Editorial Commentary: Platelet-Rich Plasma or Profit-Rich Placebo: Variability of Composition, Concentration, Preparation, and Many Other Yet-Unknown Factors Determine Effectiveness

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Abstract: Platelet-rich plasma (PRP) frequently is used in orthopaedics, and its application is supported by clinical studies for a variety of conditions. For knee osteoarthritis, it is more effective than hyaluronic acid, providing significant better pain relief and functional improvement. However, different compositions of PRP, absolute platelet counts, and many other physiological and demographic variables will influence the effectiveness. Variability of the composition of the ingredients of PRP surely has a substantial influence on outcome.

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Platelet-rich plasma (PRP) works for knee osteoarthritis. A large volume of studies supports intra-articular PRP injections, which provide significant functional improvement and reduction of pain-related symptoms.[1] In fact Lin et al.[2] recently have performed a double-blind randomized study and demonstrated that leucocyte-poor platelet-rich plasma (LP-PRP) is superior to hyaluronic acid and saline injections. Lin et al.[2] confirmed the findings of a meta-analysis by Riboh et al.,[3] who compared LP-PRP with leucocyte-rich platelet-rich plasma (LR-PRP) and concluded that LP-PRP had significantly increased Western Ontario and McMaster Universities Osteoarthritis Index scores when compared with LR-PRP, hyaluronic acid, or placebo. A possible explanation is that LP-PRP increases interleukin (IL)-4 and IL-10, which are anti-inflammatory mediators.[4,5] In contrast LR-PRP contains inflammatory mediators such as tumor necrosis factor-α, interferon-γ, and IL-1b.[1,4,5]

There is no doubt that different forms of platelet concentrations, composition, different preparations, absolute platelet counts, sites of delivery, retention and duration of platelet concentrations, the rate of mediator release, and the frequency of applications determine effectiveness and action.[6] Optimizing PRP also depends on other individual factors, such as age, sex, exercise level, and genotype.[6]

In their article "Variability of the Composition of Growth Factors and Cytokines in Platelet-Rich Plasma From Patients With Knee Osteoarthritis," Ha, Park, Jang, Kim, Kim, and Park[7] have investigated variability in the composition of growth factors and cytokines in PRP in patients with knee osteoarthritis. The main finding of their study was that there was a wide variation of growth factors and cytokines. The greatest variation was observed for basic fibroblast growth factor, IL-1β, metalloproteinase-13, and platelet-derived growth factor-BB.[7] This is a great attempt to shine light on one of the so many unknown factors with regards to PRP.

However, there are some potential flaws that may not allow the generalization of their findings. The working definition of PRP proposes a concentrated platelet count of $\geq$1,000,000/mL.[8,9] The mean count reported by Ha et al.[7] just falls short of this definition, and the range strongly suggests wide variation here, too. The question clearly is as to whether the variation of composition is not a direct result of the variation in platelet count.

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What do I mean by that? If the platelet counts were below the accepted level defining PRP as PRP, the composition of the PRP reported by Ha et al.[7] may not be accurate and hence their results may not be valid. Furthermore, the variations in age, sex, severity of osteoarthritis, and body mass index have introduced more bias, substantially reducing both internal and external validity.

The first report using PRP in "orthopaedics" was by Marx et al.[8] in 1998. The authors showed that the addition of PRP to autologous bone graft resulted in significant increases in bone maturity.[8] Since then, more than 20 years have passed, and we have used PRP for multiple pathologies with varying success. However, we still have not produced an acceptable standard for these applications, let alone proven their efficacy and benefit. The OrthoInfo website from the American Academy of Orthopaedic Surgeons states that there are still lingering questions, for example, about what exactly is PRP, how does it work, what conditions are being treated with PRP, and is PRP treatment effective.[10] The first question has been answered by now, the second question still needs to be answered. The answer to the third question is easy: we are exploring and treating just about anything. And, as long as we adhere to ethics[11] and use a systematic methodological approach signed off by an ethics committee, this is called scientific research. For the fourth question, evidence certainly suggests that it is effective for several orthopaedic problems. What we urgently need at this stage is to standardize PRP-preparation systems, establish the optimal concentration of PRP for various indications, the optimal time for injection, the effect of anesthetic (local or general) on PRP quality and composition, whether serial injections are efficacious, and what the interval between injections should be. At the end of the day, we need to know the dose−response relationship for PRP.

The study by Ha et al.[7] is a step in the right direction and despite numerous limitations provides important information: variation must be taken into consideration when investigating the clinical applications, efficacy, and indications for PRP. Taking the current evidence into consideration, it seems that PRP is more than profit-rich placebo, but the proof is in the pudding.

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