Reviewer’s report

Title: The Efficacy of Multiple versus Single Hyaluronic Acid Injections: A Systematic Review and Meta-Analysis

Version: 0 Date: 03 Sep 2017

Reviewer: Antonella Fioravanti

Reviewer's report:

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This systematic Rev and Meta-analysis is interesting, however, major revisions of the manuscript should be taken into consideration to make it acceptable for publishing.

The Authors should be discuss the different opinion regarding the use of intra-articular Hyaluronic acid reported by various guidelines for management of osteoarthritis (see ACR 2012, OARSI 2014).

The molecular weight of HA is thought to be of fundamental importance with respect to the volume/amount and number of injections, the residue time in the joint and biologic effects. Then, the efficacy and safety as well as the medium-long-term effect of IA-HA are influenced by the molecular weight of the different products. The Authors should be take into consideration and stress these aspects.

Furthermore, in vitro studies showed different biological propriety of various products due to the molecular weight of HA. In our opinion the Authors should improve the quality of the paper discussing the different activity of low and high molecular weight of HA. There is a lot of evidences suggesting various mechanism of action of different products.

A number of reports demonstrated the antiinflammatory and chondroprotective effects of HA (inhibition of metalloproteases, nitric oxide, stimulation of proteoglycan/glycosaminoglycan synthesis). See the following:

Fioravanti A ,et al. Effect of hyaluronic acid (MW 500-730 kDa) on proteoglycan and nitric oxide production in human osteoarthritic chondrocyte cultures exposed to hydrostatic pressure. Osteoarthritis Cartilage. 2005


Minor point: there are some mistakes in the Reference list

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

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