OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Archives of Pediatric Infectious Diseases
Article DOI: 10.5812/pedinfect.105301
Published in: Archives of Pediatric Infectious Diseases: 9(3); e105301

Peer Review Report for "Sepsis and Septic Shock; Current Treatment Dilemma and Role of Stem Cell Therapy in Pediatrics"

Author(s): Gokcen Dinc, Zeynep Burcin Gonen, Jafar Soltani, Mehmet Doganay

Review Timeline:

Submit Date: 18 May 2020
Revised Date: 27 Nov 2020
Accepted Date: 1 Dec 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0) 29 Jun 2020

Dear AE,
Thanks for your manuscript. There are some comments for the authors:
- There are some English grammar problems. Please correct them.
- Inclusion and exclusion criteria are not defined exactly.
- Method of your study is not complete especially explain more about mesenchymal stem cells and how to yield them for sepsis treatment.
- In the result section, you discuss the definition of sepsis and septic shock. It would be better to bring it in your method part. Moreover, you have to focus on treatment by mesenchymal stem cells, not on other modalities of therapy. If you want to discuss other treatments it is better to change your title to “treatment of septic shock with new modalities”.
- According to conflicting data in your cited clinical trials about mesenchymal stem cell therapy of sepsis among humans, the main role of successful treatment has not proved instead of animals, so you have to declare the probable role of this treatment in humans and necessity of further studies in this field.
- Conclusion should be a maximum of 6 sentences. Please shorten your conclusion.
- Please write acknowledgment in your manuscript.
Thanks.

REFEREE: Reviewer | **Revision** (0) 5 Jul 2020

Dear AE,
Thanks for the professional writing of this submission
But, I think that secondary articles or systematic reviews are used in controversy situations and title of a review article usually is a fore ground question.
In this topic about role of stem cell in sepsis management, I didn,t find any controversy.Most of the article explain positive effect of this method in sepsis management.
Why did you do this review?
Which necessity, encourage you for this review?
Thanks

REFEREE: Reviewer | **Revision** (0) 2 Aug 2020

Dear AE,
Thanks for this valuable review article.
Recommendation :
This article is related to new treatmentin sepsis including stem cell therapy, but the article is so long and a large part is written related to sepsis and different issues in sepsis, type of Microorganisms, scoring, Sirs, sofa, and treatment of sepsis.
So I think it is better to ommit some parts of the article and more description related to mesenchymal cell tetherapy as a new treatment in differnet disorders including sepsis be added. (issues including different doses dose of stem cell , time of MSC infusion, a role of not expression of MHSc class 2 in MSC therapy).
Thanks.

REFEREE: Reviewer | **Revision** (0) 3 Aug 2020

Dear AE,
Comments for the authors:
1- In review studies, the research question should be formulated clearly. With the research question unclear, search keywords will also be meaningless.
2- It should be clear what type of review your study is, then revise its design based on the type of study. The present study has no specific design.
3- After the corrections, we can comment on the content of the study
Regards

Ali Amanati: Associate Editor | **Revision** (0) 3 Aug 2020

Dear EIC,
Your manuscript has been reviewed by reviewers who's comments are appended.
The authors should reply to their comments in a point-by-point manner and highlight all new changes with a different colour in the manuscript.
Thanks.

REFEREE: EIC | **Revision** (0) 5 Aug 2020

Dear Authors,

My decision about this manuscript (major revision). please change according to reviewers comments and update it.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Associate Editor's Comments:

Dear reviewers and editors
Many thanks for your kindly critical and educative evaluation of our manuscript.
In the direction of your comments, we revise the following points in our manuscript.

R1 to R2:

The respected EIC requests (R2)

The article text was shortened and updated according to the APID Journal publication policy:

1. We referred to Table 1 in the text.
2. Manuscript word count decreased to 5190 words.

I am wondering to know if more shortening of the article is needed.

R0 to R1:

Associate Editor 1 (R1):

AE comments

1. If authors intended to discuss this treatment modality in the pediatric population, add some words in the manuscript title to clarify it.

Thank you for your comment.
We revised the title as follows.

Sepsis and Septic Shock; Current Treatment Dilemma and Role of Stem cell Therapy in Pediatrics

2. Spell out all abbreviations.

All abbreviations expanded with the first occurrences.
Thank you for your comment.
We applied it.

3. ***The last part of the introduction should follow the distinct structural format:***
What was I studying?
Why was this topic important to investigate?
What did we know about this topic before I did this study?
How will this study advance new knowledge or new ways of understanding?

Thank you for your comment.
The article has no "Introduction" according to the APID format for Narrative Review Articles. Did you mean "Context" Part? If so, it is already in the text.

What was I studying?

Why was this topic important to investigate?

Thank you for your questions.

Response: The response to these questions was already in the "context part," paragraph one and two. As mentioned in the context part in detail, we were studying sepsis and current treatment obstacles. Severe sepsis and septic shock are significant causes of death. It is also one of the high-cost diseases worldwide. Currently, sepsis's primary therapy consists of antibiotics therapy, supportive therapies, and source control of infection. The failure rate of this approach is about 20-40%. Sepsis and septic shock is a field of much debate despite advances and innovations in the diagnosis and treatment modalities. The high mortality rate of sepsis in adults and children reflects the necessity to perform the study and its objectives.

Writing the article and relevant literature review was done according to an invitation by the respected chief editor of APID from Professor Mehmet Doganay and his team during the 13th International Congress of Clinical Microbiology in Shiraz.

What did we know about this topic before I did this study?

Thank you for your question.

As mentioned in the context part, Although a significant progression in understanding pathogenesis and the treatment of sepsis has been achieved in the last four decades, the current therapeutic modalities are not highly effective. Two phases have been recognized in the evolution of the pathway leading to death due to sepsis, including the early hyperinflammatory phase, with 10% mortality and the late immune suppression phase accounting for 30% of deaths. At least 40 trial sepsis researches directed to control the early phase of sepsis have been found unsuccessful

How will this study advance new knowledge or new ways of understanding?

Thank you for your question.

As mentioned in the context part, sepsis's primary therapy consists of antibiotics therapy, supportive therapies, and source control of infection. The failure rate of this approach is about 20-40%. Stem cell therapy is a new concept. Limited studies show that stem cells might be an alternative therapeutic approach for sepsis and septic shock. Here, the authors have reviewed the current progression in stem cell therapies for severe sepsis end septic shock.

Study limitations/advantages should be discussed before the conclusion in the last part of the discussion section.

Thank you for your comment.

Dear editor

According to APID format, the Narrative Review article has four sections.

1. **Context**
2. **Evidence Acquisition:**
3. **Results:**
4. **Conclusions:**

Here is a full description of the content of this type of article:

1. **Context:** It includes 1 or 2 sentences describing the clinical question or issue and its importance in clinical practice or public health.
2. **Evidence Acquisition:** This section describes the data sources, including the research strategies, time of the study, and other sources of the used materials, such as subsequent reference searches of retrieved articles. It explains the methods used for quality assessment and the inclusion of identified articles.
3. **Results:** This section addresses the major findings of the review of the clinical issue or topic in an evidence-based, objective, and balanced style, emphasizing the available highest-quality evidence.
4. **Conclusions:** It clearly states the conclusions to answer the posed questions, if applicable, based on the conclusions of the available evidence, and it emphasizes how clinicians should apply the current knowledge.

This type of article does not include the "Discussion and/or limitation" of the study.

Reference: Gregory AT, Denniss AR. An Introduction to Writing Narrative and Systematic Reviews — Tasks, Tips and Traps for Aspiring Authors. *Heart, Lung and Circulation*. 2018;**27**(7):893-8. doi:10.1016/j.hlc.2018.03.027.

Section: "How" to Write a Narrative Review?

I wonder if you help to find some evidence denoting the obligation for the narrative review article to have a "limitation of the study." However, I agree that the Systematic Review articles should contain "Limitation of the Study."

Here is a sample of review articles written by our grand teacher and chief editor of APID, professor Abdollah Karimi and two of your co-editors published by IJP and, of course, appraised by me as an Associate Editor of IJP about four years ago. You can study and review the sections as they contain no "limitation of the study!"

Sedighi I, Karimi A, Amanati A. Old Disease and New Challenges: Major Obstacles of Current Strategies in the Prevention of Pertussis. Iran J Pediatr. 2016;26(4):e5514. Published 2016 Jun 12. doi:10.5812/ijp.5514

AE comment: The conclusion part is too long and should be shortened by more than half.

Thank you for your comment.

The requested Change was applied as follows:

Conclusion

Although an achievement in the pathogenesis, diagnosis, intensive care improvement, and new treatment modalities, sepsis and septic shock are still grave health problems worldwide with untoward sequala, high mortality, and health cost; Antibiotic resistance is also an increasing problem in ICUs and hospitals.

Cell therapy is a promising treatment option for sepsis. Indeed, immunomodulatory properties, antimicrobial activity, and the capacity to protect against organ failure enhance tissue injury resolution, tissue repair, and restoration after sepsis confer MSCs with a significant advantage to treat the immune and inflammatory dysfunctions associated with sepsis and septic shock. However, early clinical trials seem promising and have beneficial effects; we need more controlled clinical studies, especially in phase II and phase III.

Provide a table to summarize the pros and cons.

Thank you for your comment. The requested table was designed and added to the manuscript.

Reviewer 1:

To editor in Chief;
Thank you for this valuable review article .
Recommendation : This article is related to new treatmentin sepsis including stem cell theapy , but ***the article is so long*** *and a large part is written related to sepsis and different issues in sepsis , type of Micro -organisms , scoring , Sirs , sofa and treatment of sepsis .*
So I think it is better to ***ommit some parts of article and more description related to mesenchymal cell tetherapy*** *as a new treatment in differnet disorders including sepsis be added. (issues including different doses dose of stem cell , time of MSC infusion , a, role of not expression of MHSc class 2 in MSC therapy).*

Response to Reviewer 1

Dear Reviewer

Thank you for your valuable comments. We shorten some parts of the article as long as the integrity of the text was not changed. We deleted some parts related to treatment.

The title of the article has been changed according to the comment by respected AE. Now the article text is more relevant to the new title.

Reviewer 2:

Dear author
1- In review studies, the research question should be formulated clearly. With the research question unclear, search keywords will also be meaningless.
2- It should be clear what type of review your study is, then revise its design based on the type of study. The present study has no specific design.
3- After the corrections, we can comment on the content of the study
Regards

Response to Reviewer 2

Dear Reviewer

Thank you for your comments.

1. The research question was formulated clearly.

   Response: The response to these questions was already in the "context part," paragraph one and two.
   As mentioned in the context part in detail, we were studying sepsis and current treatment obstacles. Severe sepsis and septic shock are significant causes of death. It is also one of the high-cost diseases worldwide. Currently, sepsis's primary therapy consists of antibiotics therapy, supportive therapies, and source control of infection. The failure rate of this approach is about 20-40%. Sepsis and septic shock is a field of much debate despite advances and innovations in the diagnosis and treatment modalities. The high mortality rate of sepsis in adults and children reflects the necessity to perform the study and its objectives.

   Writing the article and relevant literature review was done according to an invitation by the respected chief editor of APID from Professor Mehmet Doganay and his team during the 13th International Congress of Clinical Microbiology in Shiraz.

2. *- It should be clear what type of review your study is, then revise its design based on the type of study. The present study has no specific design.*

   Thank you for your comment.

   The article type is a narrative review article. It is clearly evident from the section of the manuscript. According to APID format, the Narrative Review article has four sections.

   1. **Context**
   2. **Evidence Acquisition:**
   3. **Results:**
   4. **Conclusions:**

Reviewer 3:
Thanks for your manuscript. There are some comments:
-There are some English grammar problems. Please correct them.
-Inclusion and exclusion criteria are not defined exactly.
-Method of your study is not complete especially explain more about mesenchymal stem cell and how to yield it for sepsis treatment.
-In result section, you discuss about definition of sepsis and septic shock. It would be better to bring it in your method part. Moreover, you have to focus on treatment by mesenchymal stem cell not on other modalities of therapy. If you want to discuss about other treatments it is better to change your title as "treatment of septic shock with new modalities".
-According to conflicting data in your cited clinical trials about mesenchymal stem cell therapy of sepsis among humans, the main role of successful treatment has not proved instead of animals, so you have to declare the probable role of this treatment in humans and necessity of further studies in this field.

-Conclusion should be maximum 6 sentences. Please shorten your conclusion.
-Please write acknowledgement in your manuscript.

-There are some English grammar problems. Please correct them.

Response: Thank you for your comment. I sent the article to the English editor of Erciyes Medical Journal to read over the text one time more and update the manuscript.

-Inclusion and exclusion criteria are not defined precisely.

The inclusion and exclusion criteria were reviewed and updated as follows. Table 2 is designed to clarify the search strategy and inclusion and exclusion criteria.

Search strategy:

In the preparation of the paper, we searched electronic databases, including PubMed, Google Scholar, Web of Sciences, and the clinical trials website at the National Library of Medicine (NLM) for articles published between 2010 and 2020. (Date of the last search: Jan 30, 2020). We searched databases using these Keywords (alone and in combination): 'sepsis,' 'septic shock,' 'children,' 'stem cell,' 'mesenchymal stem cell,' 'therapy,' 'treatment,' 'animal model,' 'murine models,' 'cell therapy.' A Google Scholar Alert activated for keywords to receive notifications about newly published articles, primarily Clinical Trials, during the manuscript's preparation.

Eligibility and exclusion criteria:

We included articles types as Clinical Trials, Systematic Reviews, and Meta-analysis, Narrative Reviews for stem cell therapies. They are screened first by titles according to the relevancy criteria and categorized based on relevancy, types of articles, and publication year. The abstracts of selected articles reviewed by three authors [Jafar Soltani (JS), Zeynep Burcin Gonen (ZBG), Gokcen Dink (GD)] separately, and each relevant article re-categorized according to researcher specific field of study and academic major of the researchers. Mehmet Doganay (MD) supervised all the steps. The clinical trials included if their intervention were by intravenous infusions of stem cells tested on the previously healthy persons newly suffering from sepsis or septic shock (Table 2). However, all phase one trials independent of types of the underlying disease, so-called "condition," reviewed for untoward side effects and safety of stem cell

infusions. The clinical studies and review papers included if they have been released in the last ten years collection for the preparation of the manuscript.

Study selection:

After the inclusion of criteria, we selected 301 original articles (including 13 articles about Animal Phase I Clinical trials and basic sciences research articles, 6 Human Phase II-III Clinical trials, 12 Systematic Reviews and Meta-Analysis, 30 Review Articles), one WHO web page, and five clinical guidelines and experts consensus. One hundred fifty-two articles were not added to references to match the journal policy for a maximum of about 80 references for review articles. Lastly, MD selected eight references for designing context, ZBG included 27 references in the field of cell therapy in Sepsis (Animal Studies(, GD included 17 references in the field of preclinical studies with stem cell therapy in sepsis model, and JS selected 31 references in the field of sepsis management and current problems and human clinical trials.

Table 2 Characteristics of completed and ongoing clinical trials of stem cells on sepsis and septic shock patients searched in clinicaltrials.gov website maintained by the National Library of Medicine (NLM)

Terms	Search Results [a]	Entire Database [b]
Synonyms		
stem cell	36 studies	7,935 studies
Progenitor Cell	three studies	971 studies
cells stems	1 study	six studies
blast cell	--	79 studies
cell progenitors	--	eight studies
Mother Cell	--	three studies
cell	38 studies	63,329 studies
Cellular	three studies	4,103 studies
bile salt-stimulated lipase	--	four studies
Cholesterol Esterase	--	1 study
Lysophospholipase	--	two studies
stem	37 studies	68,119 studies
Process	33 studies	61,534 studies
Processus	--	28 studies
Sepsis	38 studies	2,211 studies
toxemia	eight studies	683 studies
Infection systemic	--	three studies

Septicemia	--	42 studies
stem cell | Sepsis	38 Studies	
Completed studies	15 studies	
Filtered by Sepsis (Condition)	six studies	
Interventional study by Stem Cell infusion	five studies	
Age Groups:		
Child (birth–17)	14 studies	
Adult (18–64)	38 studies	
Older Adult (65+)	35 studies	
Study Phase		
Phase 1 [c]	five studies	
Phase 2 [d]	seven studies	
Phase 3 [d]	five studies	
Phase 4 [e]	1 study	
Not Applicable [e]	six studies	

-- No studies found

[a] Number of studies in the search results containing the term or synonym

[b] Number of studies in the entire database containing the term or synonym
[c] Three Interventions related to stem cell infusion
[d] Two Interventions related to stem cell infusion
[e] Intervention not related to stem cell infusion
The data retrieved from https://clinicaltrials.gov/

Reviewer 3:

The method of your study is not complete, especially explain more about mesenchymal stem cells and how to yield it for sepsis treatment.

Dear respected Reviewer,

Thank you for your comment.

This study is a Narrative Literature Review. There is no so-called method part. The comparable study method part, i.e., Evidence Acquisition, is related to how we searched the literature and the policy to select and deduct the response to research questions from relevant articles. However, concerning the comment, we refer the query to "Cell Therapy in Sepsis." Word count limited us to add more texts.

Reviewer 3:

-In result section, you discuss about definition of sepsis and septic shock. It would be better to bring it in your method part. Moreover, you have to focus on treatment by mesenchymal stem

cell not on other modalities of therapy. If you want to discuss about other treatments it is better to change your title as "treatment of septic shock with new modalities".

Thanks for your comment.

The title changed according to comments by the respected Associate editor.
This article is not an original research article. The definition of sepsis is not among the required items for defining the underlying method, i.e., the "Evidence Acquisition" part.

Reviewer 3:

-According to conflicting data in your cited clinical trials about mesenchymal stem cell therapy of sepsis among humans, the main role of successful treatment has not proved instead of animals, so you have to declare the probable role of this treatment in humans and necessity of further studies in this field.

Thanks for your valuable comments.

The required texts were added to the conclusion part after revision and requested shortening as follows.

Currently, cell therapy is a promising treatment option for sepsis. A limited number of phase I clinical studies have been carried out with stem cell therapy in sepsis and septic shock. However, early clinical trials seem promising and have beneficial effects; we need more controlled clinical studies, especially in phase II and phase III.

Reviewer 3:

-Conclusion should be maximum 6 sentences. Please shorten your conclusion.

Thanks for your valuable comment.

The conclusion is shortened as recommended.

Reviewer 3:

-Please write acknowledgement in your manuscript.

Thanks for your comment.

The acknowledgment part was added at the end.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Ali Amanati: Associate Editor | **Revision** (1) 29 Nov 2020

Dear EIC,
I read the revised manuscript, I have no further comments to add. I thank the authors for their very detailed replies to my comments.
Thanks.

REFEREE: EIC | **Revision** (1) 1 Dec 2020

Dear Authors,
My decision about this manuscript acceptinG.
Thanks.