

Letter to the Editor: Comparative Efficacy of Intra-Articular Growth Factor Concentrate and Platelet-Rich Plasma Injections in Knee Osteoarthritis: An Evaluation of Clinical, Radiological, and Biomarker Outcomes

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Learning Point of the Article:

This letter to the editor underscores the shortcomings of the original study by Saraf et al. titled, "Comparative Efficacy of Intra-Articular Growth Factor Concentrate and Platelet-Rich Plasma Injections in Knee Osteoarthritis: An Evaluation of Clinical, Radiological, and Biomarker Outcomes".

Dear Editor,

We read with great interest the article published in the Journal of Orthopaedic Case Reports by Saraf et al. [1], titled "Comparative Efficacy of Intra-Articular Growth Factor Concentrate and Platelet-Rich Plasma Injections in Knee Osteoarthritis: An Evaluation of Clinical, Radiological, and Biomarker Outcomes", where the authors evaluated the efficacy of intra-articular Growth Factor Concentrate (GFC) compared to Platelet-Rich Plasma (PRP) in patients with knee osteoarthritis (OA). We would first like to commend the authors for attempting to address an important topic. However, based on our review of this article, we would like to highlight certain limitations in this study that were not addressed by the authors.

i. In the methods, the authors stated that this was a triple-blind randomized study. However, no description of triple blinding (e.g., who all were blinded? how blinding was maintained? etc.) and the randomization process (e.g., how it was carried out? block size? etc.) was stated in the manuscript.

ii. In the methods, the authors also did not state the

inclusion/exclusion criteria for patients who had prior intra-articular injection of corticosteroids or viscosupplementation.

iii. In the methods, the authors stated that patients were randomized into three groups. However, no description of the control group was provided.

iv. The authors also did not include representative radiographs or magnetic resonance imaging (MRI) to demonstrate that enrolled participants met the inclusion/exclusion criteria.

v. In the methods, Fig. 1 is completely adapted from a previously published article [2]. However, the authors neither cited the original study nor stated that permission to use was obtained.

vi. Similarly, Fig. 2 is copied from a previously published article [3]. However, the authors have neither cited the original study nor stated that permission to use was obtained.

vii. In the methods, the authors stated that a commercial GFC kit was utilized. However, no description of the Central Drugs Standard Control Organization (CDSCO) approval status of the kit was provided. Similarly, no description of the CDSCO

Author's Photo Gallery



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approval status of the tubes/kits utilized for formulation of PRP was provided. Please note that any tube/kit used to collect and separate blood, intended for reintroduction for therapeutic purposes, is regulated as a low-to-moderate risk class B product by CDSCO.

viii. In the methods, the authors stated that a second injection was administered, but no description of the duration between the first and the second injection was stated. In addition, previously published studies have utilized three monthly injections of GFC [4]; however, in this study [1] and a recently published article [2], only two doses were administered. A discussion on how two versus three doses were selected will provide necessary insights into dosing of GFC; as of date, there are no studies comparing the efficacy of two versus three doses of GFC.

ix. In the methods, the authors stated that follow-up was carried out at 6th and 9th months. It would be best to clearly state follow-up time points for all outcome measures (some outcomes are recorded at 3, 6, and 9 months; and some at 9 months only).

x. In the results, characterization of PRP (absolute platelet count, platelet concentration compared to baseline levels, red blood cell, and leukocyte counts) was not provided. In addition, no description of the frequency and duration of PRP injections was described by the authors. Please note that there are studies which have shown that an absolute platelet count of at least 5 billion is needed to obtain positive outcomes [5]. Moreover, studies have shown that three doses of PRP should be used for management of knee OA [6, 7, 8]. It appears the authors used two doses; if so, this would be suboptimal dosing and a potential bias to demonstrate inferiority of PRP.

xi. Similarly, despite adding it as a limitation of the study, there is no characterization of the GFC (presence of various growth factors/cytokines and/or extracellular vesicles, and their quantification). This leads to the logical question: what is being injected into the participants of the study? In addition, what is the composition of the GFC tube used, i.e., what are the properties of the thixotropic gel in the tube? What kind of activators are present calcium chloride (CaCl_2) and/or thrombin, along with their concentration? If this information is proprietary, then the respective patent (provisional or non-provisional) information must be included.

xii. In Table 3, the authors showed COLL 2-1 levels prior to the first injection and at 9-month follow-up for all three groups and reported changes only within the GFC group to be statistically significant. However, the authors did not perform an analysis to demonstrate whether the value at baseline/before the first

injection in the GFC group (37.51 ± 18.52) was statistically similar to or different from the PRP (29.98 ± 19.45) and control (28.76 ± 9.71) groups. In addition, the authors also did not report whether the differences at the 9-month follow-up between the groups are statistically significant or not.

xiii. Similarly, in Table 4, the authors showed the Visual Analog Score from pre-injection to 9-month follow-up. However, the authors did not report whether the value before the first injection in the GFC group (5.70 ± 2.59) was statistically similar to or different from the PRP (6.07 ± 1.55) and control (6.12 ± 1.23) groups. Please note that the authors reported the P-value to be significant ($P < 0.05$) in all groups compared to the baseline, indicating significant pain reduction in all groups. Furthermore, the authors stated the efficacy of GFC to be superior to PRP and control groups, but no data were reported to demonstrate statistically significant superiority of GFC compared to PRP and control groups at 9-month follow-up. A similar assessment holds true for the Western Ontario and McMaster Universities (WOMAC) score.

xiv. The authors also did not include any representative radiographs or MRI for either group at 9-month follow-up. In addition, no assessment was done to demonstrate similarity in WORM score before the first injection between the groups for the medial femorotibial joint, lateral femorotibial joint (LFTJ), and patellofemoral joint. Moreover, no comparison of the WORM score at 9-month follow-up between the groups is reported. Furthermore, it is interesting that in the GFC group, for LFTJ, a difference of 1.06 between 9-month follow-up (46.28 ± 6.31) and baseline (45.22 ± 5.17) was reported to be statistically significant. However, a difference of 1.21 between 9-month follow-up (46.79 ± 6.62) and baseline (45.58 ± 5.37) was found to be not significant in the PRP group.

xv. In the discussion, the authors stated that their study provided insights into the safety of GFC compared to PRP. However, no safety data (adverse events or severe adverse events) for either group is reported in this manuscript.

In summary, we hope that the authors consider our comments as constructive feedback, and addressing the aforementioned observations will further improve the methodology and provide a more balanced interpretation of the results, while ensuring repeatability and reproducibility of the findings of this work.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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