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LETTER TO THE EDITOR

# The type of platelet-rich plasma may influence the safety of the approach

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In their interesting research article, Filardo and colleagues [4] compare for the first time the safety and efficacy of two different approaches for obtaining platelet-rich plasma (PRP) in the treatment of knee cartilage degenerative lesions and osteoarthritis. In particular, authors evaluate two platelet-rich plasma products prepared following either a single (PRGF-Endoret technology [1]) or double spinning approach (home-made leuco-PRP). Results showed that both treatment groups presented a statistically significant improvement in all the scores evaluated at all follow-up times. However, interestingly, significantly more adverse events (involving pain and swelling) were detected in the group treated with the PRP prepared with the double spinning approach.

This prospective study brings some light on how different PRPs, which vary in preparation process and differ in platelet and leucocyte concentration, as well as growth factor content, may show different safety profiles. Assuming the increasing jungle of terms currently available for defining PRP products, it is absolutely necessary to distinguish each particular technology. The concept of PRP is a general and widely accepted term but it must be followed by the type of particular system that has been chosen, as the latter may have important clinical implications.

We congratulate the authors of the present article, which deals with these concerns. Scientific and medical literature lacks high evidence papers that compare the safety and efficacy of PRPs for the different clinical applications.

There are, however, some few points that we would like to clarify and discuss with the authors:

1. We have some doubts about how the PRGF-Endoret system has been prepared and used. According to the manufacturer protocol, the platelet-rich plasma fraction, that is, the volume of plasma above the leucocyte layer should be used for tissue regeneration and pain treatment. After reading the materials and methods section, it is not clear for us if authors have used the whole plasma column or just the enriched plasma fraction. This may have some clinical implications, as in our experience, the final platelet concentration of PRGF-Endoret is higher ($\geq$ 2-fold compared with blood) that the 1.5× reported.
2. Another interesting issue is that the final number of leucocytes obtained in the double spinning approach seems to be lower than some of the commercialized products, in which leucocytes are enriched even 3× to 5× compared with whole blood [3]. In our opinion, this may also have clinical implications as we hypothesized that in these commercialized leuco-PRP systems, the biosafety concerns may be more pronounced. In particular, leucocyte presence in leuco-PRP can be shown in the increased number of side effects (pain and swelling) found in the PRP group compared with the PRGF-Endoret group. The injection of leucocytes into the joint cavity may cause inflammation, albeit self-limiting, and pain. This would be completely unnecessary if you use a leucocyte-free PRP as PRGF-Endoret technology.
3. On the other hand, it would be recommended that authors specify centrifugation conditions in terms of

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'relative centrifugal force', since the value of 'g' and not the rpm is needed, in order to compare and reproduce the PRP protocol.

4. The dosage of both PRPs is also different from what others have reported. In our experience, injections of PRGF-Endoret were administered weekly instead of every 3 weeks, and the total volume of PRGF-Endoret in each infiltration was 8 mL [6].
5. Last but not least, we also have serious concerns about the freezing–thawing protocol. Platelets exposed to low temperatures lead to membrane alterations [8] and consequent damage. This could cause the content of bioactive molecules to be reduced, since it has been observed that protein synthesis occurs [9] even during platelet activation [7]. Thus, it has been shown that platelets synthesize certain proteins de novo from its mRNA [5], both in resting state (constitutively) and when activated by different stimuli [11]. Among these latter ones, it can be highlighted that Bcl-3 [10] and PAI-1 [2], respectively, involved in clot retraction and stabilization. By this way, extensive in vitro and in vivo research should be conducted to clearly justify the use of this protocol in patients.

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