# *Editorial Commentary:* Platelet-Rich Plasma Details Are Critical to Outcome…Catching Is Always Better Than Fishing

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**Abstract:** The use of platelet-rich plasma (PRP) and the spectrum of orthobiological interventions has been a major innovation in orthopedic surgery and medicine. Biological-based therapies for musculoskeletal disorders and injuries have gained popularity in the past decade and created significant expectation as the future of sports medicine, based on theoretical advantages including minimal invasiveness, greater healing potential, faster recovery, and a less expensive alternative to surgery. These therapies for musculoskeletal intervention include PRP, bone marrow aspirate concentrate, cellular-based therapies, and tissue engineering. Surgeons must always identify and respect the gap between hope, knowledge, and evidence to be successful and efficient in the care of patients. Age, body mass index, and dietary factors may have significant impact on the performance of PRP as a therapeutic intervention. It is imperative that the clinician be armed with a meticulous, comprehensive, and refined technique, protocol, and algorithm to be successful in the use of the PRP.

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The use of platelet-rich plasma (PRP) and the spectrum of orthobiological interventions has been a major innovation in orthopaedic surgery and medicine. Biological-based therapies for musculoskeletal disorders and injury have gained popularity in the past decade and created significant expectation as the future of sports medicine, based on theoretical advantages including minimal invasiveness, greater healing potential, faster recovery, and a less expensive alternative to surgery. These therapies for musculoskeletal intervention include PRP, bone marrow aspirate concentrate, cellular-based therapies, and tissue engineering. Surgeons must always identify and respect the gap between hope, knowledge, and evidence to be successful and efficient in the care of patients. So far, scientific evidence regarding PRP is limited but focused on concentration of cells and outcomes, and in relationship to comparator interventions.

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In my recent Canadian Arctic expedition, we observed the Inuit people and their survival. Over the past 20,000 years, they have been stealthy and focused on "harvesting" their catch of marine animals and fish. Consequently, they know where the bounty is, when to be there, and what equipment they will need. This precise and accurate tradition has taught us that this is not to be considered fishing. By controlling all large and intricate details, it becomes catching or harvesting.

This study by Mannava, Whitney, Kennedy, King, Dornan, Klett, Chahla, Evans, Huard, and LaPrade,[1] "The Influence of Naproxen on Biological Factors in Leukocyte Rich Platelet-Rich Plasma: A Prospective Group Study," focuses on PRP and provides a small but essential piece of a large puzzle. There is an abundance of questions regarding the ideal preparation for each therapeutic situation including PRP concentration, preparation, activation, and application that might affect platelet and ultimately growth factor quantity and quality.[2] The use of PRP aims to provide a milieu of local growth factors, which modify the inflammatory response and may affect cell proliferation and differentiation.[3] PRP was originally defined as a volume of plasma that has a platelet count "above-baseline."[4] However, this definition has more recently been amended to include quantitative criteria, requiring PRP

to contain more than 1 million platelets or 5 times the amount of baseline platelets. It is also thought that a platelet count in PRP beyond this level is required to stimulate targeted injured cells to proliferate.[5,6] Most importantly, nonsteroidal anti-inflammatory drugs (NSAIDs) exert their effects by inhibition of prostaglandin production. The pharmacologic target of NSAIDs is cyclooxygenase (COX, also known as prostaglandin synthase), which catalyzes the first committed step in arachidonic-acid metabolism.[7] Two isoforms of the membrane protein COX are known as COX-1 and COX-2 and are responsible for formation of prostanoids, including thromboxane and prostacyclin, which have diverse functions to aggregate or disaggregate platelets.[8]

So how do we as orthopaedic surgeons discover what is best? We plan, prepare, and develop the conceptual techniques rather than indiscriminately inject unknown composite interventions. We want to catch or harvest rather than go on fishing expeditions! A great step to this approach is this pilot study that utilized 15 asymptomatic healthy donors with a mean age of 36.6 years (range 25-64 years) who met the inclusion criteria and voluntarily participated. All donors documented daily use of naproxen for 1 week followed by a 1-week washout period. They subsequently evaluated leukocyte-rich (LR)-PRP, which is a high white cell concentration PRP and its anabolic growth factors such as vascular endothelial growth factor, fibroblast growth factor-2 (FGF-2), platelet-derived growth factor-AB (PDGF-AB), and platelet-derived growth factor-AA (PDGF-AA), as well as catabolic factors interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α). Peripheral blood was drawn at 3 time points: baseline, 1 week after naproxen use, and after a 1-week washout period. They found that angiogenic factors PDGF-AA and PDGF-AB had significantly declined from baseline ($P < .05$) after 1 week of naproxen use. There was a significant recovery ($P < .05$) of PDGF-AA and PDGF-AB levels after the 1-week washout, with a return to baseline levels. The catabolic factor (IL-6) also had a significant decline after 1 week of naproxen use. IL-6 then returned to similar baseline levels. TNF-α, IL-1β, IL-8, vascular endothelial growth factor, and FGF-2 did not demonstrate differences among the 3 time points. These findings are noteworthy because the use of NSAIDs is ubiquitous in our patients. Although the inhibitory effects of naproxen on PDGF and IL-6 factors in LR-PRP were observed, the authors carefully state that this may not reflect on "changes in LR-PRP's biological activity or therapeutic efficacy." The authors also recommend that "discontinuing NSAIDs for a minimum of one week prior to LR-PRP treatment may improve certain biological factor levels."

Overall, this is a small study that has limitations based on size and a short-term use of naproxen. That said, it is small step but a giant leap because it illuminates specific factors that we must consider to be successful with our clinical objectives. The baseline evaluation was highlighted by revealing inverse relationships of body mass index (BMI) and increasing age for FGF-2, anti-TNF, and IL-1B, which are important cytokines and biologically active molecules that comprise PRP. This may be a factor in the study of Kon et al.,[9] which demonstrated an inverse relationship between age and successful outcome in patients receiving low white cell (leukocyte-poor) PRP. A better understanding of the biological constituents of PRP combined with the spectrum of factors that influence these systems directly or indirectly is essential. To date, there may be other factors that are yet to be defined. In addition to age and BMI, these include gender and dietary factors.

Evanson[10] found that females had elevated concentrations of endothelial growth factor, hepatocyte growth factor, IGF, and PDGF-BB compared with males. Dietary issues also may have a significant impact on health and disease and may have significant impact on platelet function. The same Inuit as native peoples were found in the 1970s to have a low incidence of myocardial infarction and a tendency to bleed. Their diet consists of Arctic char, seal meat, and whale blubber. These are heavy in polyunsaturated fatty acids containing eicosapentaenoic acid (omega-3) that is like arachidonic acid but paradoxically does not induce platelet aggregation in human PRP, probably because of the formation of more prostacyclin over thromboxane, which causes a net platelet disaggregation.[11]

In conclusion, platelet systems are complicated, sensitive, and specific systems designed for control and have a multitude of branch points and modulators that may impact biological effects and therapeutic outcomes. Thus far, age, BMI, gender, diet, and NSAIDs are factors that impact PRP functionality. Mannava et al.[1] should be congratulated for furthering our knowledge, principles, and perspective for the clinician who uses PRP. Just like the Inuit hunter-gatherers, the clinician must be armed with a meticulous, comprehensive, and refined technique, protocol, and algorithm to be successful in the use of PRP. For the moment, we are at the tip of the iceberg!

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