Peer Reviw File

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Reviewer A:

Comment 1:

First the tittle is not correct: “Adipose derived mesenchymal stem cells in gastrointestinal system anastomosis: a narrative review”. The title does not correlate with the content: only 2 pages out from 9 in text are related to ADSCs and digestive anastomoses.

The chapters related to anastomosis in gastrointestinal surgery and potential complications; anastomotic leak risks assessment through intraoperative confirmation; traditional management techniques for preventing anastomotic leak last much more space in the paper.

In the same way, the running title is also not correct.

Reply 1: Thanks for your comment! Firstly, this review is an invited article from DMR, and the title is assigned as “Adipose derived mesenchymal stem cells in gastrointestinal system anastomosis”. In addition, pages related to “ADSCs and digestive anastomoses” have been extended according to your advice.

Comment 2:

Abstract:

In the last conclusion authors say: “transplantation in gastrointestinal system anastomosis that undoubtedly will stimulate future human studies exploring these new and exciting avenues.” It is important to remark that nowadays much more animal research is needed in this field is needed prior to test in humans. “undoubtedly” is very, very optimistic.

Reply 2: Thanks for your comment. “Undoubtedly will” has been revised into “may” in Abstract-conclusions.

Comment 3:

Abstract:

• Please further revise the abstract-Methods by adding more detailed information in the methods, e.g., "September 2008 to February 2022 by independent searches using publicly available databases, including NIH National Library of Medicine PubMed, Web of Science and MEDLINE, to search indexed and published articles".

Reply 3: Thanks for your advice. The detailed information has been added in Abstract-methods.

Comment 4:
In the Introduction section, we can mention:
• Authors mention: “this review mainly focuses on colonic anastomosis thereof” and as I have previously mentioned, this is not reflected in the tittle.
Reply 4: Thanks for your comment. Response is same as Reply 1. And this sentence has been deleted.

Comment 5:
Talking about the Methodology:
• It is very poorly described. I suggest employing or adding a flowchart.
Reply 5: Thanks for your good advice, flowchart has been added as Figure 1.

Comment 6:
• Authors use only less than two pages to summarize the published literature. Authors does not mention if there are some security concerns.
• The methodology and results of the selected studies is very, very poorly described. Some studies employ biosutures, another employ adjuvants as fibrinogen & thrombin (Yoo), cell sheets, gelatin sponge and the ASCs could be injected or instilled over anastomosis.
• Pascual et al have published two different papers with ASCs and biosutures in colonic anastomoses, one within and adhesion-free environment and one without. Only one is cited.
• Two studies are badly referenced:
• The study mentioned as of Dirk et al is in fact from Van de Putte et al.
• The study mentioned as of Panithi et al is in fact from Sukho et al.
• The study form Liu et al on digestive perforations (https://doi.org/10.1002/bjs.9724) must be included in the paper.
Reply 6:
a. Thanks for your good advice, security concerns have been described in Line 14-44, Page 13.
b. In addition, the methodology and results of the selected studies have been described more deeply in section of “4. Adipose derived mesenchymal stem cells in gastrointestinal system anastomosis”.
c. Another study of pascual et al is cited in Line 33, Page 8.
d. Dirk et al was revised into Van de Putte et al in Line 35, Page 9.
e. Panithi et al was revised into from Sukho et al in Line 15, Page 9.
f. The study form Liu et al was included in Line 15, Page 11.

Comment 7:
• The description of the selected studies results, and methodology is very poor. They must be explained deeply.
Reply 7: Thanks for your good advice, the description of the selected studies results, and methodology have been explained deeply in the section of “4. Adipose derived

mesenchymal stem cells in gastrointestinal system anastomosis".

Comment 8:
A Discussion section is lacking:
• Some paragraphs analysing critically the published literature with its strengths and weakness is very important.
• A paragraph mentioning security concerns related to stem cell therapies must be included.
• A paragraph about future directions must be also included.
Reply 8: Thanks for your good advice, a discussion section has been added in Page 14-16.

Comment 9:
Conclusions:
• The final message: "The effectiveness of ADMSCs in preventing anastomotic leakage has been proven by many studies, while the results among different studies were inconsistent and another limitation is that ADMSCs have not been studied in humans. In the future, multi-center, large-sample human clinical trials are needed to verify the effectiveness of ADMSCs on the prevention of gastrointestinal system anastomotic leak".
o First: 6 studies on colorectal anastomoses and 6 in other models only in animals are not "many" but "some".
o With this scant literature maybe it is too early to speak about "multicenter largescale human clinical trials". In fact, much more basis research is needed in this field, and when it is published, ASCs on anastomoses must do the clinical trial development (Phase I, Phase II, etc.) and not directly large-scale trials.
Reply 9: Thanks for your good advice!
a. "many" has been revised into "some" in Line 38, Page 16.
b. Yes, much more basic research is needed and sentence has been modified as "much more pre-clinical studies are needed" in Line 40-41, Page 16.

Comment 10:
Referrences:
• I suggest the authors to review and add to their reference lists some previously published reviews in this field:
o J BUON. 2015;20:1624-1629.
o Eur J Surg Oncol. 2020;46:943-954.
o Langenbecks Arch Surg. 2021;406:971-980.
o World J Stem Cells 2022; 14(1): 117-141.
Reply 10: Thanks for your suggestion!
o J BUON. 2015;20:1624-1629. Has been cited in Line 14, Page 8.
o Eur J Surg Oncol. 2020;46:943-954. Has been cited in Line 22, Page 3.
o Langenbecks Arch Surg. 2021;406:971-980. Has been cited in Line 8, Page 6.
o World J Stem Cells 2022; 14(1): 117-141. Has been cited in Line 8, Page 16.