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LETTERS TO THE EDITOR

The importance of understanding what is platelet-rich growth factor (PRGF) and what is not

To the Editor: We have read the case report by Mallo et al⁴ “Exuberant synovitis after subacromial decompression and platelet rich growth factor (PRGF) injection” with interest. The authors described a potential side effect associated with the use of platelet-rich plasma (PRP) in one patient.

In our modest opinion, however, there are significant inaccuracies and cautions in the article that may lead to wrong or false conclusions about the real therapeutic potential of PRGF. Initially, it is absolutely necessary to define PRGF correctly. In recent years, the lack of a suitable standardization and definition for platelet-rich plasma (PRP) products has provoked the appearance of a wide range of biologic preparations and a jungle of terms easily confused by mistakenly being used interchangeably. In general, the term “PRP” is used to identify all of these preparations, even if they are prepared using different protocols, differ from a qualitative and quantitative point of view, and show different biologic effects.

In 1999 we reported for the first time in the literature the concept of PRGF technology.¹ The term “PRGF” identifies exclusively 100% autologous and biocompatible formulations elaborated by a one-step centrifugation process and using sodium citrate as the anticoagulant and calcium chloride as the activator.^{2,3} PRGF has a moderated platelet concentration and does not contain leukocytes, with the aim of avoiding the proinflammatory effects of the proteases and acid hydrolases contained in white blood cells.

In theory, authors have used the autologous conditioned plasma double-syringe (ACP-DS) system from Arthrex, which is absolutely different from the original PRGF technology pioneered by BTI Biotechnology Institute. In fact, the process by which leukocyte content is separated from the plasma is easier and much more reproducible in the original PRGF system compared with ACP-DS system. Therefore, authors should have avoided the term PRGF that defines a totally different product and philosophy.

In addition, the use of PRP as described by the authors in this approach is somehow controversial. What is the indication of using PRP in this patient when tendon rupture is not present? What is the rationale of using a single shot of growth factors in the treatment of a chronic pathology? The idea of considering

the PRP as a magic bullet for treating a chronic disease is far from being optimal. Our protocol for PRP application contrasts with the present protocol and so does the clinical efficacy. In our hands, patients with tendon injuries who received 3 consecutive injections of PRGF technology (infiltrating 12 mL instead of 3 mL) recovered their range of motion earlier and took less time to take up gentle running and training.⁵

Last but not least, a complete histologic analysis of the inflamed tissue is missing. The latter will help to identify the origin of the synovitis and the potential cause and effect of the PRP. Furthermore, it is unlikely that such a side effect may have been provoked by a single shot of growth factors administered 9 months earlier. In fact, the biologic effects of these types of formulations are mainly observed some days or weeks after treatment. The authors seem to be reasonably confused about this point and even about the type of PRP they have administered. As they suggested, “... a hypertrophic process, perhaps stimulated by the delivery of the PRGF. The direct effect of high growth factor concentrations and leukocytes present in the PRGF...” This should be clarified, because the ACP-DS system should not contain leukocytes. Did the authors add the buffy coat to the PRP?

In summary, results from this clinical case report create confusion and do not provide scientific evidence of clear cause-effect relationship. Well-characterized PRP products together with standardized and rigorously defined protocols for application in patients are critical issues in medical practice. Only in these circumstances may science be the foundation of clinical knowledge and practice.

Disclaimer

The authors are familiar with PRGF technology, the original technology powered by BTI Biotechnology, Vitoria, Spain, and are fully involved in the “Foundation Eduardo Anitua” a scientific foundation that investigates the therapeutic potential of PRGF in many different areas of medicine.

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PRP or PRGF? Standardized definitions are needed

In reply: Our recent case report entitled "Exuberant synovitis after subacromial decompression and platelet rich growth factor (PRGF) injection"¹ has drawn a timely critique in a recent letter to the editor. The authors of this critique bring up several excellent points that merit further exploration. We greatly appreciate this opportunity to respond and to further stimulate interest and intellectual discussion of PRGF. In fact, this is precisely why we chose to share this case report with the orthopaedic community and likely why such a respected journal such as the *Journal of Shoulder and Elbow Surgery* deemed it worthy for publication.

First, we fully agree with the respondent's statement that it is absolutely necessary to define PRGF correctly and that in recent years there has been a "lack of suitable standardization and definition for PRP products." The respondent defines PRGF as something identifying "exclusively 100% autologous and biocompatible formulations elaborated by a one-step centrifugation process, using sodium citrate and calcium chloride as anticoagulant and activator respective." The letter to the editor goes on to suggest that "PRGF defines a totally different product and philosophy" than that of the Autologous Conditioned Plasma Double Syringe system (ACP-DS; Arthrex, Naples, FL) used in this report, and therefore we should have avoided the term "PRGF."

Interestingly, our review of the literature led us to a similar thought, and our original submitted manuscript described the ACP-DS product as a "PRP" rather than a "PRGF." Our original manuscript was returned with suggestions from 2 different *Journal* reviewers suggesting that we should change the term used in our report from "PRP" to "PRGF." Thus, clearly, there are differences of opinion regarding the proper nomenclature, and universal, standardized definitions of specific products are needed as investigations move forward.

A second point in the critique and perhaps the most important is that our described use of PRP/PRGF (depending on your definition) is controversial. This is perhaps the most important statement made and absolutely the reason why we submitted this case report for publication. The use of the PRP or PRGF as an adjunct to subacromial decompression or as a "magic bullet" for treating chronic disease has not been substantiated. The treatment described in our case report was not performed at our institution, and we absolutely do not advocate it. However, there are some orthopaedic surgeons using PRP or PRGF in this manner, and perhaps one reason is because they believe it is benign. In other words, a philosophy of "maybe it will help, but it can't hurt" guides their judgment.

To our knowledge, there are few if any reports in the literature describing adverse outcomes or complications with either PRP or PRGF formulations. We believe that our case report offers a word of caution for those who use either PRGF or PRP for anything other than indications that have been substantiated in the literature. We hope that our case report will stimulate further investigation into both the benefits and adverse effects of treatments.

In summary, we believe that our case report brings some important points to light. First, there appears to be little consensus on nomenclature when discussing the various preparations on the market, and as such, it makes investigation and study of these treatments difficult. Second, we recognize that although use of PRP or PRGF for some pathology is promising, we caution that these treatments are not benign "magic bullets" and should only be used in accordance with evidence-based medicine.

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Reference

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