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Letter to Editor

Efficacy of intra-articular platelet-rich plasma in osteoarthritis knee

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To the Editor,

We read a recently published article by Suman et al.[1] titled, "Efficacy of intra-articular platelet-rich plasma in osteoarthritis knee'. In this study, the authors evaluated the efficacy of two doses of platelet-rich plasma (PRP) administered 4 weeks apart in patients with osteoarthritis (OA) of the knee. The results demonstrated significant improvements in the Visual Analogue Scale (VAS) and Western Ontario and McMaster University Osteoarthritis index (WOMAC) pain, stiffness and physical function scores at 3 months follow-up (from date of 1^{st} injection) compared to the baseline. We have several concerns that we would like to communicate.

1. The authors indicated that this is a randomised controlled trial. However, they did not -
   (a) Provide the registration information of this trial on Clinical Trials Registry – India (CTRI) or similar repositories.
   (b) Include information regarding the institutional ethics committee (protocol number and date of approval).
   (c) Include information and/or data/outcomes for the comparator group and the method of randomization.
2. The authors didn't characterize the PRP formulation used. It is necessary that orthobiologic used, i.e., PRP, must be characterized. PRP is the most widely used autologous peripheral blood-derived orthobiologic; and yet, its efficacy is contentious, attributed to lack of standardized preparation protocol and characterization.[2,3] Studies have shown that a platelet concentration of 5-7x compared to the whole blood baseline levels and mean platelet dose of no less than 5 billion is essential to increase cell proliferation and migration, tissue regeneration and achieve positive clinical outcomes.[4–6] Additionally, too much inflammation because of presence of pro-inflammatory neutrophils can worsen instead of improving osteoarthritic pain.[5] Moreover, intra-articular administration of red blood cells is harmful, and they should be removed from the PRP formulations.[7] Thus, it is essential to characterize the PRP using one of the several available PRP classification systems and list the amount of platelets, leukocytes and neutrophils, red blood cells, and the manner in which platelet activation was performed.[5,8]
3. The authors stated use of 35-40mL blood to obtain 4-6mL of PRP. 5mL difference in starting blood volume

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and 2mL difference in PRP volume administered will lead to variable outcomes due to difference in aforementioned factors such as platelet concentration, leukocytes and neutrophils concentration, etc. Why did authors not use a uniform starting and administered volume throughout their study?

4. The authors indicated the inclusion of Grade I-IV (Kellgren-Lawrence scale) knee OA patients in their study. However, the authors didn't perform the sub-group analysis based on the degree of severity of knee OA. In addition, studies have shown no-to-mild short-term benefits of PRP in Grade IV knee OA patients.[9,10] This is in accordance with the consensus from the European Society of Sports Traumatology, Knee Surgery and Arthroscopy - ORthoBiologics InitiaTive (ESKAA-ORBIT), endorsing PRP as an effective modality for managing Grade I-III knee OA.[11] Thus, why did authors decide to include patients with Grade IV knee OA in their study?
5. The authors excluded patients who took non-steroidal anti-inflammatory drugs (NSAIDs) two days prior to the injection. How did authors decide this time-point? Studies have shown that non-selective NSAIDs lead to reduced platelet aggregation but has no effect on platelet count.[12,13] In contrast, COX-2 selective NSAIDs did not lead to decreased platelet aggregation.[12,13]
6. The authors did not inlcude any radiographs or magnetic resonance imaging for either group to allow for comparison at the follow-up visit(s) compared to the baseline.
7. The authors did not mention post-injection rehabilitation/return to activity protocol.

We believe these are some crucial points which should have been addressed in the manuscript. Thus, we kindly request the authors to submit a response to our letter and address our aforesaid concerns, as this is vital to ensure repeatability and reproducibility of outcomes of studies involving PRP for the management of OA of the knee.

1. List of Abbreviations

PRP: Platelet-rich Plasma; OA: Osteoarthritis; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster University Osteoarthritis Index; CTRI: Clinical Trials Registry – India; ESKAA-ORBIT: European Society of Sports Traumatology, Knee Surgery and Arthroscopy - ORthoBiologics InitiaTive; NSAIDs: Non-steroidal anti-inflammatory Drugs

2. Availability of Data and Materials

All relevant data is contained within the article.

3. Sources of Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

4. Conflict of Interest

The authors declare that they have no competing interests.

5. Authors' Contributions

AG conceptualized the study and wrote the initial manuscript draft. AG, SPS, CC and MJ reviewed and edited the manuscript draft. All authors have read and agreed to the published version of the manuscript.

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