An Overview about Olfactory Dysfunction and Possible Role of Platelet Rich Plasma in its Management

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Abstract
Background
The clinical evaluation of patients with olfactory dysfunction should include a thorough history taking, physical examination, psychophysical olfactory tests, and/or imaging. There have been a few case reports for a natural history of spontaneous recovery from anosmia after post-URI and head trauma, mostly within the first year. Various medical treatments have been tried, including topical and systemic steroids may improve conductive, post-viral, and idiopathic olfactory loss. Topical steroids have been used as monotherapy or adjuvant therapy.Systemic steroids can restore many patients (83%) who still complained smell loss after endoscopic sinus surgery but long-term prognosis is less promising. Platelet-rich plasma is defined as a plasma fraction of autologous blood having platelet concentration above baseline, and prepared from blood drawn from the patient. Following the application of PRP in the olfactory area of 5 patients with idiopathic anosmia in 4 sessions, the sense of smell returned in 4 patients, and one patient stated that he could smell a little but could not smell all. In a similar study conducted in 2020, although there was no significant improvement in Sniffin Sticks score in 2 patients with anosmia, it was observed that all 5 patients with hyposmia reached normosmia after 3 months of follow-up.
Keywords: Olfactory Dysfunction, Platelet Rich Plasma

INTRODUCTION

The anatomy of the olfactory bulb looks like a more than simple "telephone repeater" station. Axons of receptor cells synapse in glomeruli (spherical areas of dense neuropil) on mitral and periglomerular cells. About 25,000 receptor axons synapse in each glomerulus with 25 mitral cells (a 1,000:1 convergence ratio). Axons of mitral cells form the lateral olfactory tract (LOT) and carry impulses toward the CNS. Axon collaterals of mitral cells also make connection to other cells within the bulb. Granular cells, in deeper layers of the olfactory bulb, make dendrodendritic connections with mitral cells and with each other as well as axodendritic connections with centrifugal neurons. Centrifugal neurons synapse mainly with the granule cells and originate in the contralateral olfactory bulb (crossing via the anterior commissure), in the ipsilateral anterior olfactory nucleus and in the ipsilateral diagonal band of Broca (1).

Olfactory Cortex is area of olfactory fiber termination. The lateral olfactory tract courses ventrally over the prepyriform cortex toward the amygdaloid body and along its course fibers branch from it and spread across the cortical ventral surface to synapse in the anterior olfactory nucleus, the prepyriform cortex, the nucleus of the lateral olfactory tract and the cortical amygdaloid nucleus. Mitral cell axons from the lateral olfactory tract form axodendritic synapses with pyramidal cells in the outer molecular layer of the cortex but do not reach deeper layers. Olfactory cortex structures send secondary fibers (which have made synaptic connections with mitral cell axons) to other CNS sites. The anterior olfactory nucleus contributes fibers to the medial forebrain bundle which terminates in the hypothalamus as well as sending centrifugal fibers to the granule cells of the ipsilateral olfactory bulb. Prepyriform cortical fibers are traceable to the amygdala, the hypothalamus and possibly the hippocampus. Amygdala cells

fibers send send axons to the hypothalamus, the prepyriform cortex and the hippocampus. This is, of course, not an exhaustive list of secondary fiber connections. Only major connections are noted. Other multisynaptic CNS olfactory connections have recently been reported. These involve pathways originating in the amygdala and prepyriform cortex, passing through the thalamus and terminating in the orbitofrontal cortex. This represents a neocortical site as opposed to the more classical allocortical (old cortex) and limbic projections (2)

Nerve supply:

Chemo sensation in the nose is innerved by both the olfactory nerve (cranial nerve I) and trigeminal nerve (cranial nerve V) (3)

Olfaction physiology:

After The odorants reach olfactory epithelium, they diffuse into the mucus and are transported to the olfactory receptors by odorant-binding proteins. Binding of the odorant to the specific receptor then induces signaling. A second method of perception of odorants comes posteriorly through the nose via retro nasal olfaction, where odorants arise through the nasopharynx, ascend through the choanae of the nose posteriorly, and rise to the olfactory epithelium via this route. Retro nasal olfaction is thought to play a key role in the sensation of flavor (4).

Then olfactory sensory neurons depolarize in response to the binding of an odorant molecule to G-protein coupled receptors (GPCR). The dissociated G protein activates an intracellular cascade via adenylyl cyclase producing a molecule of cyclic adenosine monophosphate (cAMP) that binds and opens ion channels within the neuron's plasma membrane. Subsequently, an influx of positive sodium and calcium ions and an efflux of negative chloride ions occurs. Neuronal depolarization continues until the threshold potential occurs, firing a resulting action potential. The action potential travels down the olfactory nerves through the cribriform plate towards glomeruli in the olfactory bulb. The glomeruli then project to specific areas within the brain where higher-level processing, modulation, and interpretation occur (3)

Pathology:

Information regarding the pathogenesis of parosmia has been lacking but some hypotheses have been suggested:

1) partial loss of olfactory receptor neurons

2) dysfunction of olfactory bulb by in terneuronal loss

3) pathology of the interpretive central nervous system

4) abnormalities in axonal targeting from regenerating fibers after injury

5) altered olfactory map after olfactory injury. (5).

Types of Olfactory dysfunction :

1.Qualitative olfactory dysfunction

The qualitative olfactory dysfunctions are disorders of odor identification (dysosmia), which include parosmia (altered odor perception with odor present), phantosmia (perception of smell without odor present) and cacosmia (interpret the smell of all odors as unpleasant) (6).

2. Quantitative olfactory dysfunction

The quantitative olfactory dysfunctions are categorized into hyposmia (decrease in smell) and anosmia (lack of smell) compared with normosmia (normal olfactory function) (7).

PREVALENCE:

Although there have been few population-based studies, most authors reported frequencies of 1-3% of olfactory disorders. Recently, one population-based study reported that the prevalence of olfactory dysfunction was 19.1%, composed of 13.3% with hyposmia and 5.8% with anosmia. Dysosmia reported a prevalence of 4.0% in adults (8).

ETIOLOGY OF OLFACTORY DYSFUNCTION:

Aging, male, and smoking are well known risk factors for olfactory dysfunction. Smoking affects olfactory function less than age or sex, and it seems to be dose- and duration-dependent. Smoking cessation may improve olfactory function over time. Common risk factors such as head trauma, stroke, epilepsy, diabetes mellitus, depression, neurodegenerative disorder (Parkinson's disease), toxin (gasoline), medications (adrenergic and cholinergic agents), nasal obstruction, and upper respiratory tract infection are associated with increased prevalence of olfactory impairment (9).

EVALUATION OF OLFACTORY DYSFUNCTION:

The clinical evaluation of patients with olfactory dysfunction should include a thorough history taking, physical examination, psychophysical olfactory tests, and/or imaging (10).

1-History

A detailed history should be taken to characterize the olfactory and/or taste function such as onset (sudden or gradual) and severity (complete or partial) of olfactory dysfunction. Some patients with olfactory dysfunction complain of decreased or altered food flavor. Self-reporting questionnaires may be helpful to estimate the severity of olfactory dysfunction. A well-designed questionnaire can be useful to get good informations from patients. Family history should be determined to detect neurodegenerative and psychiatric disorders. Any preceding events such as cigarette smoking, occupational toxin exposure, URI, head trauma, and nasal surgery should be determined (10).

2-physical examination

A complete head and neck examinations should be performed to check the nasal cavity, oral cavity, cranial nerve functions (II-V, VII-IX, and XII) and any neurologic signs. Nasal endoscopy should be performed to identify possible causes of conductive olfactory loss (nasal polyps or tumors) (10).

3-Psychophysical(olfactory) test

Psychophysical test is detecting the severity of olfactory dysfunction by a trained specialist, and it is helpful to follow up the progression or reversal of olfactory dysfunction. As The University of Pennsylvania Smell Identification Test (UPSIT, 1984) is a quick and simple test and is a 40-items 'scratch-and-sniff' test. The patient is forced to check each odor from four choices. Malingering is suspected if a score less than 5 or 6. The Cross-Cultural Smell Identification Test (CC-SIT) is a variant of UPSIT and uses 12 items, which are commonly identified in different countries. The

Connecticut Chemosensory Clinical Research Center Test (CCCRC, 1988) use 10 stimuli (7 olfactory stimuli and 3 tri- geminal stimuli) in an opaque jar to each nostril. Patients have to choose 10 correct answers among a 20-items list. Finally, Sniffin's stick test (SST, 1997) is an olfactory test based (11).

4-Imaging study

Imaging study is not routinely indicated because in most cases it is negative and could not add more information. Still, in selected cases of structural, inflammatory, traumatic, neurodegenerative, and tumorous conditions, imaging may be helpful. Recently, the fMRI has been used to evaluate activated areas in the brain by olfactory stimulation and will be helpful in the screening and early diagnosis of Alzheimer's disease, Parkinson's disease, multiple sclerosis, or other neurodegenerative diseases. However, it is now used primarily for research (12).

TREATMENT OF OLFACTORY DYSFUNCTION:

1.Treat the underlying causes

There are currently no pharmacologic methods to treat olfactory loss especially in sensory-neural types. Any underlying causes such as smoking, systemic and local diseases should be treated first if present such as temporal lobe seizures, migraines, psychiatric disorders, and metabolic diseases (5).

2.Medical treatment

There have been a few case reports for a natural history of spontaneous recovery from anosmia after post-URI and head trauma, mostly within the first year. Various medical treatments have been tried, including topical and systemic steroids may improve conductive, post-viral, and idiopathic olfactory loss. Topical steroids have been used as monotherapy or adjuvant therapy.Systemic steroids can restore many patients (83%) who still complained smell loss after endoscopic sinus surgery but long-term prognosis is less promising. Zinc deficiency has been suggested as a possible factor for hyposmia. Other drugs such as Gingko biloba and vitamin B have not proven to be effective to treat olfactory dysfunction (13).

3.Surgical treatment

The purpose of surgical treatment (septoplasty, turbinoplasty, and endoscopic sinus surgery) primarily aims at elimination of nasal obstruction and removal of inflamed mucosa or nasal polyps. Improved olfactory function after these surgeries may be a secondary benefit (14).

4.Olfactory training

Although it has not been extensively studied, olfactory training may be helpful to improve olfactory function. Olfactory training consists of a 12 weeks program in which patients expose themselves twice daily to four intense odors (rose, eucalyptus, lemon, cloves) (15).

NeilMed® has created this kit to help facilitate the process of olfactory training.

Platelet Rich Plasma

Definition

Platelet-rich plasma is defined as a plasma fraction of autologous blood having platelet concentration above baseline, and prepared from blood drawn from the patient. Platelet count in PRP has not been yet optimized, but for therapeutic effectiveness, platelet count of 4-5 times above the baseline should be present in the concentrate This is a therapeutic modality that contains abundant autologous growth factors and proteins, which on activation are involved in different phases of the tissue healing like collagen synthesis, tissue granulation and angiogenesis (16).

Platelet Origin, contents and function

Platelets are cytoplasmic fragments of megakaryocytes, a type of white blood cell, and are formed in the bone marrow. They are the smallest of the blood cells, round or oval in shape, and approximately 2µm in diameter. Electron microscopy shows a trilaminar cell membrane with a glycoprotein receptor surface overlying and partially interspersed with and penetrating a bilayer of phospholipids and cholesterol. They contain organelles and structures such as mitochondria, microtubules, and granules (17).

The large number of growth factors contained in platelet granules, the ability of de novo protein synthesis and its antimicrobial activity and inflammation modulator promote cell proliferation and synthesis of extracellular matrix promoting healing, wound repair and other tissue lesions. These features have led to propose the use of autologous PRP for repair and regeneration of different `tissues (18).

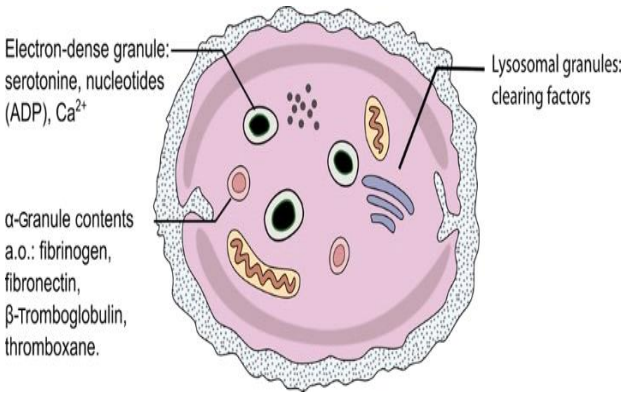

Figure (1): **Schematic drawing of a single platelet and its contents (19).**

Platelets play a role in aggregation, clot formation, homeostasis through cell membrane adherence, and release of substances that promote tissue repair. Also, they influence the reactivity of blood vessels and blood cell types involved in angiogenesis, regeneration, and inflammation (20).

Mechanism of action of PRP:

Platelet rich plasma aid at healing of different tissues, likely due to the number of bioactive molecules released and the stimulation of cell proliferation. Activated platelets secrete intracellular granules that contain platelet-derived growth factor (PDGF), transforming growth factor alpha (TGF-α) and beta (TGF-β), epidermal growth factor (EGF), basic fibroblastic growth factor, and vascular endothelial growth factor. These factors are known to regulate processes including cell migration, attachment, proliferation, and differentiation (8).

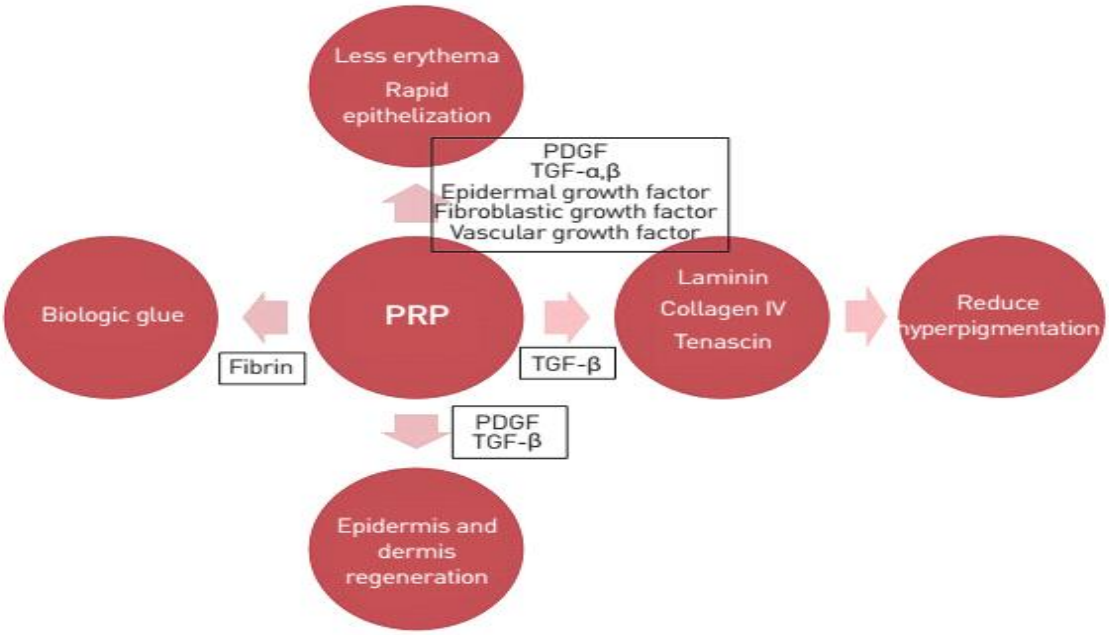

Figure (2): Schematic figure demonstrates actions of PRP and its bioactive molecules (8).

Preparation of PRP

After the proper consent & with all aseptic precautions a sample of patients' blood drawn at the time of treatment. A 10-cc venous blood draw will yield 3-5 cc of PRP depending on the baseline platelet count of an individual, the device used, and the technique employed. The blood draw occurs with the addition of an anticoagulant, such as citrate dextrose. Differential centrifugation is the process that is well known for PRP preparation, it requires approximately 15 minutes and the final product is then ready for injection. In differential centrifugation method, an initial centrifugation (first spin) has been done to separate red blood cells (RBC) is followed by a second centrifugation (second spin) to concentrate platelets, which are suspended in the smallest final plasma volume **(21).**

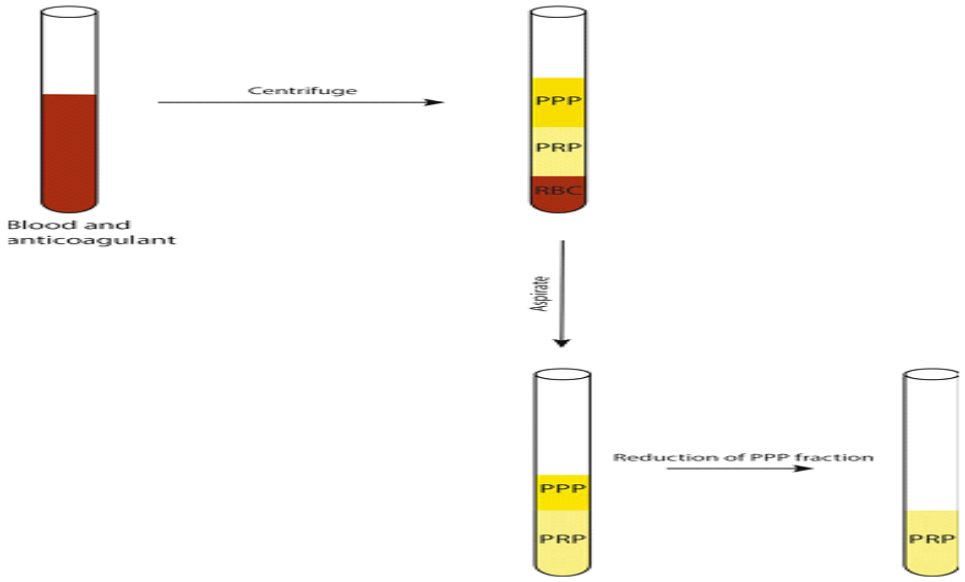

Figure (3): Platelet-rich plasma preparation (22)

Platelet activators such as thrombin or calcium chloride are used to activate PRP.Adding CaCl2 and centrifuging induce a loose fibrin matrix, which entraps growth factors and releases them over 7 days. It is used more often in procedures such as fat grafting or soft tissue augmentation due to the slower secretion over a longer time period (23).

Injection of PRP:

An important point is that clotting leads to platelet activation, resulting in release of the growth factors from the alpha granules, otherwise known as degranulation. Approximately 70% of the stored growth factors are released within 10 minutes, and nearly 100% are released within 1 hour. So, PRP must be applied within 10 minutes of activation. Small amounts of growth factors may continue to be produced by the platelet during the rest of its lifespan (1 week) (24).

Safety of PRP:

Platelet rich plasma is an autologous preparation, so is safe and tolerant on infiltration. It rarely produces mild local inflammatory reactions or post puncture infection. It is free from risk of transmission of infections like hepatitis B, hepatitis C or HIV. It lacks action on nucleus, so is devoid of any mutagenic effects (25).

Contraindications to PRP:

Treatment with autologous PRP is generally considered safe in appropriately selected patients. Potential candidates for treatment with PRP should undergo a pre-treatment hematologic evaluation to rule out potential coagulopathies and disorders of platelet function. Absolute Contraindications are platelet dysfunction syndrome, patients who are anemic and those with thrombocytopenia, hemodynamic instability, severe hypovolemia, unstable angina, anticoagulant or fibrinolytic drug therapy and septicemia (20).

PRP in olfactory dysfunction

Treatment of platelet rich plasma (PRP); in recent years, it has become a favorite material for clinicians and researchers since it accelerates tissue healing, decreases bleeding, edema and pain, and has been used in many specialties and operations with increasing frequency. Due to its advantages in wound healing, angiogenesis, use as glue material, post-operative pain and bleeding, PRP is also one of the interesting materials in otorhinolaryngology and head and neck surgery. A significant improvement in odor function was observed following platelet-rich plasma injection treatment applied in patients with anosmia (26).

PRP was first used in 2016 by Mavrogeni et al. (26), based on the view that platelets can accelerate the regeneration of the olfactory nerves in anosmia patients by secreting various growth factors and active metabolites, especially transforming growth factor. Following the application of PRP in the olfactory area of 5 patients with idiopathic anosmia in 4 sessions, the sense of smell returned in 4 patients and one patient stated that he could smell a little but could not smell all.

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In a study conducted by Yasak et al. (2018) on mice, the effects of PRP on the olfactory nerve were examined histologically, and it was found that epithelial damage was significantly less and epithelial thickness was higher in the PRP group. It was concluded that PRP use in anosmia patients has curative effects.

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