

Effect of platelet-rich plasma injection on systemic concentrations of performance-enhancing growth factors

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INTRODUCTION:

Platelet-rich plasma (PRP) therapy has the potential to accelerate muscle and tendon healing, allowing injured athletes to return to sport earlier. However, PRP and many of the growth factors it contains were added to the World Anti-Doping Agency (WADA) Prohibited List in 2010 due to concerns that it may increase levels of ergogenic growth factors. As further evidence of the controversy and lack of evidence surrounding this topic, PRP was removed from the Prohibited List in 2011. Although the contents of the PRP preparations themselves have been studied, the systemic effects and potential doping implications of PRP therapy are largely unexplored.

To understand the short-term systemic effects of local PRP injections, we will measure the plasma concentrations of GH, IGF-I, IGF binding protein type 3 (IGFBP-3), basic FGF (bFGF), VEGF, and PDGF before and during the four days following PRP injection. These molecules are of particular interest because they may have stimulatory effects that enhance athletic performance. GH may have anabolic effects on skeletal muscles and enhance performance by increasing lean body mass. The growth-promoting effects of GH are primarily mediated by IGF-I, described as the GH/IGF-I axis. Similarly, bFGF improves healing in muscles and enhances strength, PDGF is a powerful mitogen for fibroblasts and smooth muscles cells, and VEGF is an angiogenic factor that enhances oxygen transfer. Serum levels of IGFBP-3 can be used to detect growth hormone deficiencies, and are measured in conjunction with IGF-I as an indirect assay for GH doping.

METHODS:

15 patients who were receiving a single ultrasound-guided intratendinous PRP injection for treatment of tendinopathy were enrolled. Serum and plasma samples were drawn immediately before (baseline); 15 minutes after; and three, 24, 48, 72 and 96 hours after receiving PRP therapy, to detect baseline and peak concentrations of each growth factor studied. To control for the effects of nutrition, exercise and diurnal fluctuations, fasting samples were drawn at the same time each morning (excluding the 15 minute and 3 hour samples). Serum concentrations of GH, IGF-I, IGFBP-3, VEGF, bFGF, and plasma concentrations of PDGF, were quantified by ELISA and analyzed by repeated measures ANOVA using SPSS.

RESULTS:

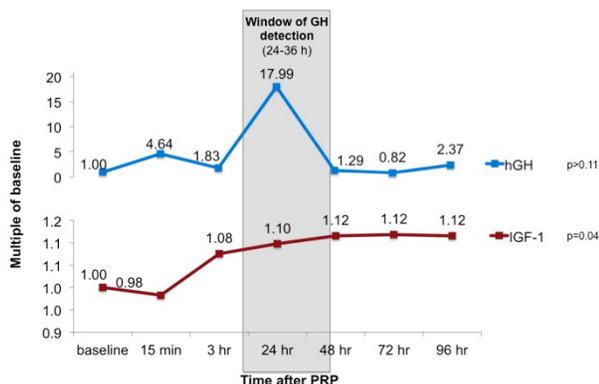


Figure 1. hGH and IGF-1 increase within 24 hours after PRP, suggesting PRP may have performance-enhancing effects.

11 males and 4 females with a mean (\pm SD) age of 40.2 (\pm 9.7) years underwent intratendinous PRP injection. Mean baseline growth factor concentrations were: 1.28 (\pm 1.53) ng/mL IGF-1, 1.93 (\pm 4.73) ng/mL hGH, 3.47 (\pm 4.59) pg/mL bFGF, 22.6 (\pm 12.5) ng/mL IGFBP-3, 316 (\pm 253) pg/mL PDGF-BB, and 322 (\pm 371) pg/mL VEGF. Paired T-tests demonstrated significant increases relative to baseline for IGF-1 and VEGF. IGF-1 increased by 9.8% ($p=0.04$) at 24h, 11.6% ($p=0.02$) at

48h, and 11.6% ($p=0.03$) at 96h, exceeding the pre-set minimum clinically significant difference of 10%. hGH increased by a mean of 4.6-fold (\pm 11.7) at 15m, 1.8-fold (\pm 3.0) at 3h, 18.0-fold (\pm 34.7) at 24h, and 1.3-fold (\pm 1.4) at 48h relative to baseline, but these changes were not statistically significant due to large variances ($p>0.11$). VEGF increased significantly by 63% ($p=0.04$) at 3h, 51% ($p<0.01$) at 24h, 45% ($p<0.01$) at 48h, 48% ($p<0.01$) at 72h, and 54% ($p<0.01$) at 96h. No significant changes were observed for IGFBP-3, bFGF or PDGF-BB.

DISCUSSION:

Circulating IGF-1 and VEGF levels are significantly elevated following PRP injection. VEGF enhances muscle strength and exercise endurance, and IGF-1 promotes cell proliferation, differentiation, and hypertrophy of skeletal muscle. IGF-1 is stably secreted and has minimal intra-individual variability, and mediates the systemic effects of hGH. Therefore, IGF-1 is the most specific marker of supraphysiological hGH exposure. hGH has been called "the most anabolic substance known," and is an important target of anti-doping campaigns in sport. It is difficult to detect because its secretion is pulsatile, and is influenced by stress, exercise, caloric intake, age, gender and time of day.

Here, we found that IGF-1 is elevated within the 24-36 hour period for maximal detection of hGH, suggesting that circulating IGF-1 may increase after PRP injection as a result of upstream effects on hGH. Furthermore, we also observed a mean 18-fold increase in hGH activity at 24 hours post-PRP. As expected, this rise in hGH was not statistically significant due to the intra-individual variability in hGH secretion, even after controlling for exercise, caloric intake and time of day.

Importantly, our data provides a molecular signature that may be used to detect athletes who have used PRP. In contrast with hGH doping, PRP treatment is associated with a rise in other molecules such as VEGF. Additional research is warranted to determine the clinical significance of these results, and to directly compare the molecular signatures of PRP and hGH.

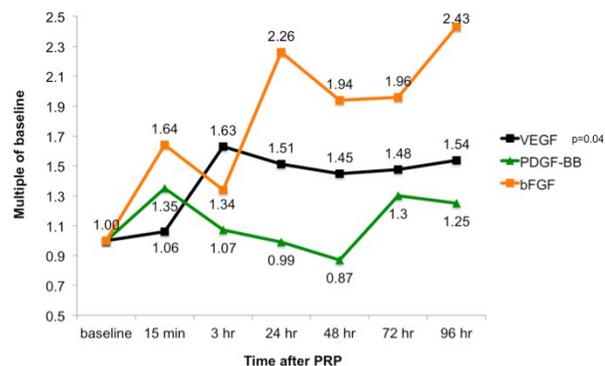


Figure 2. Changes in other molecules such as VEGF, PDGF-BB, bFGF may contribute to a molecular signature specific for PRP.

SIGNIFICANCE:

Our research provides quantitative evidence that PRP therapy does increase the systemic release of growth factors with performance-enhancing potential, which will aid regulators in making informed decisions about the use of PRP in competitive athletes. Our data will provide a molecular signature to detect patients who have received PRP.

ACKNOWLEDGEMENTS:

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