

Letter to the Editor: Efficacy of Intra-articular Growth Factor Concentrate in Knee Osteoarthritis: A Randomized Controlled Trial

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Learning Point of the Article:

This letter to the editor highlights the limitations of the original study by Shah et al. titled, "Efficacy of Intra-articular growth factor concentrate (GFC) in Knee Osteoarthritis (OA): A randomized controlled trial".

Dear Editor,

We read with great interest the article published in the Journal of Orthopaedic Case Reports by Shah et al. [1], titled "Efficacy of Intra-articular growth factor concentrate (GFC) in Knee Osteoarthritis (OA): A randomized controlled trial," where authors evaluated the effectiveness of intra-articular GFC on pain reduction, functional outcomes, and disease progression in patients with moderate OA of the knee, through patient-reported outcome measures, biochemical markers, and advanced imaging. Based on our review of this manuscript, there are certain shortcomings we would like to underscore that were not addressed by the authors.

1. The authors stated that this is a randomized controlled trial. However, descriptions such as block size and blinding were omitted in the methodology section of this manuscript.
2. No baseline representative radiographs and magnetic resonance imaging (MRI) were included in the manuscript to demonstrate meeting of inclusion/exclusion criteria.
3. The authors stated that a specialized vacutainer was used to formulate GFC. However, no description regarding the manufacturer (name, city, and country) was provided. In

addition, no description of the Central Drugs Standard Control Organization (CDSCO) approval status of the specialized vacutainer was provided. Per CDSCO guidelines, any tube/kit used to collect and separate blood, followed by reintroduction of separated layer(s) into the participants for therapeutic purposes, is regulated as low-to-moderate risk class B device.

4. The manuscript lacked detailed methodology on how biochemical (through serum Coll2-1NO2) and WORMS (using MRI) analyses were performed.

5. Authors stated that two intra-articular injections of GFC or normal saline were administered 4 weeks apart. This is in contrast to previously published studies [2], where 3 monthly injections of GFC were administered. A discussion on how two versus three doses were selected will provide necessary insights into dosing of GFC; as to date, there are no studies comparing the efficacy of two versus three doses of GFC.

6. There is no characterization of the GFC (presence of various growth factors/cytokines and/or extracellular vesicles, and their quantification). Even though the authors stated it as a limitation of their study, this still leads to the logical question – what is being injected into the participants of the study? In addition, what is the

Author's Photo Gallery



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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, i.e., calcium chloride (CaCl₂) and/or thrombin along with their concentration? If this information is proprietary, then the respective patent (provisional or non-provisional) information must be included.

7. Citations for figures in the results section are incorrect. VAS score is shown in Fig. 5, but the authors cited Fig. 1 in the text. Similarly, errors exist for WOMAC score (should be Fig. 6), serum Coll2-1 (should be Fig. 7), and WORMS (should be Fig. 8).

8. Fig. 1, 2, 3, and 4 should have been cited in the methods section but are incorrectly cited in the results section.

9. In Figures 5, 6, 7, and 8, no error bars (to indicate standard deviation or standard error of mean) or marks (like * or #) were included to demonstrate statistical significance within and between the groups.

10. For VAS and WOMAC scores, the authors reported data at baseline (before 1st injection) and at 1-month (before 2nd injection) and 6- and 9-month follow-up. However, no comparison at various time points within the groups except at 9-month versus baseline was shown. Similarly, comparison between the groups at various time points was omitted.

In addition, authors did not highlight whether the difference in pain score at baseline between the groups (Group A, GFC: 6.48 ± 1.00 ; Group B, normal saline: 5.54 ± 1.25) was statistically significant or not.

Moreover, authors did not highlight whether the difference in WOMAC score at baseline between the groups (Group A, GFC: 62.58 ± 10.88 ; Group B, normal saline: 51.48 ± 10.56) was statistically significant or not.

11. Similar to the aforesaid point, authors did not perform an analysis to demonstrate whether the difference in serum Coll2-1 levels at baseline between the groups (Group A, GFC: 34.40 ± 36.62 ; Group B, normal saline: 21.93 ± 2.89) was statistically significant or not.

12. Authors also did not include any representative radiographs or MRI for either group at 9-month follow-up. These are essential as authors reported preservation of cartilage in the GFC group while further degradation in the saline group.

13. Authors in the results section stated, "Growth Factor Concentrations: Comparisons of growth factor levels (platelet-derived growth factor [PDGF], vascular endothelial growth

factor, fibroblast growth factor, insulin-like growth factor 1 [IGF-1], transforming growth factor beta [TGF- β]) between the groups at the time of assessment showed no statistically significant differences ($P > 0.05$ for all), indicating comparable baseline biochemical profiles (Fig. 5)." This is strange as how authors even managed to measure growth factors in the control group, i.e., normal saline. Moreover, Fig. 5 shows VAS scores, and there is no figure in the manuscript demonstrating the levels of growth factors in the two groups.

14. The authors stated in the discussion that, "Comparison with Ozcan et al. (2024): Our study supports the conclusion that growth factor-based therapies (like CGF or GFC) provide superior functional improvement compared to traditional HA or standard platelet-rich plasma (PRP)." In the current study, authors compared the efficacy of GFC to a non-active comparator, i.e., normal saline. How can this be extrapolated to conclude that GFC is superior to active comparators like PRP or viscosupplementation/hyaluronic acid (HA)?

15. The authors included a subsection on mechanism support in the discussion section attributing the success of GFC to the presence of growth factors, including PDGF, TGF- β , and IGF-1. However, the current manuscript lacks any qualitative or quantitative characterization of GFC to infer such results.

16. The authors added a concluding statement, "Structural Preservation: MRI evaluations using WORMS indicated not only the preservation of cartilage thickness but also signs of potential cartilage regeneration and decreased synovial thickening." However, no imaging or data are included in the manuscript demonstrating cartilage regeneration and reduced synovial thickening.

In summary, we anticipate that the authors will consider our remarks as constructive criticism and that addressing them will enhance the robustness of their manuscript, while ensuring repeatability and reproducibility of the findings of this manuscript.

Clinical Message

In this letter to the editor, we highlighted the shortcomings in the original study by Shah et al., which must be addressed to enhance robustness of the original manuscript and to ensure repeatability and reproducibility of the results. In the meantime, pending response to this letter, the conclusions of the original study should be interpreted with caution.

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



References

1. Shah S, Chincholi S, Saraf A, Chandak S, Phogaat M, Shah D. Efficacy of Intra-articular growth factor concentrate in knee osteoarthritis: A randomized controlled trial. J Orthop Case Rep 2026;16:528-35.

2. Gupta A, Maffulli N. Growth factor concentrate (GFC) for the management of osteoarthritis of the knee: A systematic review. Indian J Orthop 2024;58:829-34.

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