

## JOURNAL EDITOR-IN-CHIEF'S 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

**Journal Editor-in-Chief (Associate Editor):** Shengwen Calvin Li

**Country/Territory:** United States

**Editorial Director:** Jia-Ping Yan

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair		<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Major revision

### JOURNAL EDITOR-IN-CHIEF (ASSOCIATE EDITOR) COMMENTS TO AUTHORS

Specific comments from EIC: First: Figure titles must carry self-explanatory information. An ideal figure title should give complete information to the reader even without reading the text. The figure should be provided with a governing title followed by the descriptive interpretation of panel contents. All the figure legend descriptions were not written in keeping this point in mind in the current manuscript version. e.g., "Figure 4 Long-term effectiveness of mesenchymal stem cells plus fibrin glue for treating complex perianal fistula. MSCs: Mesenchymal stem cells; CI: Confidence interval." In the text: "Long-term efficacy of MSCs for complex PF (MSCs + FG vs FG alone) Cell therapy strategies using MSCs carried in FG have shown promising results in regenerative medicine. The biological properties of FG as a growth environment for MSCs have been reported in several studies[20]. However, the use of local FG plus MSC therapy in complex PF cases is not supported by sufficient evidence. In our study, three studies were identified[14,15,17], with low heterogeneity

between the studies ( $I^2 = 0\%$ ). In a fixed-effects model, MSCs plus FG had more long-term efficacy for fistula healing than FG alone (OR = 2.30; 95%CI: 1.21, 4.36;  $P = 0.01$ ) (Figure 4).” Neither the text nor the figure legend gave sufficient details of why and what, and how these studies should be interesting and of importance. The above text of conflicting: “However, the use of local FG plus MSC therapy in complex PF cases is not supported by sufficient evidence. In our study, three studies were identified[14,15,17],” – what did they mean by “our study?” In fact, none of the citations of 14, 16, or 17 was “THEIR study.” Second, their definitions of the terms crawl around the pages without strict boundaries. E.g., what was the QC of MSC used in each study by what standard and from what sources? Third, “The key long-term therapeutic goals for the treatment of complex PF are to: (1) Resolve fistula discharge; (2) achieve fistula healing; (3) prevent fistula recurrence; (4) maintain fecal continence; (5) avoid long-term diversion (proctectomy with stoma), and hence; and (6) improve and maintain QoL for patients.” They should make a table of these elements and compare these criteria with their citations that specifically met them. Fourth, clarity is missing in certain spots. E.g., “Therefore, fecal incontinence is associated with complex PF and not only affects its treatment but also is a devastating consequence of PF surgery” [out of context]. “In recent years, local injection of mesenchymal stem cells (MSCs) has shown notable promising results in the treatment of PFs[11]. MSCs are a heterogeneous subset of stromal stem cells. They can be isolated from a wide variety of tissues and expanded in vitro to obtain large quantities. MSCs are characterized by multilineage differentiation and powerful immunomodulatory effects and are able to mitigate inflammatory states.” what was the QC of MSCs of what organs were used in each study by what standard and from what managements? Fifth, “To our knowledge, this is the first meta-analysis to evaluate the long-term safety and efficacy of local MSC therapy for complex PFs” – what was the definition of the meta-analysis” if they got only “After screening, 6 studies met the inclusion criteria?” such as the sources of stem cells, the routes of administration, the effect criteria or the outcome measures should be consistent. E.g., Table 1 did not specify the nature of the sources: ASCs, BMSCs, are different in stem cell capacity. Neither could the authors draw comparisons nor specify the differences but stated MSCs as a generic agent. Again, this statement is misleading, as you can compare apples and oranges. Sixth, Discussion: “We speculate that for localized digestive tract diseases, local application and delivery seems more logical because side effects can be minimized and the cells are kept in direct contact with the at-risk tissue. Therefore, local MSC therapy seems to be a more promising treatment approach for further research. In our study, all eligible patients received a fixed dose of MSCs (one-time local injection or a second dose). Although most patients in our study received two doses of MSCs, some studies have indicated a relationship between cell dose – or even the number of doses and efficacy [35,36].” Neither citations #35 nor #36 belong to the authors’ study, which misled the readers. Thus, their discussion did not tie in with their results. Seventh, A meta-analysis is a statistical method used in research that systematically analyzes and combines data from multiple independent studies on a specific topic or research question. It is a quantitative approach that aims to provide a more comprehensive and precise estimate of the effect or relationship being investigated by pooling



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**https://**[www.wjgnet.com](http://www.wjgnet.com)

data across studies. A reader comes to read such a study, expecting to gain vision in the field, which is beyond the regurgitalith of the original articles; however, this manuscript did not show such vision. Neither did they identify any problems, nor did they provide solutions.