Investigating the impact of Platelet-Rich Plasma Infusion

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ABSTRACT

Objective: To investigate the impact of Platelet-rich plasma infusion on performance enhancing growth factors and find molecular markers to distinguish athletes treated with such infusions.

Study Design: Prospective, Double-blind, Randomized controlled study.

Place and Duration: Department of Dental Education and Research, Altamash Institute of Dental Medicine, Karachi from 15th January 2022 to 20th June, 2022.

Methodology: The ergogenic growth factors FGF-2 that are basal fibroblast growth factor, vascular endothelial growth factor, IGF-1 (insulin-like growth factor), IGFBP-3 (insulin-like growth factor binding protein-3), and platelet-derived growth factor-BB (PDGF-BB) WADA are tracked that were measured in 25 patients before (baseline) and 0.25, 3, 24, 48, 72, and 97 hours after the test. Patients under observation were prohibited from any movement or any food intake three hours prior to the exam. The change from each participant's baseline was calculated using an enzyme-linked immunosorbent assay to assess growth factors.

Results: Total sample size was 23. Platelet-Rich Plasma had considerably higher levels of PDGF-BB (67% higher than standard 392 pg/ml), vascular endothelial growth factor (6.04% higher than standard 236 pg/ml), and bFGF (45% higher than standard 5 pg/ml), than serum, while IGF-1 and hGH levels were unchanged. IGF-1, bFGF, and vascular endothelial growth factor serum levels all significantly rose 24 and 48 hours after Platelet-Rich Plasma injection, as well as 3, 24, 48, 72, and 96 hours afterwards. Additionally, all 23 patients who had Platelet-Rich Plasma therapy had higher levels of vascular endothelial growth factor and success rate is 100% luckily.

Conclusion: Serum levels of PDGF-BB, vascular endothelial growth factor, and bFGF significantly increase after Platelet-Rich Plasma injection, suggesting that Platelet-Rich Plasma have ergogenic effects. Following Platelet-Rich Plasma, the IGFBP-3 3 IGF-1 product, an indirect biomarker of hGH doping, significantly rose. All Platelet-Rich Plasma patients exhibited elevated vascular endothelial growth factor.

Keywords: PRP Injection, Platelet-Rich Plasma, Human Growth Hormone, Growth Factors, Ergogenic Growth Factors, Insulin Growth Factor, Vascular Endothelial Growth Factor

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INTRODUCTION

An autologous blood product called platelet-rich plasma (PRP) is used to treat tendon, ligament, and muscle injuries. Intramuscular PRP injections in professional athletes were forbidden by the World Anti-Doping Agency (WADA) in 2011. The restriction on PRP was lifted in 2011 however the growth factors in PRP continue to be illegal. Platelet-rich plasma (PRP) is a treatment that uses a person's own blood to promote healing. PRP injections are a newer, non-surgical option for treating injuries and joint conditions. This study is being conducted to evaluate the potential effectiveness of platelet-rich plasma (PRP) injections in treating a variety of conditions. The platelets and growth factors found in PRP injections can promote healing and regeneration of soft tissue and bone[1]. This treatment is still considered to be somewhat experimental, but there is some evidence that it may be effective in reducing joint pain and improving joint function. As a supplement to the body's organic healing procedure, an autologous blood component is platelet-rich plasma (PRP) high in platelets and the growth factors they are linked with, is administered when a muscle or tendon damage has occurred. The theory behind PRP is that because platelets are the first to reach an injured tissue location, they may release growth factors that are essential for healing. Although PRP was first utilized in the 1970s, its usage for treating sports-related injuries has recently increased, and it is currently used to cure approximately 86,000 athletes each year in addition

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to many others around Europe.

PRP may help certain athletes heal more quickly after tendon and muscle injuries, according to some studies, albeit its effectiveness has not yet been confirmed beyond a reasonable doubt. World Anti-Doping Organization/agency is also growing increasingly apprehensive that PRP injections can be considered an offence for doping since PRP includes a lot of ergogenic growth elements. The effects and possible consequences of PRP for doping therapy remain unknown, despite the fact that the ingredients of the PRP preparations itself have indeed been researched.

Because of worries about the growth factor insulin-like (IGF-1) & the possibility of misuse as an ergogenic agent, athletes' usage of growth hormones is forbidden in accordance with S2 of the 2014 WADA illegal. World Anti-Doping agency (WADA) originally restricted platelet-derived preparations, such as PRP, under the 2011 Banned List due to worries that the higher growth factor concentrations in PRP would provide treated athletes an unfair advantage. The rules governing PRP therapy varied Depending on where the therapy is being provided: Only those with a therapeutic use exemption were authorised to utilise intratendinous PRP, whereas intramuscular PRP injections were outright forbidden[2] . To allow for more study in the area and in consideration of the paucity of data to establish a performance-enhancing impact, WADA lifted the prohibition on PRP in 2011.

Athlete performance is known to benefit from these processes; hence the 2010 Prohibited List likewise outlawed any molecules that may impact protein synthesis/degradation, vascularization, energy use, fiber type switching in muscles, tendons, regenerative capacity, or ligaments[3]. According to the Prohibited Lists for 2011, 2012, and 2013, these drugs are still prohibited.

Although PRP should be used with caution because to the possibility of misuse, there is now insufficient proof of its particular systemic effects, as far as we are aware, just one research has been written about how locally applied PRP affects the body as a whole. [2] Up to 24 hours following PRP therapy, there was a decrease in the blood concentration of 5 patients have epidermal growth factor but no statistically noteworthy variation vascular endothelial growth factor concentration. However, athletes, the wider sports medical community, and anti-doping organizations like Partnership for Clean Competition and WADA are all very interested in and concerned about the prospect that PRP may have ergogenic systemic effects[4]. This study's objective was to evaluate Platelet-rich plasma infusion on performance enhancing growth factors[5] and find molecular markers to distinguish athletes treated with such infusions.

METHODOLOGY

The Department of Dental Education and Research at the Altamash Institute of Dental Medicine in Karachi received approval from its Institutional Review Board before beginning this study. A prospective, double-blind, randomised controlled study was conducted from 15th January 2022 to 20th June, 2022, to explore the effect of platelet-rich plasma injection on signalling pathways for performance-enhancing effects, as well as to evaluate the effect of platelet-rich plasma injection for identifying athletes who have undergone treatment. Four of the doctors who are also the authors of this study conducted out this experiment with the approval of the Department Head.

A minimum number of 25 patients would be needed, according to the research, to identify a 10% variation in IGF-1 with 80% power. The study's eligibility was determined by screening all patients who underwent local ultrasonic infusion of intrathecal PRP at our facility between Jun 2020 and September 2021; 25 individuals were finally recruited. Current treatments of, diabetes, nutritional problems[6] cancer or hormone substitution[7] medications were all disqualifying considerations since it is known that these circumstances change the circulating growth factors. All scheduled appointments for the purposes of the study had to be kept, according to the patients.

Using the Biomet Gravitational Platelet Separation System in accordance with the manufacturer's instructions, leukocyte-rich PRP (LR-PRP) was produced. Direct training from the producer was provided to medical workers that process PRP. In order to get 4 to 7 mL of LR-PRP, a total of 40 to 70 mL of blood were collected, according to the amount of PRP essential for the specific tendon injury. Prior to injecting PRP, local anesthetic was provided by intradermal injection of bupivacaine 0.25% without epinephrine. Every intratendinous, extravascular PRP shots were performed by a musculoskeletal radiologist while using ultrasound guiding, & the amount of PRP administered was documented. 2 mL of PRP was kept wherever possible for growth factor analyses. Anti-inflammatory drugs were not to be taken by patients for 5 days prior to and following the injection. Venipuncture samples of blood were drawn at predetermined intervals: baseline, 0.25, 3, 24, 48, 72, & 96 hours following PRP treatment. Blood was taken in accordance with WADA guidelines in the same manner every morningat least two hours after a meal, and at least one hour after exercising in order to account for the impact of dietary modifications, acute exercise sessions, and daily fluctuations in serum human growth hormone (hGH). Blood was drawn from the untreated arm for those receiving upper-extremity PRP injections to make sure the samples represented systemic instead of local and state levels. BD Vacutainer tubes for serum separation for serum & ethylenediaminetetraacetic acid (EDTA) tubes using plasma as a source collect 7 mL of blood at each time point. Serum & plasma subsequently sub-cultured into 2-mL polyester tubes as storage at -75 C after samples were processed in accordance with the manufacturer's instructions.

By using Enzyme-linked immunosorbent test for quantikine (ELISA) equipment from R&D Systems in Minnesota, Minneapolis, six drivers of growth, and associated compounds in PRP preparations that are focused were assessed using a direct immunoassay in PRP and blood[8]. The results are shown in Table I. The following growth elements were looked at: Human growth hormone (hGH), platelet-derived growth factor-BB, insulin-like growth factor binding protein-3 (IGFBP-3), insulin-like growth factor-1 (IGF-1), and basic fibroblast growth factor (bFGF or FGF-2) are a few examples of growth factors (PDGF-BB). A reliable detection required the use of a high-sensitivity ELISA kit since bFGF is only found in the blood at extremely low quantities. The manufacturer's specified values were exceeded if the variability coefficient was greater than all samples

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& controls combined. A maximum of thrice was allowed between thawing and freezing blood samples.

Table - I: Growth Factor Assays using ELISA

Growth Factor	Assayed Blood Fractions	ELISA Kit
hGH	Serum, PRP	DGH00
IGF-1	Serum, PRP	DG100
IGFBP-3	Serum, PRP	DGB300
bFGF	Serum, PRP	HSFB00D
VEGF	Serum, PRP	DVE00
PDGF-BB	Plasma, PRP	DBB00

insulin-like growth factor (IGF)-1, Human growth hormone (hGH), insulin-like growth factor binding protein (IGFBP)-3, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF-BB), and platelet-rich plasma (PRP) are all examples of ELISA tests.[9]

Data Analysis: Using 95% confidence intervals and 2-tailed paired t tests, at every follow-up time point, variations from the baseline (e.g., T24h) & % change from the starting point (e.g., T24h) were computed and evaluated (CIs). Statistical significance was defined as a CI excluding 1.0. This study's exploratory and descriptive nature precluded the use of numerous statistical tests, hence no modifications were done. The Pearson correlation coefficients were used to assess the dose response.

RESULTS

Experiment was performed at 23 patients of which 18 were males and 5 were females, all with a standard variation of 11 years and a mean age of 39, In terms of collecting high-quality blood samples were collected from each participant at each of the 7 time points, we had a 95% follow-up rate. The average amount of PRP administered intratendinously was 3.7, 6, 1.3 mL. Table II displays the normalized growth factor concentrations at baseline in blood and PRP.

Table - II: Blood and PRP Circulating Growth Factor Concentrations at Baseline (0 Hours). (N=23)

Growth Factor	Blood (Serum / Plasma)	PRP	PRP Increase
pg/mL, hGH	1719 +/- 4053	1631 +/- 3762	<1.0%
ng/mL, IGF-1	128 +/- 123	83 +/- 97	<1.0%
ng/mL, IGFBP-3	21,061 +/-10,643	13,290 +/- 7216	<1.0%
pg/mL, bFGF	5 +/- 5	227 +/- 154	48.5%
pg/mL, VEGF	336 +/- 597	1426 +/- 940	5.7%
pg/mL, PDGF-BB	395 +/- 395	26,288 +/- 14,619	67.16%

Except where otherwise stated differently, Data are presented as means +/- SD. All compounds except PDGF-BB, where the reported plasma concentration, have serum concentrations reported. PRP, hGH, and IGF-1 are acronyms for platelet-rich plasma, human growth hormone, and insulin-like growth factor, respectively; Insulin-like growth factor binding protein 3 is known as IGFBP-3.; Basic fibroblast growth factor is referred to as bFGF; Vascular endothelial growth factor is referred to as VEGF; and Platelet-derived growth factor-BB is known as PDGF-BB[10]

The considerable disparities in growth factor concentrations between patients were accounted for by estimating the circulating levels after PRP injection as multiples of each participant's own baseline level for that molecule[11]. Dose of PRP injections (mL) & change in growth factor concentrations did not significantly correlate.

As expected for the stimulation of the hGH-IGF-1 axis, after receiving PRP treatment, human growth hormone dramatically increased during the first 24 hours, nonetheless, because of the wide range, these results were just not significant. Additionally, IGF-1 rose above within three hours of PRP and stayed at baseline higher for the next 24 and 48 hours, with the rise being statistically significant at both time periods. Additionally, bFGF increased considerably at 73 and 97 hours, while VEGF increased significantly at 3 hours and at all subsequent time periods. More than 88% of patients showed increased VEGF from 4 to 97 hours following PRP injection, at each time point. At 96 hours following injection, IGFBP-3 serum levels and IGFBP-3, a product of IGF-1, were both markedly increased.

DISCUSSION

The current study's objectives were to ascertain whether PRP raises circulating concentrations of growth factors that might be ergogenic in contrast to patient's pre-injection levels consequently to identify relevant molecular markers[12] that may be utilized to differentiate between both athletes and athletes who haven't had local PRP injections.

Immediately after one injection of PRP intravenously, there was a marked rise in the amount of circulating growth factors with the potential to improve performance. In fact, within 24 hours following PRP, IGF-1 is substantially higher than expected, within the anticipated window of detecting the activity IGF-1 and hGH axis.

Similar to hGH, hGH peaked during the 24-hour window, however because to the high variation, the results weren't really significant. In addition, IGF-1 is the most precise indicator of exposure to supraphysiological hGH and in reaction to hGH, the liver produces[13]. IGF-1 secretion, in contrast to hGH, is rather steady, little intraindividual variation fluctuation over a 24-hour time frame. This value peaks 37 to 97 hours after the use of exogenous hGH and has now been evaluated as something of an oblique assay for supraphysiological hGH. The "discriminant function," created by Kniess and colleagues19 and used to detect the use of exogenous hGH by athletes, is used in an IGF-1 stimulation test to demonstrate that healthy pubertal kids can reach a maximum blood IGF-1 level slightly higher compared following the test, to double the basal level[14].

The concentrations of IGFBP-3, serum IGF-1, and N-terminal propeptide of type III pro-collagen make up the mathematical equation that represents the discriminant function[15]. Measurements of IGFBP-3and IGF-1 were made in this study rather than PIIINP because these markers are specific; their contributions to the hGH axis are well supported by several research published, and trustworthy ELISA kits are readily available in the market[16].

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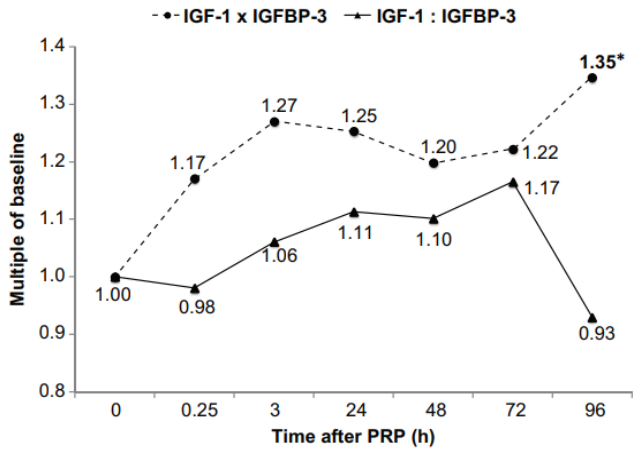

Figure – 1: Results of tests employing the proximal indicator of insulin-like growth factor binding protein-3 (IGFBP-3), human growth hormone (hGH) doping. Significant statisticallyi i.e., p-Value <0.05.

The IGFBP-3 IGF-1 products showed a statistically significant 35% rise following Five PRP injection days; this is comparable to the 30% rise following five days of exogenous hGH. This evidence supports local PRP injection may be able to imitate hGH's actions on the IGF-1-hGH axis and may also interfere with the findings of hGH anti-doping tests. Similar to how bFGF and VEGF surged following PRP therapy.

Basic fibroblast growth factor interaction between PDGF-BB and TGF-b promote increasing satellite cell numbers, which are the mature muscular stem cells, & helps to promote angiogenesis by promoting the development of endothelial cells[17]. The basic fibroblast growth factor, which causes muscle hypertrophy and boosts oxygen transfer, may improve athletic performance[18]. VEGF or vascular endothelial growth factor is potent angiogenesis stimulator & may significantly improve achievement if it were to circulate throughout the body and affect tissues other than the area of damage[19].

Instead of acting as a delivery system for existing growth factors, platelet-rich plasma seems to enhance the amount of circulating growth factors via stimulating cellular processes. Observed increase in IGF-1 levels in the blood following PRP therapy can't be ascribed to IGF-1 dosage inside PRP because IGF-1 levels in PRP were lower than they were in serum at the beginning; rather, it is caused by PRP activating the IGF-1- HGH axis. This is also supported by the fact that, despite the extremely high PDGF-BB dosage present in PRP (392 pg/mL in plasma vs 26,285 pg/mL in PRP), there was no appreciable rise in plasma PDGF-BB following PRP therapy. In other words, we would envisage circulating PDGF-BB to boost greater than IGF-1, which either wasn't the situation, if the growth factors found in PRP were the only ones why these growth factors' circulating levels have increased.

The degree of PRP's systemic effects may also be influenced by the particular commercial method of PRP production and activation[20]. In this study, a (LR-PRP) leukocyte-rich preparation was employed, which has been proven to cause the release of both anabolic and catabolic growth factors[21]. Varied PRP formulations, such as PRP with few leukocytes, may result in a different degree of release of the anabolic growth factor. Furthermore, upon intratendinous injection, in vivo interaction with collagen activated PRP rather than exogenous techniques like thrombin and calcium chloride. Anabolic growth factors are known to be released more steadily after collagen activation than after thrombin activation[22].

The question of whether statistically noteworthy possible improvements in growth factors to improve performance, such as VEGF, IGF-1, and bFGF, inevitably bring forth clinically significant ergogenic advantages, is crucial. This question is made more difficult by proofs from some animal studies that suggest there may be local ergogenic effects even in the seeming absence of growth factor alterations. Local IGF-1 exogenous application enhances local muscle strength and mass without systemic increases in IGF, according to these studies[23].

The precise threshold levels where the growth factor concentrations in humans become clinically significant are not well supported by published data. A noteworthy point is that WADA really hasn't established a threshold for athletes' permissible blood hGH levels, mostly due to an accurate drug test must take into account significant intra- & inter-individual variance. Table III lists the systemic molecular alterations that have been seen in various pertinent experimental scenarios, such as those following an intense exercise session or an exogenous hGH dosage.

Table - III: Modification of Growth Factors by Different Experimental Models (N=23)

Experimental Model	Changes
hGH	16x
Acute bout of exercise	14x
IGF-1	+9% (1.09x)
Per day dosage of exogenous hGH in young adolescents in good health	+106% (2.06x)
athletes' daily exogenous hGH dosage	+90% (1.9x)
Acute bout of exercise	+20% (1.2x)
IGFBP-3	+26% (1.26x)
Acute bout of exercise	+18% (1.18x)
IGF-1 3 IGFBP-3	+35% (1.35x)
IGF-1 3 IGFBP-3 is produced following daily exogenous hGH dosage	+30% (1.3x)

Our findings demonstrated IGF-1, hGH, and IGFBP-3 elevations they are pretty similar to those that are observed following an intense bout of exercise. Additionally, we saw a greater rise in IGF-1 3 and IGFBP-3product than what was found following five days of consuming daily exogenous hGH doses. One PRP injection was given to research subjects, the comparative trials, however, used daily hGH injections for at least five days. Despite the fact that we discovered IGF-1 increases less in response to exogenous hGH dosages (.90%) than it does in response to PRP injection (9%) our study's participants only received a single PRP injection. Overall, our results show that PRP induces a similar-sized increase in growth factors observed following a short burst of activity or a low dosage of exogenous hGH. Since it is well accepted that both exercise and the injection of exogenous hGH have ergogenic effects, our findings may be construed as

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showing that local PRP injections can also have ergogenic effects.

We did not assess the effect of PRP treatment on actual athletic performance because the main the current study's objective was to assess PRP's molecular effects. According to anecdotal data PRP injections helped our 25 patients go back into sports but didn't significantly improve their above-average physical fitness or endurance their pre-injection levels. PRP, in our opinion, will at most return athletes to pre-injury levels of competitiveness, but it's unlikely to offer wounded athletes a competitive advantage over healthy one's competitors since PRP is frequently used by athletes to treat excruciating soft tissue injuries that have impaired their performance.

PRP includes substances that are now forbidden by WADA, according to the current study and several other papers that have been published in the past. According to this study, PRP has VEGF and bFGF concentrations that are 6 times higher, 48 times higher, and 67 times higher than baseline serum as well as plasma concentrations. The effects of PRP may affect the outcomes of anti-doping tests even if the drug itself is not considered to be illegal. Athletes who receive PRP treatment run the risk of falsely testing positive for hGH since it induces some, but not all, of the anticipated modifications brought on by doping of hGH[24]. Another issue with PRP is that athletes might inject hGH or other exogenous drugs using it as a delivery system. Testing for PRP could discourage people from using it on purpose to improve performance. All of these problems suggest the need for a special PRP test. Given that IGF-1, bFGF, and VEGF were all massively increased at twice or more periods, these substances may make up a "molecular signature" that may be used to identify athletes who have received PRP therapy. However, only 62% of individuals had raised IGF-1 levels, and Just 55% of individuals exhibited elevated bFGF concentrations in with relation to their own starting point. A test using each of Over 50% of the athletes who received PRP treatment might not receive these molecules since many individuals who received PRP did not see a significant increase in circulating IGF-1or bFGF. On the other hand, given that all 23 research participants experienced it improving at least once periods following PRP therapy, VEGF may be a crucial aspect of a "molecular signature" to recognize players who have had PRP. At 3 hours, average circulating Significantly, VEGF concentrations increased by 1.50 times, and at every successive time point, they increased by 1.30 to 1.50 times (24, 48, 72, and 96 hours). In addition, 88% of the participants in this research had high VEGF at any given time point. According to this, VEGF may be accurately identified It may thus be incorporated into the testing protocol used to determine athletes who have received PRP during a 4-day period[25]. To assess how long the detection limit lasts after injection, more longitudinal studies are needed since a successful PRP detection approach should ideally continue to be sensitive for weeks following therapy.

Study Limitations and Strengths: To guarantee that blood samples are reliable as well as the repeatability of results, which are necessary for any study of development factors, our study procedure conformed to strict guidelines. This study's limitation is that we were unable to contrasting the treated group with the untreated group that had not received any treatment. This would be an important next step towards creating and describing a valid PRP test. Additionally, because No intramuscular treatments existed carried out at our institution throughout the research session, we were unable to compare the differences in the effects of intratendinous vs. intramuscular PRP injections on the body as a whole. Although these local alterations were not the focus of this work, platelet-rich plasma may potentially cause local tissue alterations that improve healing and may affect how well function locally muscles, Furthermore, PRP injections often referred to as dry-needling, which are independent of the amount or composition of PRP administered, may have effects just by piercing the tendon. Future research should precisely in a variety of volumes, contrast the effects of dry-needling alone with dry-needling combined with PRP injection to further explore the potential for a dose-dependent advantage of PRP for improving performance. Lastly, monitoring levels of growth factors and after receiving a local PRP injection, athletic performance also would directly demonstrate a PRP's ergogenic effect.

CONCLUSION

Serum levels of PDGF-BB, vascular endothelial growth factor, and bFGF significantly increase after Platelet-Rich Plasma injection, suggesting that Platelet-Rich Plasma have ergogenic effects. Following Platelet-Rich Plasma, the IGFBP-3 3 IGF-1 product, an indirect biomarker of hGH doping, significantly rose. All Platelet-Rich Plasma patients exhibited elevated vascular endothelial growth factor.

AUTHOR'S CONTRIBUTION

Rizvi SH: Designed Research Methodology, Data analysis, Manuscript writing and Final critical review of manuscript, Manuscript final reading and approval.
Asphandiar DC: Data Collection, Literature Search.
Arshad T: Manuscript drafting, Literature Search, Data Interpretation.
Hashmi FA: Data collection and compilation.

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