

Reviewer 2

Comments and Suggestions for Authors

Dear authors,

I have read your article entitled "Comparative Efficacy of Intra-Articular Injection, Physical Therapy, and Combined Treatments on Pain and Sarcopenia Indices in Knee Osteoarthritis" with great interest. I found your study to be well-organized and informative, and I believe that your findings make a valuable contribution to the field of osteoarthritis treatment. Below are my comments on your article:

Response

We thank all the reviewers for their comprehensive review and their comments regarding our manuscript. We have made all necessary modifications to our originally submitted manuscript (Manuscript ID: ijms-2274985), based on reviewers' comments, point by point.

1. The title does not mention the focus on sarcopenia indices in KOA, which is an important aspect of the study. Optional - a more accurate title could be "Comparative Efficacy of Intra-Articular Injection, Physical Therapy, and Combined Treatments on Pain, Function, and Sarcopenia Indices in Knee Osteoarthritis. Besides, PRISMA guidelines recommend mentioning the type of review – systematic review and meta-network analysis: "Identify the report as a systematic review, meta-analysis, or both".

Response

Thank you for the constructive comment. We revised the title as follows:
"Comparative Efficacy of Intra-Articular Injection, Physical Therapy, and Combined Treatments on Pain, Function, and Sarcopenia Indices in Knee Osteoarthritis: A Network Meta-Analysis of Randomized Controlled Trials"

2. The abstract seems insufficient in information and volume. The abstract lacks important information on the inclusion and exclusion criteria used for selecting the RCTs and on the types of intra-articular injections analyzed. This could be important for readers to assess the validity and generalizability of the study findings from the abstract.

Response

We added information regarding selection criteria of RCTs in the abstract as follows:

“All RCTs which had treatment arms of IAI agents [autologous conditioned serum, botulinum neurotoxin type A, corticosteroids, dextrose prolotherapy (DxTP), hyaluronic acid, mesenchymal stem cells (MSC), ozone, platelet-rich plasma, plasma rich in growth factor, and stromal vascular fraction of adipose tissue] in combination with PT [exercise therapy, physical agent modalities (electrotherapy, shockwave therapy, thermal therapy), and physical activity training] were included in this NMA. A control arm receiving placebo IAI or usual care, without any other IAI or PT, was used as the reference group.”

3. The introduction of your article clearly identifies the research gap and highlights the importance of your study. It provides a good overview of the current state of knowledge in the field and sets the context for your research question.
4. The methodology of your study is sound and robust, and the use of network meta-analysis is appropriate for this type of research. You have also taken care to report the methods and results in a transparent and clear manner.
5. Your results provide useful insights into the comparative efficacy of different treatment options for KOA. The finding that combined IAI + PT treatments offer more benefits than their corresponding monotherapies is particularly noteworthy.
6. The use of meta-regression analyses to explore potential moderators of treatment efficacy is a valuable addition to your study. The finding that disease severity moderates treatment efficacy provides important information for clinicians and researchers.
7. The discussion section of your article is well-written and clearly explains the implications of your findings. You have also highlighted the limitations of your study and provided suggestions for future research.
8. Relevant articles should be discussed presenting OA as a whole joint/body disease. After all, our understanding of osteoarthritis (OA) has evolved to recognize its complex interaction with the human body as a whole, necessitating a redefinition of the disease concept. Thus, any future conservative disease-modifying treatment for knee osteoarthritis (KOA) should adopt a multimodal, holistic approach that considers the osteoarthritis joint in the context of the entire body, and not limit itself only to intraarticular injections [e.g.: PMID: 32803403].

Response

Following the reviewer’s insightful comment, we made an additional subsection in the discussion section to elucidate the multimodal, holistic approach for KOA as

follows:

Section 4.6 (Lines 590–602).

“The clinical presentation of KOA is multifactorial and can be characterized by phenotypes across multiple dimensions including articular construction, biochemical markers, psychological distress, and patient characteristics (e.g., sex and body weight) [82–84]. Therefore, the complexity of the modern concept of KOA has been recognized as impairments of the whole joint, and not simply of joint cartilage [85]. This supports the needs of multimodal approach (i.e., the combined use of two or more interventions) to treat KOA as a whole joint disease and to meet patient expectations [86]. Results in the present NMA may strengthen the recommendations of multimodal approach by combining pharmacological and nonpharmacological treatments, particularly IAI+PT, in KOA [7, 81, 85, 86]. Importantly, the comparable compliance and safety among combined regimens and its corresponding monotherapies identified by NMA in this study further underline the suggestion that the optimal use of IAI is attainable in combination with other interventions such as PT [81].”

Overall, I think that your study is well-conducted and provides valuable insights into the comparative efficacy of different treatment options for KOA. I appreciate your contributions to this field and look forward to seeing future studies building on your work.