Letter to the Editor

Platelet-rich plasma therapies: Building the path to evidence **Keywords:**

Platelet-rich plasma
Regenerative medicine
PRP
PRGF

Dear Editor,

We have read with great interest the recent article published in the *Journal of Orthopaedics* by Yilmaz et al.¹ and entitled “*Is there a treatment protocol in which platelet-rich plasma is effective?*” The aim of the authors of this article was to shed light on potential tips in order to achieve both a standard and a effective platelet-rich plasma (PRP). There are, however, some points that we would like to clarify and discuss with the authors.

It draws our attention that the authors have only selected ten scientific articles of PRPs applications in the field of traumatology and orthopedic surgery. We believe that further studies should be included. For example, in the treatment of knee osteoarthritis, several studies have not been taken into account which we believe that met their inclusion criteria and that also show promising results in the treatment of this condition.² Furthermore, these studies apply *plasma rich in growth factors* (PRGF), a type o leukocyte-free PRP that have exhaustively characterized both at molecular and at cellular level. On the other hand, we agree with the authors that more research is required in order to perform dose-response clinical trials with different PRP formulations, thus modifying the concentration of both platelets and leukocytes. In this connection, we would propose the elegant study by Boswell et al.³ as an example to help clarify this issue.

Regarding this therapy mechanisms of action, the authors should consider that the PRP is a complex combination of hundreds of proteins and other bioactive molecules and to unravel the exact molecular mechanism for each disease is a complex challenge. While there have been several attempts, it is true that combined efforts are needed to define the exact mechanism of action, which would have a direct translation in the improvement of treatments.

Another issue we consider relevant is the release of growth factors in PRP. The authors¹ indicate that “Recent well-proved studies have reported that half-life of growth factors is maximum 2 min” and even further “were applied after that period, bioactivity decreased and even vanished”. We would like to respectfully

discuss that, since in our and other’s experience, these data are not accurate. For example, we have observed in *in vitro* assays that there is a clear release of several growth factors for at least 3 days, and that the PRP matrices (without leukocytes) were stable for at least 8 incubation days.⁴ It is true that after platelets’ activation, there is a large initial release of growth factors (burst), but many of them are retained in the fibrin scaffold and released more gradually.

We commend the purpose of the authors of clarifying whether there are prospective suggestions to achieve a standard and effective PRP, and we encourage them to continue working in that direction because it is of great value for the benefit of our patients. Finally, we want to emphasize that our research group tries to deeply characterize both the product (PRGF) and the optimal dose to be used. We would also like to point out, as an example of this characterization, the *in vitro* study we have recently conducted in which several key parameters are described, such as hematology values (platelets, erythrocytes and leukocytes), platelet activation, growth factor content, coagulation and clot retraction time, and biological response among others.⁵

Conflicts of interest

The authors declare the following competing financial interests: E.A. is the Scientific Director of and R.P., and G.O. are scientists at BTI Biotechnology Institute, a dental implant company that investigates in the fields of oral implantology and PRGF-Endoret technology.

References

1. Yilmaz I, Akkaya S, Isyar M, et al. Is there a treatment protocol in which platelet-rich plasma is effective? *J Orthop*. 2016;13:316–321.
2. Anitua E, Sanchez M, Aguirre JJ, Prado R, Padilla S, Orive G. Efficacy and safety of plasma rich in growth factors intra-articular infiltrations in the treatment of knee osteoarthritis. *Arthroscopy*. 2014;30:1006–1017.
3. Boswell SG, Schnabel LV, Mohammed HO, Sundman EA, Minas T, Fortier LA. Increasing platelet concentrations in leukocyte-reduced platelet-rich plasma decrease collagen gene synthesis in tendons. *Am J Sports Med*. 2014;42:42–49.
4. Anitua E, Zalduendo MM, Prado R, Alkhraisat MH, Orive G. Morphogen and proinflammatory cytokine release kinetics from PRGF-Endoret fibrin scaffolds: evaluation of the effect of leukocyte inclusion. *J Biomed Mater Res A*. 2015;103:1011–1020.
5. Anitua E, Prado R, Troya M, et al. Implementation of a more physiological plasma rich in growth factor (PRGF) protocol: anticoagulant removal and reduction in activator concentration. *Platelets*. 2016;27:459–466.

Eduardo Anitua^{a,b}

^aEduardo Anitua Foundation for Biomedical Research, Vitoria, Spain

^bBTI-Biotechnology Institute, Vitoria, Spain

Roberto Prado

BTI-Biotechnology Institute, Vitoria, Spain

Gorka Orive^{a,b,c,*}

^aEduardo Anitua Foundation for Biomedical Research, Vitoria, Spain

^bLaboratory of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of the Basque Country, Vitoria, Spain

^cNetworking Biomedical Research Center on Bioengineering, Biomaterials and Nanomedicine, CIBER-BBN, SLFPB-EHU, Vitoria, Spain

*Corresponding author at: c/ Jacinto Quincoces, 39, 01007 Vitoria, Spain

E-mail address: gorka.orive@ehu.es (G. Orive).

Received 25 August 2016

Available online 27 October 2016