Use of Platelet Rich Plasma in Post Covid 19 Anosmia Treatment

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Abstract:

The role of PRP in neuro-olfactory regeneration in the setting of anosmia in post covid 19 infected patients is promising. Importantly, there were no adverse outcomes following intranasal PRP injections and there are no intranasal symptoms or decreases in the sense of smell.

Keywords: Covid-19, Anosmia, PRP.

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Introduction

Olfactory dysfunction caused by COVID-19 has a rapid onset of impairment, which may or may not be accompanied by other symptoms. Italian COVID-19 hospitalised patients were more likely to have impaired taste or smell if they were younger and female. Olfactory problems may be healed in two weeks or less, according to unpublished studies and individual testimonies. Due to a lack of long-term follow-up, it is unclear how many individuals might have chronic postinfectious olfactory impairment. (1)

Since nasal epithelial cells have high levels of angiotensin-converting enzyme 2 receptor, which is required for SARS-CoV-2 entrance, coronaviruses are one of several pathogenic organisms that can result in postinfectious olfactory dysfunction. Inflammatory alterations in the olfactory neuroepithelium may affect olfactory receptor neuron function, induce further damage to olfactory receptor neurons, and limit subsequent neurogenesis if cells in the olfactory neuroepithelium are altered. Olfactory impairment caused by such alterations could last for a while or be chronic. (2)

The olfactory neuroepithelium and olfactory filae, peripheral nerve fibres that traverse the cribriform plate and enter the nasal cavity, may be used as therapeutic targets in patients with olfactory dysfunction because they may regenerate. Platelet-rich plasma (PRP), an autologous biologic product with a high platelet content, is produced from recently obtained whole blood. The overexpression of growth factors including transforming growth factor, vascular endothelial growth factor, epidermal growth factor, and insulin-like

growth factor is one of PRP's anti-inflammatory and pro-regenerative qualities. In numerous therapeutic contexts, it has been employed as a secure and effective treatment for inflammation, wound healing, and peripheral neuropathies. PRP has been shown to aid in axon regeneration and neurodegeneration. (3)

Platelet Rich Plasma Promotes Peripheral Nerve Regeneration

As an autogenous active substance, PRP has high levels of platelet, growth factors, leukocytes, fibrin, and various bioactive factors, including fibronectin, osteonectin, and vitronectin). These components are critical for tissue repair. First, platelet activation can stop bleeding and release various growth factors. Different growth factors influence all aspects of tissue repair. White blood cells help clear local pathogens and necrotic tissues. Fibrin can form a three-dimensional network structure in injured tissue and provide a scaffold for tissue regeneration. (4)

There are six evidences of PRP's potential to promoting nerve regeneration: 1) neuroprotection and prevention of neuronal apoptosis, 2) stimulation of vascular regeneration, 3) promotion of axonal regeneration, 4) regulation of inflammatory response in the microenvironment, 5) alleviation of nerve collateral muscle atrophy, and 6) improvement of human nervous system parameters. (5)

In 2014, Choukroun used centrifugation at 1,500 rpm for 14 minutes to create advanced plasma- rich fibrin (PRF).(6) This PRF is looser and more porous than earlier PRFs, which promotes cell growth and the diffusion of nutrients and oxygen. Chemical bonds between cells and growth factors and fibrin can reduce the loss of cells and growth factors during production. 2017 saw the introduction of injectable-PRF (I-PRF), which was produced by centrifugation at 700 rpm/60G for three minutes. This PRF has much greater plasticity than conventional PRF, overcoming the drawbacks of applying PRF like a gel.

Regulation of Platelet Rich Plasma on Schwann Cells (SCS)

SCs play critical roles in the healing and regeneration of peripheral nerve damage. During the mature stage of nerve regeneration, SC proliferation and migration can differentiate into myelin sheath, bridging the nerve stump to form the Bungner band and promoting axon regeneration by secreting various active substances, including neurotrophic factors. High concentrations of growth factors found in PRP encourage SC migration and proliferation. Platelet-derived growth factor (PDGF-BB) and insulin peripheral -like growth factor-1 (IGF-1) may be the primary cytokines affecting SC proliferation and migration. (7)

Regulation of Platelet Rich Plasma on Inflammatory Cells

Several inflammatory cells, including macrophages, are involved in the repair of peripheral nerve damage. The two phenotypes of macrophages are the traditionally activated macrophage M1 and

the selectively activated macrophage M2. Nitric oxide synthase (NOS) is primarily expressed by proinflammatory M1 macrophages, which are also involved in antigen presentation. Arginase type 1 (Arg-1) is primarily expressed by M2 macrophages, which also secrete regular cytokines, inhibit immune responses, and play important roles in tissue repair. M1 macrophages, which phagocytize the myelin sheath and other cell debris upon distal nerve disintegration, are primarily linked to early stage nerve injuries. Consequently, substances that hinder nerve regeneration are removed, and a favourable environment is created for nerve regeneration. M2 macrophages are the predominant phenotype in the late stages of an inflammatory reaction, where they encourage fibrosis and tissue regeneration. (8)

PRP growth factors, which are autologous platelet concentrates, control the inflammatory response to injury. This can encourage macrophage aggregation, which improves phagocytosis and antigen presentation. PRP additionally encourages M2 macrophage transformation, supporting tissue regeneration and repair. According to in vivo research, PRP encourages macrophage aggregation during tissue repair, and its impact on inflammatory cells is influenced by the quantity and makeup of white blood cells, platelets, and red blood cells. Leukocyte Rich PRP (LR-PRP) can cause an inflammation that is more overt, and the aggregation and infiltration of inflammatory cells speed up tissue repair. On the other hand, LR-PRP can accelerate the proliferation and regeneration of tissue cells since it more powerfully promotes metabolism (8).

Promoting Axonal Regeneration

As a platelet concentrate, PRP contains various cytokines that promote regeneration, including VEGF; a powerful angiogenic factor. which is specific to the vascular endothelium, has chemotaxis effects, and promotes the proliferation and migration of the vascular endothelium. VEGF is a crucial modulator of angiogenesis during embryonic development and regeneration of peripheral nerves. Additionally, it promotes neuronal survival and axonal growth.VEGF is also neuroprotective and can improve motor neuron survival and reduce their susceptibility to ischemic environments. An *in vitro* study of the application of VEGF gene therapy to nerve regeneration found a positive correlation between increased vascularization and enhanced nerve regeneration, suggesting that VEGF application may support and promote the growth of regenerated nerve fibers through the combined effects of angiogenesis, neurotrophy, and neuroprotection. (9)

Takeuchi et al. Evaluated the promotion of PRP on axon growth, and added neutralizing antibodies against VEGF to the cocultures with PRP. The results indicated that addition of PRP to the cocultures promoted axon growth, and the axon growth was significantly suppressed by the addition of neutralizing antibodies against VEGF.(10)

Besides VEGF, brain-derived neurotrophic factor (BDNF) in PRP also

promotes nerve regeneration. There are few reports to demonstrate the positive effect of PRP-derived BDNF on neuron or axon elongation. Due to the low concentration of BDNF in PRP. However, Recent *in vivo* studies(11) show that BDNF promotes the survival and differentiation of neurons as well as endothelial cell survival to maintain blood vessel stability. Castro reported that the PRP could increased the expression of BDNF in nerve trauma site. And Zhao's (12) study further indicated the positive combined effect of PRP and BDNF on axonal remyelination. The neural regeneration process and the effect of PRP was summarized in Fig (1).

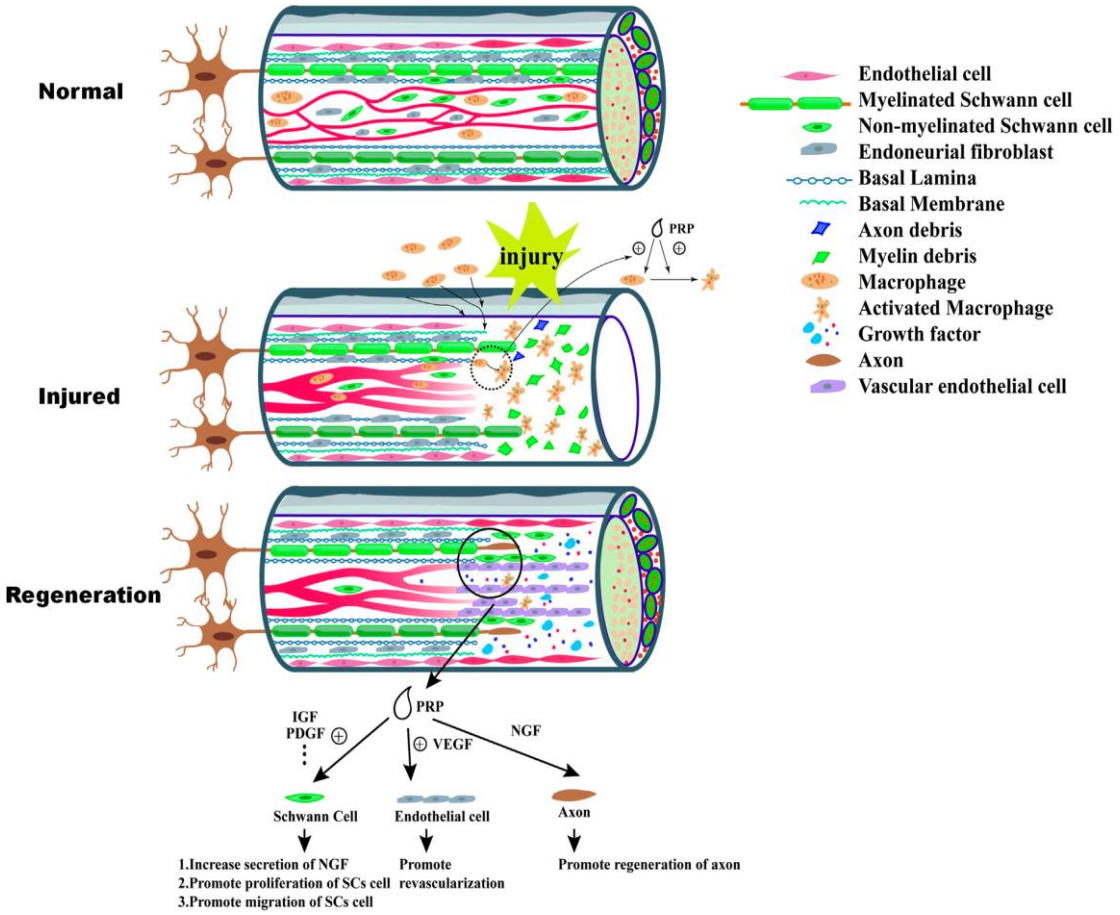

Fig 1: Wallerian degeneration (12).

PRP in post covid anosmia

Three theories have been proposed to explain the pathophysiology of COVID-19-induced olfactory impairment, including the following ones: mechanical obstruction caused by inflammation around the olfactory cleft, which prevents odorants from binding to olfactory receptors; infection of supporting cells that express ACE-2, in particular the sustentacular cells of the olfactory epithelium; and direct invasion of olfactory neurons by SARS-COV-2, which Platelet-rich plasma might be a good option

for treating refractory olfactory impairment, according to the second and third theories (13).

Regeneration is possible in the basal cells that make up the olfactory epithelium. Horizontal basal cells (HBC) and globose basal cells (GBC) are the two types of progenitor cells. Whereas HBCs are normally dormant and increase after lesions, GBCs are continually active and help with the regeneration of olfactory epithelium cells. Hence, turning on HBC is thought to help the olfactory system function better. Several investigations have been carried out recently to evaluate the usage of growth factors for activating HBCs in the olfactory epithelium. Statins, for example, improved degenerative anosmia by promoting olfactory nerve regeneration. The olfactory epithelium improved due to decreased inflammation and the activation of genes associated with cell development and neurogenesis, which resulted in cell proliferation and neuroregeneration. (14)

Treatment with intranasal basic fibroblast growth factor (bFGF) has been successful. A multifunctional growth factor called bFGF promotes neuronal sprouting and inhibits the death of nerve cells, which may result in the regeneration of the olfactory epithelium. Platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), neurotrophin-3, angiopoietin-1, and other GFs and neurotropic factors can be found in high concentrations in PRP. Hence, it is anticipated that administering it will have a therapeutic and neuro-regenerative impact; it may also be employed as a stimulator of basal cell regeneration in the treatment of anosmia. PRP may activate and produce new olfactory system receptors, according to earlier studies. (8)

It has been demonstrated that platelet-rich plasma possesses neuro-regenerative abilities in damage to the peripheral and central nervous systems. PRP encourages the growth of new nerve axons and the restoration of neurological functions after injury to peripheral nerves through three different mechanisms: it changes the fibrin in the nerve gap from a passive supporter to an active promoter of nerve axon regeneration; it directly encourages the growth of new nerve axons; and it encourages the proliferation and upregulation of neurotrophic and other growth factor production by the Schwann cells in the central and distal segments of the nerve. increase the production of axon regeneration-promoting substances and the differentiation of mesenchymal stem cells into Schwann cells.(7)

In a previous study, three three-weekly PRP injections in the olfactory cleft resulted in a highly substantial improvement of post-COVID olfactory parosmia, with a significant difference between the case group and the control group favouring the case group (12). According to a review of the prior research, several authors evaluated platelet-rich plasma's effectiveness in treating anosmia without mentioning post-COVID olfactory impairment (13) . In a research by Mavrogeni et al., (14) five individuals with anosmia got injections of platelet-rich plasma. After the third and ultimately fourth session, four patients said

that "their smell came back." On the other hand ,the last patient, asserted that he could smell "a lot, but not everything." According to the scientists, a promising, last-ditch treatment for total anosmia would include injecting platelet-rich plasma into the olfactory region.

In a study conducted by author (15), seven patients with olfactory dysfunction who had lost their sense of smell for more than six months, showed no symptoms of sinonasal inflammatory illness, and did not improve with olfactory training or topical budesonide rinses were treated with platelet-rich plasma. All patients first noticed a subjective improvement in fragrance, but this improvement gradually stabilised. Three months after starting treatment, two patients with functional anosmia showed no appreciable improvement. Several hyposmia patients showed progress at the three-month checkup, with 60% achieving normosmia.

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