized them in a table. However, It is worth mentioning that all the trials were safety trials.
9. Authors did not discuss or comment on how TBSA affects systemic inflammation in the reviewed studies. Three out of the 8 papers (almost 50%) did report the TBSA. Such an important parameter in burn treatment should be discussed adequately.
We thank the reviewer for this comment. We agree with the reviewer that TBSA significantly affects the inflammatory response. We have clarified that in the discussion section.

10. The authors discuss MSCs and MSC-exosome in the same context and do not differentiate between the two modes of this therapy; cellular vs acellular or cell-derived. The authors need to discuss the efficacy of these therapies in the paper reviewed? Are they different in their outcomes? Which one is better or worse?
We thank the reviewer for this important comment. We have briefly discussed the definition of exosomes and the results from the studies utilizing exosomes. The results from exosomes studies are summarized in Table 1 as well. However, the authors cannot rach a conclusion about the superiority of exosomes from the current literature. Further comparative studies could answer this question.

Figures and tables:

* It is difficult to understand why the toll-like receptor pathway was chosen for the graphical abstract. This needs to be justified.

We thank the reviewer for this important comment. We have removed the toll-like receptor pathway and replacrd it with a summary of MSCs anti-inflammatory and immunomodulatory effects.

* Table 1; Reporting the outcome variable was confusing and repetitive in some parts. Though summarized in table 1, however, authors chose to arrange papers chronologically which is not justified by the authors let alone it's confusing to jump from one outcome with different variables (cell source, number and animal model) to another set of variables with different outcome. Authors should either justify their choice of chronological order or try another order to make closely related papers in sequence.

We thank the reviewer for this important comment. We have rearranged the studies in the table as recommended to group the studies utilizing each type of MSCs together. However, jumping from one set of one to another set of variables is inevitable is such tables.

* Figure 1; it's mentioned that after a 1st round of selection authors had 40 articles left. On each, they performed a full length reading review and excluded another 32. However, it's confusing why they did not exclude these 32 articles from the first round since all reported reasons are (being reviews, conference papers or editorials) already fall in their Inclusion/Exclusion criteria as mentioned in Methods.

We thank the reviewer for this comment. At the stage of title and abstract screening, we prefered to be as broad as possible to avoid excluding any study that may turn out to be eligible.We do not believe this affects the credibility of our search.

* Figure 2 and table 2; both are representing same information. One of which could be removed for more clarity. Figure 2 especially is confusing as (+) and (-) marks were not explained in figure 2 legend as signs of bias presence or absence. Only by comparing table 2 and figure 2 reader can understand that (High) bias in table 2 is represented as (-) in figure 2. Figure 2 legend should be modified to with appropriate description.

We thank the reviewer for this important comment. We removed figure 2 as recommended.

* Figure 4; the UC MSCs effect is produced by MSCs exosomes as mentioned in page 6. However, in figure 4 and in figure 4 legends there is no mention for exosomes which might be misleading. Figure 4 and figure legend should be modified accordingly.

We thank the reviewer for this important comment. We have modified the figure legends accordingly.

* Figure 5; fig. 5 is an illustration of the results published in paper (Yagi et al. 2010) as reviewed by authors. The figure is adequately illustrated and explained.

We thank the reviewer for this comment.

Reviewer #4

1. Preface: There are too little details about the concept, characteristics, mechanism of SIRS and how the SIRS occurs in the process of burns. It is also recommended to discuss this part in the discussion section.

We thank the reviewer for this important comment. We have expanded our discussion about SIRS in burn as recommended by the reviewer.

2. Results section: authors summarize the research conclusions of the 8 experiments, the structure is not clear, the segmentation is unreasonable, and all the experimental conclusions are not summarized;
We thank the reviewer for this important comment. We have modified Table 1 to be more representable and easier to follow. However, we believe that dividing the results section into "Study characteristics", "Desription of intervention", and "Summary of outcomes" is easier to follow than reporting all the results in a single section. We have tried to summarize the most important experimental details in Table 1.

3. Discussion section: There are too many details about the experimental research. You can consider putting it in the results section. Some paragraphs are unclear, for example:
① It is recommended to discuss the prognosis of burn-induced SIRS and prognostic factors together;
We thank the reviewer for this important comment. We have followed the reviewer's recommendation and discussed prognostic factors of both conditions together.
② The immune regulation and anti-inflammatory effects of MSCs are suggested to be discussed together;
We thank the reviewer for this comment. We believe we are discussing both effects in the same section in the manuscript.
③ Burn-induced liver, kidney, and lung injury are recommended to be discussed together with blood-brain barrier damage, and the role of MSCs and exosomes in reducing organ damage is recommended to be discussed together;
We thank the reviewer for this important comment. We believe that discussing liver, kidney, lung, and blood brain barrier might confuse the reader. Therefore, we have divided the discussion into sections.
4. This paper deals with the therapeutic effects of exosomes secreted by MSCs on SIRS and organ damage after burns, but it does not systematically introduce exosomes before the preface or paragraph, but only when citing a literature. A brief introduction to the concept of exosomes is given. Its characteristics, advantages, and connection with MSCs are not mentioned, and it is suggested to supplement.
We thank the reviewer for this important comment. We have followed the reviewer's recommendation and expanded our discussion on exosomes.

Reviewer #5

- Interesting systematic review of MSC effects on burns

We thank the reviewer for this comment. We are glad and humbled that the reviewer found this review interesting.

- Authors are transparent in the potential biases and limitations

We thank the reviewer for this comment. We have used the SYRCLE's tool to asess the risk of bias in the included studies. SYRCLE's tool is a validated tool for assessing the risk of bias in animal studies.

- Did the authors account for possible variations that can affect derived conclusions if there is heterogeneity in the types of MSCs, source etc.?

We thank the reviewer for this critical comment. We agree with the reviewer on the importance of clarifying this point in the manuscript. Therefore, we have commented on the effect of hetereogeneity of the included studies on the possibility of conducting a meta-analysis or reach a definitive conclusion.

- although 2 separate tables/figures dedicated to comparing the various biases in the included studies, very little discussed within the manuscript

We thank the reviewer for this essential comment. We agree with the reviewer that we should further discuss the bias in the studies. However, the manuscript is close to 5000 words.Therefore, we chose to summarize the risk of bias in table 2 with brief discussion on selection bias and performance bias.

1 Sungkar T, Putra A, Lindarto D, Sembiring RJ. Intravenous umbilical cord-derived mesenchymal stem cells transplantation regulates hyaluronic acid and interleukin-10 secretion producing low-grade liver fibrosis in experimental rat. Med Arch 2020;74:177-182.
2 Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. Syrcle's risk of bias tool for animal studies. BMC Med Res Methodol 2014;14:43.

2nd Editorial decision
19-May-2022

Ref.: Ms. No. JCTRes-D-22-00021R1
Systemic Anti-inflammatory Effects of Mesenchymal Stem Cells in Burn: A Systematic Review of Animal Studies.
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: