EDITORIAL COMMENTARY

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Editorial Commentary: Platelet-Rich Plasma Outlasts Hyaluronic Acid for Knee Osteoarthritis, but the Product, Not the Acronym, Is the Prescription

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Abstract: Intra-articular platelet-rich plasma (PRP) is among the most frequently administered orthobiologic treatments for symptomatic knee osteoarthritis. PRP is not a single intervention. Preparations differ in platelet concentration, total platelet dose, leukocyte and erythrocyte content, injection volume, activation method, and injection interval, such that 2 products sharing the acronym may constitute fundamentally different biologic treatments. The randomized literature supports a small symptomatic advantage of PRP over hyaluronic acid in mild-to-moderate disease. That advantage appears to emerge at 12 months rather than early and is best framed as symptom modification rather than cartilage regeneration. Whether any particular formulation drives the effect is far less certain. Reported associations between platelet concentration, leukocyte enrichment, activation status, and outcome are biologically plausible, yet they are typically carried by small and heavily overlapping sets of trials in which these variables cannot be separated from one another. Platelet concentration is furthermore not equivalent to platelet dose, which is the product of concentration and injection volume. Until absolute dose, leukocyte composition, activation, and final volume are consistently reported, comparisons of high versus low concentration remain uninterpretable. In our practice, PRP and hyaluronic acid are increasingly combined for a theoretical synergistic impact because viscosupplementation and biologic signaling address distinct components of the osteoarthritic joint. Standardized product characterization, dose-defined randomized trials, responder-based outcomes, and improved patient selection are warranted. The acronym is not the prescription; the product is.

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Intra-articular injection therapy remains among the most frequently employed nonoperative treatments for symptomatic knee osteoarthritis, and platelet-rich plasma (PRP) has become the most intensively studied of the available orthobiologics. PRP is not a single intervention. Preparations differ in platelet concentration, total platelet dose, leukocyte and erythrocyte content, injection volume, activation method, capture efficiency, and injection interval, such that 2 products sharing the acronym may constitute fundamentally different biologic treatments. Much of the available literature has treated that acronym as though it were a specification. The relevant clinical question has shifted accordingly: not whether PRP is effective, but which formulation, at what dose, on what schedule, and in which patient.

Zhong, Wang, Hu, Yuan, and Wang address this question in "Platelet-Rich Plasma Provides Small but Superior Short-term Pain Relief and Functional Improvement Compared With Hyaluronic Acid for the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-analysis."[1] The key finding of that analysis, which pooled 21 randomized controlled trials and 1790 patients, is that PRP yielded no advantage over hyaluronic acid (HA) in visual analog scale pain at 3 or 6 months but resulted in significantly greater improvement at 12 months (standardized mean difference [SMD] 0.76; 95% confidence

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interval, 0.14 to 1.38; $P = .016$). Western Ontario and McMaster Universities Osteoarthritis Index scores favored PRP at all time points (SMD 0.64, 0.33, and 0.70 at 3, 6, and 12 months), whereas International Knee Documentation Committee and Knee Injury and Osteoarthritis Outcome Score scores did not differ. Subgroup analyses favored high-concentration, leukocyte-rich, and activated preparations at 12 months, and metaregression identified platelet concentration as a positive predictor of effect (Western Ontario and McMaster Universities Osteoarthritis Index at 12 months, coefficient 1.456; $P = .004$).

Several aspects of this work deserve credit. The authors restricted their analysis to randomized evidence, reported direct between-group effect sizes rather than the within-arm change scores that have inflated much of this literature, and sought to establish which PRP preparation was appropriate rather than stopping at whether PRP was appropriate. The title itself is appropriately measured in describing the benefit as small, which is consistent with the effect sizes reported.

Three observations nonetheless temper our enthusiasm. First, the reported advantage is delayed rather than short-term. PRP conferred no analgesic benefit over HA at 3 or 6 months, and the 2 treatments separated only at 12 months. Whatever PRP offers relative to viscosupplementation appears to be durability rather than speed.

Second, and most important, the moderator analyses are collinear. The 12-month visual analog scale estimate rests on 7 comparisons from 6 trials with an I^2 of 89.1%. Within that small pool, the same trials populate every favorable subgroup. Su et al.[2] appears simultaneously in the high-concentration, leukocyte-rich, and activated strata; Duymus et al.[3] and one arm of Yaradilmis et al.[4] contribute to both the high-concentration and leukocyte-rich analyses; and the activated subgroup at 12 months comprises only 2 trials, both of which are also high-concentration. When 3 putative moderators are carried by an overlapping handful of studies, they are not 3 findings; they are 1 finding described in 3 ways. Study-level metaregression cannot resolve this, and we read the authors' cautious framing as a genuine limitation.

Third, concentration is not dose. Total platelet dose is the product of concentration and injection volume, and injection volumes across the included trials ranged from 2 to 10 mL. Trials classified together as high concentration may have delivered substantially different platelet loads, and trials separated by concentration category may have delivered comparable ones. The platelets, activation, white cells and dose, efficiency, purity, activation classifications and the Minimum Information for Studies Evaluating Biologics in Orthopaedics guidelines were developed precisely to prevent this ambiguity.[5-7] The dose-response relation is furthermore unlikely to be linear, although its direction remains contested. Simental-Mendia et al. reported greater clinical benefit with platelet fold increases below fourfold,[8] whereas Bensa et al. found high-platelet preparations to provide superior and more durable improvement.[9] Neither analysis could account for delivered volume. Work classifying trials by total delivered platelets rather than by concentration alone has reported better outcomes with greater dose,[10] and it can therefore be hypothesized that a proportion of the heterogeneity attributed here to concentration in fact reflects uncontrolled variation in delivered dose.

The leukocyte signal warrants the same caution. Those subgroups were compared indirectly against HA rather than against one another, and the supporting metaregression coefficient sits at the threshold of significance. In a double-blind randomized trial designed specifically to address this question, Di Martino et al. observed no clinically meaningful superiority of leukocyte-rich over leukocyte-poor PRP.[11] Leukocyte content should not be considered in isolation from platelet dose, osteoarthritis phenotype, degree of synovitis, and patient tolerance.

A broader point deserves emphasis. SMDs permit pooling across instruments, but no patient experiences an SMD. Patients experience whether they can climb stairs, sleep through the night, return to activity, or defer a further intervention. Whether an SMD of 0.33 at 6 months crosses a threshold that a patient would perceive is precisely what these analyses cannot establish. Reporting of minimal clinically important difference attainment, Patient Acceptable Symptom State, and durable improvement without additional treatment is warranted in future trials.

In the senior author's (B.J.C.) practice, we have moved away from treating PRP and HA as competitors and toward combining them. The rationale is mechanistic rather than pragmatic. HA contributes viscoelastic and boundary-lubricating properties that PRP does not, whereas PRP delivers growth factors and modulates the intra-articular inflammatory environment in ways that HA does not. These actions appear complementary rather than redundant, and framing the 2 agents as a head-to-head contest may be the wrong question altogether. Preliminary support exists within this dataset, as Fossati et al., one of the included trials, studied combined PRP and HA injection in a prospective, randomized, double-blind design.[12] Combination therapy has been shown to improve pain and function relative to HA alone,[13] although superiority over PRP alone has not been established.[14] We are careful not to overstate this. The present analysis did not evaluate combination therapy as a separate comparator and neither supports nor refutes our approach. But it does expose a conspicuous gap. A 3-arm trial comparing dose-defined PRP, HA, and their

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combination, with prespecified responder outcomes, would be among the more useful contributions this field could make in the next several years.

For appropriately selected patients with symptomatic mild-to-moderate knee osteoarthritis who have completed nonoperative treatment, PRP remains a viable treatment option, and this analysis strengthens that position. Patients should understand that improvement is gradual, that durability beyond 1 year remains undefined, and that PRP has not been established as a cartilage-regenerative treatment. It does not replace weight management, exercise therapy, correction of substantial malalignment or instability, or arthroplasty in advanced disease. Current consensus statements reach comparable conclusions while conceding that formulation-specific recommendations cannot yet be made.[15,16]

Zhong et al. add meaningful weight to the conclusion that PRP provides more durable symptomatic relief than HA through 12 months.[1] Yet, their data neither establish that high-concentration, leukocyte-rich, activated PRP is universally superior nor identify an optimal protocol, and defining the product, the dose, and the patient remains the unmet need in this field. The acronym is not the prescription; the product is.

A more fundamental limitation is inherent to systematic review and meta-analysis itself: no synthesis method can produce evidence more homogeneous than the literature it draws upon. The 21 included trials here span 13 years of evolving PRP technology, 10 countries with differing standards of care, and osteoarthritis severities ranging from Kellgren-Lawrence grade I to IV—variability that persists in the pooled estimate no matter how carefully the synthesis is performed. I^2 and metaregression can quantify this variation, but they cannot resolve it, which is why the confidence intervals here remain wide despite careful methodology. Initiatives such as the Biologics Association Registry and Biorepository, a multicenter collaboration collecting standardized product and patient-level data prospectively, represent one attempt to overcome many of the limitations of the Zhong et al. article in an effort to generate literature less heterogeneous from the outset. The importance of gaining real-world experience while quantifying a patient's baseline hematologic and biomarker parameters in addition to characterizing the injections themselves is critical to gaining an accurate understanding of the benefits of these therapeutic agents. Without this level of rigor, firm evidence-based conclusions will remain elusive.

DISCLOSURES

The author (B.J.C.) declares the following financial interests/personal relationships which may be considered as potential competing interests: B.J.C. reports grants or contracts: Arthrex and Medipost; royalties or licenses: Arthrex, Enovis, and Elsevier; consulting fees: Arthrex, Smith & Nephew, Regentis, Pacira, Ossio, Enovis, Hippos, Kinamed, Medipost, Vericel, ActiveImplant, JRF, Brixton, and EpiBone; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events: Arthrex, Ossio, Enovis, Medipost, and Vericel; stock or stock options: Regentis, Ossio, Hippos, Patient IQ, Kaliber, Kinamed, StreamMD, Theracell/Tetrous, Band Grip, Brixton, EpiBone, and Agyl. The other authors (J.A., M.T.K., L.R.F., A.S., K.C.) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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