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Platelet Concentration Thresholds in PRP—The Need for Standardized Quantification and Dose-Response Modeling: Response

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Authors' Response:

Thank you for the opportunity to respond to the letter on our recent article "PRP Injections for the Treatment of Knee Osteoarthritis: The Improvement Is Clinically Significant and Influenced by Platelet Concentration. A Meta-analysis of Randomized Controlled Trials."[1] We appreciate the authors' insightful comments, and we are happy to address the issues posed. Specifically, the letter highlights 2 relevant aspects, the need for standardized platelet-rich plasma (PRP) characterization and the value of formal dose-response modeling, that can contribute to advancing the field and are aligned with the rationale and implications of our work.

As a premise, the authors of the letter focused on scrutinizing what was reported in our study as a secondary finding, which we already described as exploratory and useful to spark further discussion and direct field efforts. In fact, while demonstrating the overall superiority of PRP versus placebo for the treatment of knee osteoarthritis (OA), we investigated what may have driven those results. The amount of platelets injected turned out to be important, probably even more important than the presence of leukocytes, which has been the focus of so much attention in the last decade. Accordingly, we suggested refocusing attention on this aspect and working in this direction to improve the field.

Therefore, regarding the first point raised by the authors of the letter, we agree that heterogeneity in PRP preparation and reporting, including platelet quantification methods and platelet viability, represents a major methodological challenge. This variability pertains to a considerable part of the studies available in the PRP literature, with different counting technologies and unreported viability assessments representing a relevant concern for both numerical and functional platelet quantification. This heterogeneity is explicitly reflected in our discussion, where we underlined the variability of PRP products and called for more standardized preparation and reporting to enable meaningful comparisons. Despite the limitations intrinsic to the available literature, our analysis still represents a rigorous synthesis of the highest level evidence on intra-articular PRP injections for knee OA, with the inclusion of only randomized controlled trials and with outcomes interpreted through minimal clinically important difference thresholds to ensure not only the statistical but also, and most importantly, the clinical relevance of the results.

Within this framework, platelet concentration was explored as one of the few consistently extractable and clinically interpretable variables. The use of the 1,000,000 $\pm$ 20% platelets/μL cutoff was not intended as a simplistic or arbitrary dichotomy but as a pragmatic choice grounded in the existing regulatory and scientific background.[4] We acknowledge that the risk of any individual cutoff is to oversimplify a likely continuous biological gradient. For this reason, in our article, we framed platelet concentration as one important, but not exclusive, contributor within a multifactorial scenario, including several factors that could have an influence on the clinical efficacy of PRP for knee OA, besides treatment indications.[2,3,5-7] As such, our results should not be interpreted as a definitive quantification of a universal numerical threshold but as clinically oriented evidence that, within the constraints of currently reported data, platelet concentration matters. In this sense, the integration of Emax or similar nonlinear dose-response models in future investigations could build upon the findings of our meta-analysis, contributing to further exploring this important aspect of PRP preparation.

Overall, the points raised in the letter further reinforce one of our central messages: the rigorous and standardized characterization of PRP products is needed, and future well-designed studies should prioritize providing detailed evidence on platelet concentration and dose, alongside the other interacting factors that contribute to treatment effect, with the goal to move the field forward and ultimately maximize the benefits of intra-articular PRP for knee OA in clinical practice.

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