

Editorial Commentary: Hype, Hope and Everything in Between. What Produces the Real Effect for Blood-derived Products Including Platelet-Rich Plasma?



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Abstract: Biological approaches have a promising future in the orthopaedic field because of their potential benefits that include their minimal invasiveness, potential for accelerated healing, and promise for rapid recovery. However, as the initial hype for these therapies starts to fade, it should be replaced by solid basic and clinical science research to tailor each compound to a determined patient/pathology. Blood contains several products that can be both beneficial and detrimental for every specific tissue, and therefore a one-fits-all approach should be avoided. Although beneficial effects have been consistently reported for certain pathologies such as lateral elbow tendinopathy, as an adjunct for rotator cuff repairs and the symptomatic treatment of osteoarthritis, other conditions' outcomes with biologic treatment remain nebulous such as for Achilles tendinopathy. To determine the real effect of these therapies, it is important to maintain strict inclusion criteria in an attempt to isolate the effect of one biologic product that already has many inherent intrinsic variables per se.

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Scientific knowledge is being increasingly geared toward more biological, less invasive solutions. These biologic treatments are thought to be more "organic" (a word that is linked to "more natural" in our brains). However, as the pace of science accelerates, doctors' and patients' expectations should not become unreasonable, seduced by an industry bent on profits and false advertising of nonvalidated exceptional outcomes.¹

As we advance the field of the use of biologics, it is essential to study the effect of only one variable at the time because the complexity of blood-derived products could lead to comparing studies that are evaluating apples and oranges if not carefully selected. In addition, reporting of key processing steps should be standardized to allow for comparison and outcome assessment

between studies.² It is becoming clearer that there are many products in blood products that are both beneficial and detrimental to different types of orthopaedic injuries and pathological processes (e.g., platelets are detrimental for muscle healing, and thus, platelet poor plasma should be used to treat muscle strains,³ vascular endothelial growth factor is detrimental for cartilage formation⁴ and beneficial for ligament healing,⁵ etc.). Therefore, going forward, it is important to ensure that we assess these points.

In the study "Meta-analysis Comparing Autologous Blood-derived Products (Including Platelet Rich Plasma) Injection Versus Placebo in Patients with Achilles Tendinopathy,"⁶ Meng-Ting, Ching-Fang, Chueh-Hung, Hui-Hsuan, and Yu-Kang seek to compare the effectiveness of a lumped together group of autologous blood-derived product injections with that of placebo in patients with Achilles tendinopathy. The authors tackle a topic that remains unclear to many orthopaedic surgeons: the optimal management of Achilles tendinopathy. In this regard, we believe that there are 2 things that need to be considered to achieve a successful outcome after biological treatments. The first is that tendons have significant structural differences throughout the body, and therefore, algorithms for each pathology should be tailored based on their locations (intra- or extra-articular) and their particular

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anatomy. In this regard, the treatment of Achilles tendinopathy can present unique challenges because of its limited blood supply, the great loads that it has to withstand, and unlike most tendons, the Achilles does not have a true tendon sheath (which helps with tendon lubrication, nutrition, and protection). These characteristics should be considered when treating Achilles tendinopathy as well as the timing of the pathology (because the intratendinous milieu can dramatically change in acute/chronic conditions).

Second, as we are in the beginning of determining which specific growth factors,⁷ platelet concentration (if needed at all),⁸ and whether the presence of progenitor cells are needed for each pathology,^{9,10} comparing different biological approaches (with/without platelets, with/without progenitor cells) can aid in determining which is more beneficial or truly needed. To this point, the authors attempted to perform a systematic review and meta-analysis of the available literature to compare the effectiveness of autologous blood-derived product injection with that of placebo in patients with Achilles tendinopathy in 7 randomized clinical trials.

Although the purpose and the hypothesis of the study are valid, the methods of the study cannot be as precise, mostly due to the heterogeneity of the preparations, deficient processing reporting,² different outcome measures used,^{11,12} additional treatment methods performed (eccentric exercise program, which is widely validated for the treatment of Achilles tendinopathies), and the low number of studies included, making a comparison between the groups significantly challenging. Irrespective of this limitation, which is generalizable to several topics in the literature, it has been reported that for example, autologous blood products (ABPs) are often efficacious for the treatment of lateral elbow tendonitis, for rotator cuff surgery (small to medium tears, and using a solid form of platelet rich plasma), and after the harvest of a bone patellar bone graft after an anterior cruciate ligament reconstruction.¹³ As stated by the authors, previous publications reported that Achilles tendinopathy treated with blood-derived products yielded inconsistent results, with most of the reports indicating that its use is not beneficial either for its use as an adjunct therapy during surgery or for conservative management of Achilles tendinopathy (as an injection in the lesional site).^{13,14}

The authors concluded that “ABP injection was not more effective than placebo (sham injection, no injection, or physiotherapy alone) in Achilles tendinopathy, and that no association was found between therapeutic effects and duration of symptoms.” This is consistent with previously published systematic reviews evaluating the same topic,^{13,14} and highlights the inherent difficulty in performing systematic reviews involving topics that have limited data surrounding their outcomes, which often times gather underpowered studies with short follow-up.¹⁵ Although this situation may

generate further interrogations, we believe that condensing the information is particularly valuable because it delivers the best available data in one location, exposes the missing information, and often clarifies the results by pooling and expanding on the number of patients scrutinized. However, when performing these studies, we urge that making advancements in this field will require strict inclusion criteria that should be established a priori to try to isolate one specific biologic product effect (which already has many inherent intrinsic variables per se).

Systematic reviews (and meta-analysis) are critical for the orthopaedic literature to summarize the most current data available to help provide answers to questions that can have equivocal evidence throughout the literature, and that is easily digestible for most clinicians and surgeons.¹⁶ Despite this, there are inherent limitations in systematic reviews, even when performed with appropriate methodology and statistical scrutiny.¹⁷ Although limited “answers” may be found when systematic reviews are completed, the promotion of further research and query into difficult areas is likely worth the effort.

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