

PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 85624

Title: Up-to-date meta-analysis of long-term evaluations of mesenchymal stem cell therapy for complex perianal fistula

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05743633

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Poland

Author's Country/Territory: China

Manuscript submission date: 2023-05-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-05-15 05:13

Reviewer performed review: 2023-05-18 08:34

Review time: 3 Days and 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this meta-analysis authors evaluate the effectiveness of MSC transplant in complex perianal fistula (PF) therapy. They included 6 trials with 161 interventions and 146 controls in total. Given the limited number of available studies on this treatment strategy obtained numbers are satisfactory. The main outcome of this meta-analysis is somehow not surprising since all included reports showed improvement of clinical parameters in patients affected by PF and this article is in line with that. I do not see any major issues as regards the design, methodology and data presentation. I think this study could be useful for clinicians seeking for reassurance that MSC therapy is safe and effective although very limited number of medical centers actually use this technique probably due to lack of experience and still low popularity in guidelines. Overall, I think this manuscript is worth publishing with no minor or major corrections.

PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 85624

Title: Up-to-date meta-analysis of long-term evaluations of mesenchymal stem cell therapy for complex perianal fistula

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04022623

Position: Peer Reviewer

Academic degree: PhD

Professional title: Adjunct Professor, Surgeon, Surgical Oncologist

Reviewer's Country/Territory: Spain

Author's Country/Territory: China

Manuscript submission date: 2023-05-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-05-25 20:59

Reviewer performed review: 2023-06-06 20:46

Review time: 11 Days and 23 Hours

Scientific quality	<input checked="" type="radio"/> Grade A: Excellent <input type="radio"/> Grade B: Very good <input type="radio"/> Grade C: Good <input type="radio"/> Grade D: Fair <input type="radio"/> Grade E: Do not publish
Novelty of this manuscript	<input checked="" type="radio"/> Grade A: Excellent <input type="radio"/> Grade B: Good <input type="radio"/> Grade C: Fair <input type="radio"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="radio"/> Grade A: Excellent <input checked="" type="radio"/> Grade B: Good <input type="radio"/> Grade C: Fair <input type="radio"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	[<input checked="" type="checkbox"/>] Grade A: Excellent [<input type="checkbox"/>] Grade B: Good [<input type="checkbox"/>] Grade C: Fair [<input type="checkbox"/>] Grade D: No scientific significance
Language quality	[<input checked="" type="checkbox"/>] Grade A: Priority publishing [<input type="checkbox"/>] Grade B: Minor language polishing [<input type="checkbox"/>] Grade C: A great deal of language polishing [<input type="checkbox"/>] Grade D: Rejection
Conclusion	[<input type="checkbox"/>] Accept (High priority) [<input type="checkbox"/>] Accept (General priority) [<input checked="" type="checkbox"/>] Minor revision [<input type="checkbox"/>] Major revision [<input type="checkbox"/>] Rejection
Re-review	[<input checked="" type="checkbox"/>] Yes [<input type="checkbox"/>] No
Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous
	Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

Firstly, I would like to congratulate you by the high quality of the submitted paper. The information provided has a highly potential clinical relevance. Maybe I would like you to develop more deeply some aspects in your paper. In the following sections, aspects I consider modifiable or revisable of the submitted manuscript will be highlighted. The presented manuscript is very interesting because it reviews deeply with a highly valuable methodology a very interesting issue. I think that authors must do some very minor changes and maybe add more information to the paper in some of its parts. I believe those modifications would made the manuscript more complete. In the INTRODUCTION section, we can mention:

- Page 1 at the end. I think it could be very useful to define what a complex PF is. There are some consensus definitions and it is very interesting because maybe only colorectal surgeons know what is really a Complex PF.
- Page 1, last line. "...complex PF, which often causes faecal incontinence..." is not well written. It is not frequent that the PF causes and incontinence, unless the PF soils; faecal incontinence could be associated to PF and condition its treatment or could be a devastating consequence of PF surgery. It must be better explained the importance of FI.

- Page 2: “In addition, the risk of the development of neoplasia in patients with complex PF is considered related to perianal disease duration [4].” I think it could be better presented as: “ there is a risk of developing a neoplasm in the PF area related with the complexity and perianal disease duration...”
- Page 2: [[Patients with complex PF tend to have poor treatment outcomes or experience frequent relapses, and most interventions are ineffective in providing long-term healing [6].]] It could be interesting to provide a range of these mentioned published results. I.e “long term healing under 60% for complex PF...” (not real data).
- The following two sentences in that paragraphs start by the same word (additionally), try to use a synonym.
- Page 2 last paragraph: [Complex PF is thought to arise from an epithelial defect, which may be caused by ongoing inflammation. As we have mentioned before, Current treatments frequently cannot maintain long-term healing of the disease. Possible alternative treatments include cell therapy, especially MSC therapy. The most performed approach to deliver MSCs is local administration. After being delivered] I suggest consider adding the highlighted sentences.
- Page 3: [However, the efficacy and safety evaluation time of the study was short and middle term [8].] I think that 2 years of follow-up could be considered more than “short-term”. In the MATERIAL AND METHODS and in the RESULTS sections:
 - A global commentary... considering the results published by García Olmo D research network, it seems that there are different scenarios to be considered, or maybe relevant to analyse separately:
 - o Autologous MSCs seem to be less effective than allogeneic MSCs.
 - o Crohn’s patients maybe have better outcomes with SCs.
 - It could be possible to perform separated analysis considering these situations (i.e Crohn versus no Crohn?). Maybe it could impact the observed findings...
- Talking about DISCUSSION:
 - I suggest to include at the beginning a cite to the seminal article in this field from García Olmo D in 2003 (Int J Colorectal Dis. 2003 Sep;18(5):451-4. doi: 10.1007/s00384-003-0490-3).
- Page 10, when authors speak about MSC significantly improves QoL... It could be useful

to compare with long-term data of other available therapeutic options if possible (in terms of effectiveness, QoL, healing rate,...) • Page 11 first paragraph, authors speak about FG: [The use of FG has been found to be uniformly safe, with minimal adverse effects, an early return to normal activity, and no negative impact on continence]. It could be useful to add a commentary about FG alone y PF in the literature, short and long term. • Page 11, last paragraph: [Notably, this is a minimally invasive surgery (with curetted fistula, locally injected MSCs, and closed internal opening) and does not produce faecal incontinence]. Some technical aspects appear to be essential to obtain the better results as it has been published by Georgiev-Hristov et al. J Gastrointest Surg. 2018 Nov;22(11):2003-2012. doi: 10.1007/s11605-018-3895-6. • Page 13: [In addition, all eligible patients suffering from complex PF may have branches with multiple tracks involving an extensive area that cannot always be adequately treated with a fixed dose of cells. Maybe the cell dosage must be related to the length of fistula tracts and cavities. In future research,] I suggest adding highlighted sentence. • Page 13, last paragraph (about limitations). [(3) All patients underwent surgical procedures . This may be beneficial to the clinical remission of the fistula and cause our results to be overestimated]. Which surgeries? Explain better... For example Garcia-Olmo et al proposed and performs minimally aggressive surgeries (curettage + internal opening closure) not comparable to the standard surgical procedures (fistulectomy, flaps, LIFT,...). It is a very interesting issue to remark, with a very minimal aggressive procedure, with minimal risk for continence, MSCs obtain similar or better results to surgery... In the REFERENCES section: • Number 4: the first author is Panes, not Anes. Newly I would like to congratulate authors for their work. Keep working in this way and trying to publish your research.