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Bench to Bedside

Bench to Bedside: Platelet-rich Plasma—How Do We Adequately "Untranslate" Translational "Breakthroughs" in an After-market Setting?

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While most of my *Bench to Bedside* columns focus on topics that are poised to jump from the laboratory to popular clinical practice (or soon will be), it seems important to "untranslate" something that may have infiltrated practice far ahead of adequate evidence—platelet-rich plasma (PRP). Defined simply as "a sample of autologous blood with concentrations of platelets above baseline value" [8], PRP is ostensibly rich in proteins such as platelet-derived growth factor, vascular endothelial growth factor, and human growth factor. Fibrinogen has also been detected at high concentrations in PRP.

There are now more than 40 formulations of PRP on the market [8], and platelet, white blood cell, and protein concentrations can vary not only among formulations and proprietary preparation techniques, but also within a given formulation between patients, or even samples. Furthermore, it remains unclear what the ideal concentrations (if any) of platelets, cells, and growth factors for efficacy actually are, and it is probable that these nebulous values vary amongst therapeutic indications. The ideal timing for PRP administration also remains undefined, and may also vary based on the aforementioned factors [9]. Most importantly, evidence of clinical efficacy for most indications is decidedly lacking.

Still, the last several years have witnessed a virtual explosion in the clinical utilization of PRP for myriad orthopaedic applications. Yes, PRP has gone viral. Advertisements touting amazing benefits seem ubiquitous and surgeons, sports medicine practitioners, and even academic medical centers, tout expertise in PRP ther-

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apy—often a noninsured, cash-only endeavor—on their websites. Such is the hyperbole that one is quickly reminded of the surge in oral glucosamine/chondroitin and viscosupplementation for knee osteoarthritis that we witnessed in the last two decades. These interventions have been (or should be) largely abandoned because of their inefficacy [5, 10, 16].

Perhaps the best evidence of efficacy for PRP exists for the treatment of lateral epicondylitis, with randomized trials demonstrating superior outcomes versus corticosteroid injections, one as long as 2 years followup [7]. However, even for this indication, another study found essentially no differences between PRP injection and injection with whole blood, essentially a placebo given the purported mechanism of effect and critical concentrations of proteins in PRP [14]. This suggests that the problem may be no benefit, or even harm, from corticosteroids [4], rather than a boost from PRP. Other soft-tissue applications such as augmentation of Achilles tendon repair, rotator cuff repair, and ACL reconstruction have demonstrated either transient benefits, mixed results, or no clinical benefit whatsoever from PRP [9, 12]. For management of knee osteoarthritis, mixed results have been reported in two trials comparing PRP therapy to viscosupplementation—which, as noted, is itself probably just a little better than placebo, if that [3, 6, 10]. For osseous applications, two randomized trials demonstrated no benefit for high-risk foot fusions and actual harm for spinal fusion, respectively, when PRP was compared to autograft alone [2, 17]. So if PRP is beneficial for something, one has to question: (1) What that something is, and (2) whether, for an expensive treatment, said benefit meets the requisite threshold of being a minimal clinically important difference for most patients?

Notably, the purported efficacy, indications, and even brand loyalty to specific types of PRP and related products remain contentious and controversial, particularly amongst investigators with research and financial conflicts of interest in this regard [1, 13]. To my knowledge, no clinical trial has performed a head-to-head comparison of different proprietary formulations of PRP for any indication. This is entirely appropriate. Given the generally deficient evidence that PRP is effective at all for most indications, we should not be collectively endeavoring to detect incremental differences among competing products. However, a very generous (i.e., marketing) continuation of this line of thought would suggest that, if Name Brand X PRP is purportedly better than the competition, then the lack of a competitor's demonstrable efficacy for a certain indication does not mean that Name Brand X is not efficacious. Extrapolated across the multitude of potential indications for PRP, as well as the dozens of "proprietary blends," this argument of selectively interpreting favorable evidence, discounting the unfavorable, and marketing on the basis of the former could be carried out to infinity. That is, "Name Brand X hasn't been proven ineffective for that indication." This is neither the type of scientific rigor nor the efficacy metric we should be demanding of invasive, expensive interventions for our patients or ourselves.

And let us not forget safety. While the FDA has specific definitions regarding the evidence required to deem a device "safe" [15], in reality, it isn't until postmarket surveillance that we really know the answer to the question of safety [11]. This is because many more patients are required to demonstrate safety than efficacy. There is minimal, if any, evidence showing that PRP treatment is harmful beyond the perhaps expected local reactions experienced by some patients or the risks of any injection. But the simple truth is that we don't know. Anyone who tells you differently is probably selling something, and that something is likely to be PRP.

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It is not my intention to be some sort of anti-PRP Luddite. Unless one is actively involved in a clinical trial or developing a patent, one never wants to be either the first or the last person on the proverbial bandwagon. Compelling scientific evidence of efficacy is almost never our first exposure to a new technique, device, or intervention. Likewise, when a compelling body of evidence has accumulated that a new technique is likely to be beneficial, we owe it to our patients to critically examine this evidence and begin to judiciously incorporate that technique into our practices. There will always be separate cohorts of so-called early adopters versus persistent skeptics for anything "new." But we should demand good evidence that these new interventions are effective and, ideally but usually later, safe. Thus, while there is essentially no evidence that PRP is unsafe, we have collectively ignored that critical threshold of efficacy.

Disclosure Dr. Potter has never given a PRP injection, but knows colleagues, who shall remain nameless, who have.

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