Platelet-rich Plasma in Orthopaedic Applications: Evidence-based Recommendations for Treatment

To the Editor: This letter is a response to the article "Platelet-rich Plasma in Orthopaedic Applications: Evidence-based Recommendations for Treatment" by Wellington K. Hsu et al.[1] Their review, analysis, and subsequent recommendations concerning the application of autologous platelet-rich plasma (PRP) therapies on orthopaedic conditions were exquisitely developed and carefully built. Notwithstanding their general insight and the logical consistency of their recommendations, there are nevertheless several issues that we believe require more thorough reflection and a more perspicacious analysis that would invite, rather than close off, further use of this highly relevant treatment.

Based on a rather fragmentary definition of PRP, the authors take into account only a general description of platelets as biologic agents within PRPs, leaving out other significant plasmatic biomolecules such as human growth factor (HGF), insulin-like growth factor (IGF), and fibrinogen, which all play a key role in the repair process of soft tissues.[2-5] As a pleiotropic blood protein that regulates coagulation, inflammation, and, hence, tissue repair, fibrinogen engenders a transient biologic fibrin scaffold when polymerized. This three-dimensional fibrin–extracellular matrix-like malleable structure assembles in situ after the injection of a liquid-to-gel transition product obtained from autologous platelet-rich plasma, which has been previously activated.[6] By literally bridging the gap in damaged tissue, the fibrin scaffold, which is either infiltrated in its liquid formulation or placed as a thin gel membrane, fulfills both the structural and biologic tissue-repair functions.[5,7,8] The functionality of the fibrin scaffold is grounded in the following known elements:

1. It contains binding sites for cell adhesion and proteins such as thrombospondin-1, α-1-antitrypsin fibronectin, acute-phase proteins, or proteins related to lipid metabolisms.[9-11]
2. The scaffold serves as a highway for mechanical energy to transit from the environment to the cell, thereby bridging cell-to-cell tissue transition, promoting multicellular assembly, and providing mechanical support and plastic-elastic stiffness, which has a drastic impact on the fates of diverse cell types such as muscle stem cells,[12,13] and endowing tissues with a suitable mechanical and chemical microenvironment for biologic restoration.[14]
3. By heparin-binding domains, the scaffold may sequester growth factors such as platelet-derived growth factor, fibroblast growth factor, HGF, brain-derived neurotrophic factor, and vascular endothelial growth factor[4,10,15] and gradually release them later, exerting a synergistic action on tissue repair.[4,15]

Because this dynamic sponge-like fibrin-matrix scaffold is autologous, bioresorbable, biocompatible, and, in some PRPs, free of leukocytes and red cells, fibrin scaffolds may well be

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considered the best tailored among all the tissue-engineering materials.[10,16,17]

A second contention concerns the application of PRP on osteoarthritis (OA) of the knee. There are already two published randomized clinical trials evaluating plasma rich in growth factors (PRGF) versus hyaluronic acid in the treatment of symptomatic knee osteoarthritis (OA).[18,19] In both studies, PRGF showed superior beneficial effects compared with hyaluronic acid on reducing knee pain, stiffness, and physical function in patients with knee OA in both the short and long term (6 and 12 months, respectively).

A third critical point concerns the remark referring to the systemic effects of intratendinous infiltration of PRP[20] and the possible beneficial role such effects might play in tissue healing, as Hsu et al[1] mention. Wasterlain et al[20] presume a cause-and-effect relationship between the intratendinous infiltration of PRP and the increases of circulating levels of growth factors with performance-enhancing potential. This presumption is grounded in their attribution of an activation of the human growth hormone (hGH)–IGF-1 axis as the effective biologic pathway. We should not forget, however, that participants underwent five blood withdrawals in the first 24 hours of the study, which overlapped with PRP infiltration. This medical intervention could have strongly influenced the hGH–IGF-1 activity and would therefore point to a quite different biologic interpretation of cause-and-effect.[21]

Orthopaedic surgery is going through a serious paradigm shift: instead of simply removing and replacing damaged tissues with artificial devices and materials, autologous platelet-rich plasma therapies in orthopaedics are aimed at triggering and enhancing the natural in vivo tissue morphogenesis and regenerative capacity of damaged tissue.[22] Nevertheless, aside from the pitfalls that arise from differences in some key properties of these "platelet rich plasmas," including the platelet concentration and the type of activation of them, as well as the presence or absence of proinflammatory leukocytes among others, it has become commonplace to infiltrate PRPs in the treatment of musculoskeletal injuries as a kind of scatter shot instead of adopting a well-thought-out and specifically crafted biologic approach that must take into account the complex biologic processes, such as the immune system, hemostasis and clotting, and fibrogenesis, that are aimed at self-maintenance.[23]

As the body of knowledge about the regenerative effects of PRPs grows, expansion of its applications and new challenges arise. We are aware that we must continue optimizing the procedure at the same time that we continue to draw on its healing power. But the time has come when we should no longer compare the biologic and therapeutic efficacy of very distinct products in musculoskeletal orthopaedic surgery by lumping all autologous platelet- and plasma-derived products together. In the field of PRP products, we must not take oranges for apples simply because they are both fruit.[24]

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The Author Replies: Thank you for your comments regarding our most recent publication on PRP.[1] As you have pointed out, we attempted to perform a concise review of the mechanism of action and the accompanying clinical literature regarding its application to many different orthopaedic conditions. As a result of the restrictions of space for such a large topic, there were certainly areas of interest that we were not able to fully address.

You have highlighted an area that a different type of publication would address in greater detail: the many components of PRP that may exhibit a clinical effect when used in patients. Although we focused on the hundreds of growth factors and the importance of cell type in the healing process, there are certainly other components, such as fibrinogen, that may also have an effect. We certainly recognize the breadth of literature that supports the role of a fibrin scaffold that can offer a mechanical stability for tissue to regenerate. However, its exact role in the clinical results of tissue healing is difficult to discern because there have been no comparative studies isolating this component of PRP (such as that for leukocytes). In any case, we welcome the notion for the potential of other components of PRP that may have a critical role in regenerative tissue processes.

To address your contention regarding the application of PRP on OA of the knee, we would agree that there are other publications that were not formally reviewed in our paper, as was the case with other conditions. The discussion of the treatment of OA with PRP was meant to suggest that, although results were favorable for PRP in comparison with hyaluronic acid in many studies, there were other level I studies that concluded otherwise (eg, Filardo et al[25]). For this reason, and the fact that space is limited for a review of this nature, all of the positive studies in favor of PRP for treatment of OA were not individually reviewed in this section.

The third point regarding the systemic effects of intratendinous infiltration of PRP is a valid one. It is true that multiple blood withdrawals can certainly affect relative systemic cytokine levels, and this is a well-established criticism with any study attempting to show these differences.

The comment on Wasterlain et al[20] was meant to indicate that growth factors can be affected by the presence of PRP, not to draw conclusions on the relative concentrations of such factors. No cause-and-effect relationship was intended with this citation of this study.

We agree that PRPs have been subject to "scatter shot" in terms of the applications to musculoskeletal injuries. We also concluded in this review that "lumping all autologous platelet- and plasma-derived products together" is counterproductive and prevents research from determining the cost-effective applications of such a technology. It is our hope that our review in *JAAOS* may provide an impetus for future projects to answer these important questions. We appreciate your interest.

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