Need for Proper Classification of PRP: Letter to the Editor

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Dear Editor:

It was with great interest that we reviewed the article by Cole et al[3] published in the *American Journal of Sports Medicine*. More than a decade has passed since the initial use of platelet-rich plasma (PRP) for orthopaedic conditions, and controversies continue as to whether this treatment is effective for various conditions including chronic tendinopathy, ligament injuries, and articular cartilage lesions. As noted in the literature, a great deal of this controversy is related to the lack of standardization of what we refer to as "PRP."[9,10] As the science of PRP evolves, it has become apparent that not all PRP processing systems yield the same parameters, and final PRP injectates vary greatly.[1,4,8] Due to these variations in PRP, terminology and classification have become imperative, and the most updated classification system has attempted to quantify PRP and determine appropriate dosing to improve objective outcome measures.[10] From a biological standpoint, the characterization of the presence of cells (such as leukocytes) is a critical step, but many other parameters should be considered, such as the rate and quantity of platelet collection, the rate and quantity of leukocyte collection, and detailed composition of the cells during collection and centrifugation. The activation of the cell content during or after centrifugation is also important for the biological properties of these products.[10] Other technical parameters should be considered as well, because they directly affect the possibility of using these techniques in daily clinical practice: These parameters include the size of the centrifuge; the duration, cost, and ergonomic properties of the preparation procedure; the final volume of product; and its form (liquid, light gel, or solid gel material).[10]

Although the study by Cole et al provides valuable data on PRP, the study fails to quantify the type of PRP used through any other classification system.[8,10] The article fails to appropriately describe the dose of PRP provided (ie, the actual platelet count), which is a major flaw of the study. According to the data provided in the article, the platelet concentration is less than 2 times the baseline concentration of platelets in all the subjects injected. Given the normal range of platelet concentration in the average population of 100,000 to 400,000/μL, the subjects in this study would have received platelet concentrations of anywhere from 200,000 to 800,000/μL. This would be considered a low platelet concentration for the treatment of primary knee osteoarthritis given that other studies have demonstrated the efficacy of PRP at concentrations greater than 5 times the baseline.[2,6,7,11]

Another parameter that adds to the variability of PRP is the spin time. Cole et al chose a spin time of 5 minutes, which is less than the time supported by current practice and literature.[5,6,11,12] The authors provide excellent background on the hyaluronic acid dosing profile but do not provide a proper dosing profile for the PRP arm; the novice reader looking at the title and conclusions of the study would thus be misled. The authors did not clarify whether their 3-mL blood draw was made through the same venous access as the 10-mL port for PRP preparation, thus not accurately accounting for platelet discrepancy. The report of the 2015 AOSSM Biologics Think Tank outlined that while PRP holds promise, 2 particular challenges must be met in order to advance the science: characterizing active elements in PRP injectate and finding the appropriate dosing regimen.[13] The cytokine profile chosen by Cole et al was novel compared with profiles reported in the current PRP literature; however, only 2 of 10 catabolic parameters showed significance at one time point, and the paper did not disclose the variability in analysis of 2 mL of synovial sample. A wider panel of anabolic chemokines would have added valuable information in the context of anabolic-catabolic ratio.

The study by Cole et al adds to the growing body of evidence regarding the safety profile of PRP. The paper highlights that this particular PRP product failed to show significance in the primary outcome (ie, Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain scale); however, multiple study endpoints demonstrated statistically significant differences and showed superiority of even this low-dose PRP product compared with hyaluronic acid, including reductions in visual analog scale (VAS) pain score and International Knee Documentation Committee (IKDC) knee evaluation scores at 24 and 52 weeks.

Like several other studies examining PRP, the study by Cole et al is a prospective, double-blind, randomized controlled trial whose design appears to be at the highest level of science; however, the actual PRP product lacks an up-to-date characterization. Thus, this article fails to advance the science regarding the PRP product used, its effect on osteoarthritis compared with hyaluronic acid, and its effect on various important synovial biochemical constituents found in patients who have osteoarthritis. We encourage the editors of *AJSM* and other journals of high scientific quality to require strict characterization of the PRP content prior to acceptance of future articles on this topic. This will greatly assist readers in properly assessing the scientific evidence of this treatment.

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Need for Proper Classification of PRP: Response

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Authors' Response:

We would like to thank Drs Malanga and Jayaram for their thoughtful questions related to our recent *AJSM* publication, "Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-Articular Biology for the Treatment of Knee Osteoarthritis."[6] By way of this response, we hope to address their concerns.

As Drs Malanga and Jayaram point out in their letter, many factors should be considered when evaluating a platelet-rich plasma (PRP) system, especially in the context of clinical research. We chose a leukocyte-poor, single-spin PRP system (ACP; Arthrex) that is widely known and commercially available.

Recent literature indicates that leukocyte-poor, single-spin PRP reduces pain and increases function as an intra-articular injection for osteoarthritis (OA) of the knee.[1,8] Several studies have shown PRP to be superior to hyaluronic acid (HA) for the treatment of OA, particularly in young individuals with mild to moderate disease.[5,8] In addition, our group's in vitro work corroborates that leukocyte-poor, single-spin PRP has promising anti-inflammatory and anti-catabolic effects on chondrocytes.[3,13,14] Our decision to pursue our double-blind, randomized controlled trial between HA and PRP was based on this evidence.

In our study, we quantified the fold change in platelets and all cellular components by performing a complete blood cell count on an aliquot of blood and resultant PRP from every patient in the study. The content of anabolic and catabolic cytokines in this particular form of PRP has been well characterized in previous studies, and such characterization was not repeated in our clinical study.[2,7,11] As a practical matter, all PRP was obtained per the manufacturer's specification. As Drs Malanga and Jayaram have pointed out, the increase in platelets was less than 2-fold in some cases, which brings into discussion how the ratio of platelets to white blood cells may be more relevant than the absolute fold increase in platelets.

We agree that numerous biomarkers could be investigated in an OA treatment study. We focused on tumor necrosis factor α, interleukin 1, interleukin 6, and interleukin 8 because their effects on the intra-articular inflammatory milieu of the knee have been well documented by our group and others.[4,9,10,12,14]

Related to Drs Malanga and Jayaram's comments on the characterization of PRP, we documented and reported what we found to be the necessary information based on previous literature without complicating this data-intense study. As indicated, we decided to characterize our PRP by the presence of leukocytes, the ratio of platelets to peripheral blood, the number of spin cycles completed, and the use of anticoagulants or additives, because, at the time of study design, these were the variables of interest in the literature.

The ACP system makes recommendations on relative centrifugal force, spin time, volume of peripheral blood collection, and volume of PRP administration. To design a clinically reproducible study, we remained within the confines of these recommended parameters. Of note, during the design and execution of this study, we found the blinding process, administration of PRP, and collection of synovial samples within the confines of a busy clinic to be the most challenging aspects of the study for our group. We thus spent significant effort documenting these methods in the hope that others studying the effects of PRP may benefit from our experimental design.

Finally, as pertains to the AOSSM Biologics Think Tank on articular cartilage, our study was designed and executed prior to this seminal publication. We, however, are happy to report corroborating conclusions regarding the efficacy of PRP as a safe agent with anti-inflammatory effects for the treatment of OA. In addition, we add to

the science in the publication's proposed areas of need: namely, improving the characterization of active elements and further standardizing dosing by using an easily reproducible and available method of administration.[15]

We again thank Drs Malanga and Jayaram for their insightful and in-depth commentary on our most recent publication, and we look forward to continued work in the development of safe and effective treatments for our patients who have OA.

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