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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 60089

Title: Orthobiologics in the treatment of hip disorders

Reviewer's code: 02565460

Position: Peer Reviewer

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Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Brazil

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-10-16 06:34

Reviewer performed review: 2020-11-09 08:01

Review time: 24 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The work deals with the description of orthobiologics in the treatment of hip disorders. For each orthobiologic product described, a brief description is given about the methods of preparation, its biological activity and finally the application potential in hip pathologies. Over the last decade, hundreds of works have been devoted to the description of the biological characteristics of orthobiologics, and dozens of works have focused on joint pathologies. Describing the salient data of this extensive literature is not easy. Indeed, this work falls into one of the most obvious risks of this type of literature: an excessive simplification of the description of products and their application. Too many arguments to deal with. The intentions are positive, but it is not easy to understand what is new compared to the literature already published. Readers of this work would like to know in-depth what regenerative medicine has proposed for hip disorders in recent years. The authors do this only partially. For example, discussing the role of expanded MSCs in a half-page final paragraph is insufficient to inform a reader about their therapeutic possibilities and the state-of-the-art of the literature. Furthermore, this is quite confusing since expanded MSC application is discussed in several other paragraphs of the paper. Furthermore, some claims should be better justified with more recent literature. References should be carefully checked: there are several inaccuracies. INTRODUCTION: “The theoretical advantages of orthobiologics are minimal invasiveness, greater healing etc”: What do the authors mean with “minimal invasiveness”?. The collection of adipose tissue or of bone marrow tissue can be considered a "minimal invasive" procedure? I think that this concept applies to some but not all orthobiologics. HA: “It may be produced from animal sources (avian) or …..”: are the authors sure that HA only animal source is avian? “As an example, there is the combination of calcitonin, dextrose, platelet-rich plasma …..”: The sentence should be rewritten. Here the concept should be" a combination with calcitonin etc has

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been proposed". Furthermore, references should be added. PRP: "PRP was used alongside hip arthroscopy surgery for a variety of pathologies….": "was used" or instead is used? "The technique consists in the administration of 4.5 mL of PRP into the repaired hip…." - here is not clear if the volumes proposed for the therapy are a standard, are instead derived from a paper, or are the results of the personal experience of the authors. Could you please explain and introduce some reference if necessary? "PRP can also be used in combination with different orthobiologic products, such as HA and bone marrow" - Should "BMAC" be used here instead of "bone marrow"? "With this technique, we obtained 3-5 fold platelet concentration increase and 2-4 fold white blood cell from baseline." - Do the authors mean 2-4 fold increase regarding to white cells? i.e are they using L rich-PRP? This should be clear to the reader. "PRP can usually be combined with HA, or even bone marrow aspirate concentrate (BMAC), which can improve pain and function of the injured hip." - This concept has already been introduced before. BONE MARROW: In my opinion, the section entitled Bone marrow is over-simplifying the field. In particular, statements as "HSCs are thought to be the true drivers for enhancing cartilage and bone regeneration" should be discussed more clearly and extensively. The same applies to the statement that "non-cultured cells presents some advantages…..". This is a matter of active discussions and many studies have tried to address the issue. The cited reference is not particularly recent. New references should be added to support this observation. The iliac crest is a well-known, common site for bone marrow collection, so the sentence "It has already been shown that a pool of MSCs could be obtained from the iliac crest" should be rewritten. BMAC: "In comparison to PRP, there is a significant variation in the final products achieved. Fortier et al. evaluated the constituents of PRP and BMAC, showing a reduction in platelet content and an increase in white blood cell content in BMAC [47]. The differences between these products could represent a different mechanism of action [47]." That PRP

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and BMAC have different cellular composition is expected. The cited work was mainly aimed to assess repair ability of BMAC in an experimental model. To my knowledge, the work does not report a direct comparison between PRP and BMAC role. ADIPOSE-DERIVED TREATMENTS: What does “the interference of collagenase” mean? “ The authors should check reference 63. They explain results from Cuervo et al but the first author is not mentioned. An accurate check of the bibliography is suggested. The work by Nava et al, is not described clearly. Reading the sentence, it seems that it is the first case of viable AD-MSC preparation, that of course is not true. It should be clear that the work indeed describes how viable MSCs exhibiting anti-inflammatory properties can be obtained from microfragmented adipose tissue. Furthermore, the characterization and the clinical use of microfragmented adipose tissue has been reported by a number of papers, not cited here. EXPANDED MESENCHYMAL STEM CELLS Again: in my opinion, this chapter does not adequately describe the complexity of the subject. It should be improved. I think that the paper could be interesting, but a revision of different chapters is needed.