of the treatments they offer their patients and to make informed therapeutic choices.

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Poor Standardization in Platelet-Rich Therapies Hampers Advancement

To the Editor:

We have read the article by Valentí Nin et al.[1] entitled "Has Platelet-Rich Plasma Any Role in Anterior Cruciate Ligament Allograft Healing?" with great interest. The authors evaluated the effect of a particular platelet-rich (PR) therapy (referred to as platelet-derived growth factor [PDGF]) in anterior cruciate ligament (ACL) surgery in a randomized trial and concluded that their intervention (PDGF) does not work under these circumstances. To establish the degree of generalization for their results in the field of PR therapies, however, it is logical to analyze 2 essential issues—the manufacturing procedure and the protocol for PDGF application during surgery. The manufacturing procedure may result in varying qualities of plasma products and efficacies from patient to patient. It should be noted that PDGF has not followed US Food and Drug Administration (FDA) 510(k) or European regulatory agency (CE marking) submission. These submissions allow the FDA or European authorities to determine whether a device is "substantially equivalent" to a similar one (predicate) already on the market. Compliance ensures important parameters, such as reproducibility, platelet functionality, and clot properties. Furthermore, CE and FDA registration also implies the use of material compliant to ISO 10993, which involves studies for cytotoxicity, mutagenicity, hemolysis, and other appropriate parameters that ensure biocompatibility and biosafety and that may influence the efficacy of the PR plasma.

For this reason, the results of this clinical trial with PDGF cannot be generalized. The so-called PDGF does not have a substantial equivalent; it is obtained by means of an in-house procedure involving a 2-step centrifugation and several manual manipulations that are difficult to understand. The authors misapply several terms, challenging comprehension (e.g., they indiscriminately use "serum" for "plasma," although serum is the liquid fraction released after blood coagulation and plasma is the fluid part of the blood with all of its clotting mechanism intact). With regard to terminology, their use of the term "PDGF" is blurred and confusing. In scientific writing, PDGF stands for 1 particular platelet-released protein among the 300 proteins identified in the platelet secretome (products secreted by a platelet).[2] In addition, the composition of the clot is only described in terms of platelet enrichment; other relevant parameters (e.g., platelet functionality, clot strength, leukocyte content, or growth factor concentrations) are omitted.[3]

Many ways in which PR therapies may be applied in ACL surgery have been described to date, making it difficult to assess the value of the principles underlying this technique and compromising the applicability of the results. Valentí Nin et al.[1] showed no efficacy of the PR intervention when they sutured their clot along the allograft. Conversely, our protocol for PR plasma preparation and application in ACL reconstruction[4] stands in contrast to the present protocol and so does the clinical efficacy of our procedure. Indeed, we condition the graft by injecting liquid-activated plasma throughout the length of the tendon, following the direction of the collagen fibers. In addition, after ACL reconstruction, we fill the joint with liquid-activated plasma. These actions intend to deliver appropriate cues in proximity to target

cells and to promote cell migration from the biological environment.

In conclusion, the results of this clinical trial may not be meaningful to other PR therapies. Well-characterized plasma products used along with rigorously defined protocols for application in the patient are critical conditions for research. Only when these conditions are met may randomized clinical trials be the foundation of clinical knowledge and practice.

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Author's Reply

First, we thank the authors for the feedback in their letter because this team has among the most extensive experience in the world related to growth factors applied to the musculoskeletal system.

The method we used was described previously in the literature, with some variation in centrifugation.[1] According to that article, this procedure was started at our institution in 2003, by the maxillofacial surgeons, and we began to apply it in anterior cruciate ligament (ACL) replacement when the research was designed in 2005.

We agree that the manufacturing procedure may result in varying qualities of plasma products and efficacies from patient to patient, as well as that it is possible to find different efficacies according to the protocol used for the application of the product. One of the conclusions of this research was that more clinical studies will be needed to show the efficacy and use of these factors in daily practice in ACL reconstruction, which leaves the door open to other protocols and manufacturing procedures that could be successful.

It has never been the purpose of our trial to generalize our results with this product to all platelet-rich plasma products, but rather, we sought to emphasize the need for more Level I, prospective, randomized, double-blind studies on this topic because, as the authors of the letter state, "Many ways in which PR [platelet-rich] therapies may be applied in ACL surgery have been described to date, making it difficult to assess the value of the principles underlying this technique and compromising the applicability of the results."

When our results were first presented at the meeting of the Spanish Arthroscopy Association in 2007, we received feedback from one of the authors of the letter related to the protocol and the product we had used in the research. After we finished our series of 100 patients for this study, we started a new series of patients with another platelet-rich plasma product described by the authors of the letter[2] and with a similar protocol, conditioning the graft (bone-tendon-bone allograft) "by injecting liquid-activated plasma throughout the length of the tendon, following the direction of the collagen fibers." These series are just finished but need a proper follow-up for the results to be evaluated in a similar way to our first trial. We hope to be able to publish those results in the near future.

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