Innovations

Platelet Rich Plasma in Treating Oral Potentially Malignant Disorders

Dr. Bhuvaneshwari. M.
Post Graduate, Department of Oral Medicine and Radiology
Thai Moogambigai Dental College and Hospital
Mogappair, Chennai – 600 107

Dr. Priya Ramani M.D.S.
Professor and H.O.D., Department of Oral Medicine and Radiology
Thai Moogambigai Dental College and Hospital
Mogappair, Chennai – 600 107

Dr. Supreeda. S
Post Graduate, Department of Oral Medicine and Radiology
Thai Moogambigai Dental College and Hospital
Mogappair, Chennai – 600 107

Dr, Raj Vikram. N M.D.S., Ph.D
Professor Department of Orthodontics
Thai Moogambigai Dental College and Hospital
Mogappair, Chennai – 600 107

Dr. K.Ponni M.D.S
Department of Dental surgery, Chengalpattu Medical College, Chengalpattu

Dr. K. Pazhanivel. M.D.S.
Senior Lecturer, Department of Oral Medicine and Radiology

Corresponding Author: **Dr. Bhuvaneshwari. M.**

Abstract:
Potentially malignant disorders are the onesthat have a high chance of turning into a malignant lesion or condition. It is also necessary and important to diagnose and treat them at an early stage. Oral Submucous Fibrosis (OSMF), Oral Lichen Planus, Leukoplakia, and Erythroplakia are some common potentially malignant disorders. The etiological factors vary from deleterious habits to immune-mediated conditions. Management depends upon the severity of dysplasia and the treatment optionsstart from habit cessation counseling, antioxidants, topical and systemic corticosteroids, intralesional injection of steroids, cryotherapy, and surgical excision. This article has been written to highlight the management of these potentially malignant disorders using platelet-rich plasma (PRP) and discuss about its benefits.

Key-words: *Potentially malignant disorders, Leukoplakia, Oral Submucosa Fibrosis, Lichen Planus, Platelet Rich Plasma (PRP).*

Introduction:

World Health Organization held a workshop in 2005 where the terminology of oral lesions with a predisposition to malignant transformation was discussed and recommended to use of the term "potentially malignant disorders"[1]. Oral Potential Malignant Lesion (OPML) has been defined as a group of oral mucosal lesions with an increased risk of malignant transformation [2]. The etiologyof oral precancerous lesions is multifactorial. Tobacco chewing, tobacco smoking, alcohol, local injury, and Epstein Barr virus play a potential role in turning these lesions into malignant conditions[3].

Leukoplakia:

Schwimmer of Budapest coined the term "leukoplakia" in 1877. Leukoplakia is defined as a keratotic white patch or plaque that cannot be scrapped off and cannot be characterized clinically or pathologically as any other disease by WHO [4]. Leukoplakia clinically may affect the oral cavity and oropharynx; they are classified into two subtypes: Homogenous and Non-Homogenous [5].The homogeneous type is uniformly white, thin, and flat in appearance with a shallow crack on the surface [6]. In the Non-Homogenous variety, there are erythroplakia, speckled or nodular type leukoplakia, verrucous leukoplakia, and proliferative verrucous leukoplakia. However, these types of non-homogeneousleukoplakia have a high risk for malignant transformation [7]. Dysplastic or malignant transformation in oral leukoplakiaranges from 15.6% to 39.2% in several studies, in the Indian population it ranges from 0.13% to 2.2% per year. The global transformation rate according to a systematic review by Petti is 1.36% per year [8]. The most common site is the commissure of the lip, buccal mucosa, gingiva, and tongue but the floor of the mouth and lateral border have more chances of turning into malignancy [4]. The most common treatment options are surgical excision, CO2 laser therapy, photodynamic therapy, cryotherapy, and non-surgical treatment modalities are Carotenoids, vitamins (C, E, A), and bleomycin [9-11].

Oral submucous fibrosis:

Schwartz in 1952 was the 1st to describe OSMF. The etiology is multifactorial, chewing of betel quid with areca nut plays a major role [12,13]. Burning sensation due to spicy food and blanching of the mucosa are the early signs. In the mature stage, it leads to palpable fibrous bands, causing fibrosis resulting in trismus [5]. The current treatment modalities include medical management such as intralesional steroid injection, interferon gamma, placental extracts, immunized milk, pentoxifylline, buflomedil hydrochloride, nylidrin, isoxsuprine, beta-carotene, lycopene, vitamins, micronutrients, collagenase, hyaluronidase, chymotrypsin and aloe vera; physical management includes mouth opening exercise, microwave diathermy; surgical management is by excision of palpable fibrotic management [14-20].

Lichen planus:

Lichen planus is a chronic potentially malignant inflammatory mucocutaneous immunological disease. Middle-aged females are most commonly affected. Oral lichen planus affects 0.5% to 2% of general population [21]. Clinically there are 6 types namely papular, plaque, atrophic, erosive, and bulbous. The erosive type is of major concern because of its malignant transformation [22]. Oral lichen planus has multifactorial pathogenesis that is involvement of both antigen-specific and non-specific mechanisms, mast cell degranulation,and activation of matrix metalloproteinase. Chronic potentially malignant disease could be explained by deficient antigen-specific transforming growth factors[23]. Clinically the oral lesions are bilaterally symmetrical as white or grey-white lesions surrounded by liner, circular interlacing striae (Whickham's striae) [24,25]. The treatment varies from topical to systemic corticosteroids and surgical management. Corticosteroids have been used as 1st line of treatment because of their anti-inflammatory and anti-immunological properties [26]. Systemic steroids are only used in situations when the topical

treatment haven been proven ineffective. In conditions such as erosive, atrophic, bullous, and mucocutaneous involvement systemic corticosteroids have been effective [24].

Platelet-rich plasma:

The autologous preparations and enrichment of platelets from plasma concentrate were referred to be PRP in the 1970s [27]. Also known as thrombocytes, platelets are created in the bone marrow of mammals from megakaryocytes in mammalian bone marrow [28]. This form is the initial line of cellular defense after vascular and tissue integrity is compromised and is essential for homeostasis, innate immunity, angiogenesis, and wound healing [29]. The average blood sample contains roughly red blood cells (RBCs), platelets, and white blood cells in the ratio of 94%, 6%, and 1% under normal circumstances. Reversing the RBC-to-platelet ratio to achieve 95% platelets and 5% RBCs is the entire point of enriching PRP [30]. The enriched fraction of PRP is highly successful in tissue reparative efficacy and contains high levels of growth factors and cytokines that stimulate the regeneration of tissue and healing [31]. The main functions of platelets are to aggregate and to support homeostasis by adhering to one another, becoming activated, and aggregating. Before, it was believed that platelets only had a hemostatic function. A new understanding of platelet's role in controlling inflammation, angiogenesis, SC migration, and cell proliferation has emerged as a result of recent research [27].

Characteristics of PRP [32]

- Source – venous blood
- Composition - Growth factors, cytokines
- Mechanism of action- Anti-inflammatory and regenerative
- Efficacy - Effective in younger patients with minimal side effects
- Complications- Few adverse reactions are seen with no major adverse effects

Components of prp and their functions[33]

- PDGF (platelet-derived growth factor)- cell growth, new generation and repair of blood vessels, and collagen production
- IGF 1 (Insulin-like growth factor)- regulates normal physiology in all cell types and improves the early healing of tendon defects.
- FGF (Fibroblast Growth Factor)- Tissue repair, cell growth, collagen production, hyaluronic acid production.
- EGF (Epithelial Growth Factor)- Promotion of Epithelial cell growth, angiogenesis, promotion of wound healing.
- HGF (Hepatocyte Growth Factor)- Angiogenesis stimulator
- IL Cytokines like IL-1, IL-6, and IL-4 help in the healing of muscle injury and transdifferentiation of fibroblasts into myofibroblasts.
- TGF-BETA (Transforming Growth Factor) Growth and neogenesis of epithelial cells and vascular endothelial cells, promotion of wound healing
- VEGF- (vascular endothelial growth factor) Growth and new generation of vascular endothelial cells.

Platelet-rich plasma preparation:

Autologous blood can be collected and prepared for PRP at the dental clinic or hospital on the same visit according to Mostafa et al., 2013:

- Step 1: A tube containing anticoagulant sodium citrate (1.2 ml) is infused with 12 ml of peripheral blood in a ratio of 1:10 (tube 1). The peripheral blood is collected from the patient's antecubital fossa.
- Step 2: Shake the tube gently for complete mixing of the blood with the anticoagulant.
- Step 3: To obtain the best result, the tube is left for 45 minutes at rest.
- Step 4: First spin: The tube is centrifuged at a speed of 50 rpm for 10 mins using a standard common centrifuge. This step helps for the separation of the whole blood into 3 layers.
- Red blood cell (RBCs) is seen in the bottom layer.
- White blood cells (buffy coats) are seen in the middle layer.
- At the top, the highest concentration of platelets is seen.
- Step 5: Using a sterile Pasteur pipette the upper plasma layer and middle layer are aspirated and transferred to a new tube (tube 2). The bottom layer is discarded.
- Step 6: Second spin: Tube 2 will centrifuge at a speed of 1000 rpm for 5 min, gradually increasing to 1500 rpm for the next 5 min thus leaving the platelets at the bottom layer and PPP at the upper layer.
- Step 7: With the help of a sterile Pasteur pipette the upper layer of PPP will be aspirated into a new tube (tube 3), which is discarded.
- Step 8: The remaining 1.5ml of serum and concentrated platelets (PRP) which is settled at the bottom kept at room temperature and used for treatment [34].

Clinical application of PRP[32]

PRP is used as a therapeutic tool which made a significant improvement in the fields of regenerative medicine, dermatology, and musculoskeletal regeneration such as

- Wound healing
- Skin regeneration
- Dentistry
- Cosmetic surgery
- Plastic surgery
- Fat grafting
- Bone regeneration
- Tendinopathies
- Ophthalmology
- Hepatocyte recovery
- Aesthetic surgery
- Orthopaedics
- Soft tissue ulcers
- Skeletal muscle injury
- Jumper's knee
- Osteoarthritis
- Hair growth
- Tissue regeneration
- Scar revision

Merits and demerits of prp[30]

MERITS	DERMITS
Immediate preparation of PRP, which does not require any preservative facilities	Does not have major demerits
Deemed secure and organic because the preparation utilises personal cells without being altered in any way	Applications of PRP may cause infection at the injection site, damage to the nerves or blood vessels, or injection site morbidity.
The treatments do not trigger an immunological reaction.	Scar tissue and calcification are developed at the injection site with acute pain or soreness has also been reported in some patients
The preparations are made from the same individual, thus reducing the contaminated bloodborne diseases.	

Conclusion:

As PRP has been used in various clinical fields as mentioned above, it is important to establish an effective and efficient treatment for potentially malignant disorders. However, few studies have been conducted for erosive oral lichen planus, and OSMF, and promising results have been achieved. However, in the previous studies of OSMF management using PRP, they have not mentioned which grade of OSMF was included in their study, the number of palpable bands (vertical and circumoral bands), the elasticity of buccal mucosa, and improvement in burning sensation was not addressed. To our knowledge, no study has been conducted to prove the above-mentioned drawbacks and management of leukoplakia (speckled, erythroplakia, and verrucous type). In the future, these drawbacks will be addressed and prove effective and efficient management of these conditions using PRP.

References:

1. *Aluckal E, Li, Pei, Lee, Al-Shma, Abraham(20220. Premalignant Lesions of the Oral Cavity: An Update. Journal of Orofacial Research11(3): 49-55.*
2. *Lorini.L, Atín ,Thavaraj, Müller-Richter, Ferranti, Romero et al (2021). Overview of Oral Potentially Malignant Disorders: From Risk Factors to Specific Therapies. Cancers 13(15):3696.*
3. *Vlková B, Stanko, Minarika, Tothova, Szemes, Banasova, et al (2012). Salivary markers of oxidative stress in patients with oral premalignant lesions. Archives of oral biology 57(12):1651-1656.*
4. *Kaur J (2019). Oral Cancer and Precancerous Lesions: A Review. Journal of Advanced Medical and Dental Sciences Research 7(3):4-7.*
5. *Swain SK (2021). Premalignant lesions of the oral cavity: Current perspectives. Int J Res Med Sci. 9(6):1816-1822.*
6. *Dhariwal R, Ray JG, Pattanayak S, Swain N (2012). Oral submucous fibrosis: a report of two pediatric cases and a brief review. Journal of Indian Society of Pedodontics and Preventive Dentistry30(1):85-88.*
7. *Van der Waal I (2009). Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral oncology45(4-5):317-323.*
8. *Petti S (2003). Pooled estimate of world leukoplakia prevalence: a systematic review. Oral oncology39(8):770-780.*
9. *Yardimci G,Kutlubay, Engin, Tuzun (2014). Precancerous lesions of oral mucosa. World Journal of Clinical Cases2(12):866.*

10. Krahl D, Altenburg, Zouboulis (2008). Reactive hyperplasias, precancerous and malignant lesions of the oral mucosa. JDDG: Journal der DeutschenDermatologischen Gesellschaft6(3):217-232.
11. Ribeiro AS, Salles, Silva, Mesquita (2010). A review of the nonsurgical treatment of oral leukoplakia. International journal of dentistry23
12. Arakeri G, Brennan PA (2013). Oral submucous fibrosis: an overview of the etiology, pathogenesis, classification, and principles of management. British Journal of Oral and Maxillofacial Surgery51(7):587-593.
13. Auluck A, Rosin.P, Zhang, Sumanth KN (2008). Oral submucous fibrosis, a clinically benign but potentially malignant disease: report of 3 cases and review of the literature. Journal of the Canadian Dental Association. 74(8).
14. Arakeri G, Brennan PA(2014). Oral submucous fibrosis: an overview of the etiology, pathogenesis, classification, and principles of management. Egyptian Journal of Oral & Maxillofacial Surgery. 5:26-32.
15. Bhadage CJ, Umarji, Shah, Välimaa (2013). Vasodilator isoxsuprine alleviates symptoms of oral submucous fibrosis. Clinical oral investigations17:1375-1382.
16. Angadi PV, Rao S (2010). Management of oral submucous fibrosis: an overview. Oral and maxillofacial surgery.14:133-142.
17. Haque MF, Meghji.S, Nazir.R, Harris.M (2001). Interferon-gamma (IFN-γ) may reverse oral submucous fibrosis. Journal of oral pathology & medicine.30(1):12-21.
18. Sudarshan R,Annigeri.G, Vijayabala (2012). Aloe vera in the treatment for oral submucous fibrosis–a preliminary study. Journal of oral pathology & medicine.41(10):755-761.
19. Alam S, Ali, Giri, Gokkulakrishnan, Natu.S, Faisal(2013). Efficacy of aloe vera gel as an adjuvant treatment of oral submucous fibrosis Oral surgery, oral medicine, oral pathology, and oral radiology116(6):717-724.
20. Banu AF, Murthykumar K, Dhanraj(2016). Effect of Lycopene on Oral Lesions: A Short Review. Research Journal of Pharmacy and Technology9(7):964-966.
21. Edwards PC, Kelsch R. Oral lichen planus: clinical presentation and management (2002). J Can Dent Assoc; 68(8):494-499.
22. Ahuja US, Puria, More. B, Gupta. R, Gupta.D (2020). Comparative evaluation of the effectiveness of autologous platelet-rich plasma and intralesional corticosteroids in the management of erosive oral Lichen planus-a clinical study. Journal of Oral Biology and Craniofacial Research10(4):714-718.
23. Hijazi A, Ahmed, Gaafar. Efficacy of intralesional injections of platelet-rich plasma in patients with oral lichen planus: A pilot randomized clinical trial (2022). Clinical and Experimental Dental Research8(3):707-714.
24. Sriram S, Hasan , Alqarni , Alam , Kaleem, Aziz(2023). Efficacy of Platelet-Rich Plasma Therapy in Oral Lichen Planus: A Systematic Review. Medicina59(4):746.
25. Alrashdan MS, Cirillo, McCullough(2016). Oral lichen planus: a literature review and update. Archives of dermatological research. 308:539-551.
26. Lodi G, Scully, Carrozzo, Griffiths, Sugerman, Thongprasom(2005). Current controversies in oral lichen planus: report of an international consensus meeting. Part 2. Clinical management and malignant transformation.Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology100(2):164-178.
27. Pietrzak WS, Eppley BL (2005). Platelet rich plasma: biology and new technology.Journal of Craniofacial Surgery16(6):1043-1054.
28. Naik B, Karunakar, Jayadev, Marshal (2013). Role of Platelet-rich fibrin in wound healing: A critical reviewJournal of conservative dentistry16(4):284.
29. Currie LJ, Sharpe JR, Martin R (2001). The use of fibrin glue in skin grafts and tissue-engineered skin replacements.PlastReconstr Surg.108 (6):1713-1726.
30. Lyras DN, Kazakosa, Agrogiannis, Verettas, Kokkab, Kiziridisa, et al (2010). Experimental study of tendon healing early phase: is IGF-1 expression influenced by platelet-rich plasma gel.Orthopaedics& Traumatology: Surgery & Research.96(4):381-387.

31. *Banerjee I,Fuseler, Intwala, Baudino(2009). IL-6 loss causes ventricular dysfunction, fibrosis, and reduced capillary density, and dramatically alters the cell populations of the developing and adult heart. American Journal of Physiology-Heart and Circulatory Physiology296(5):694-704.*
32. *Reddy SH, Reddy.R, Babu.N, Ashok.GN(2018). Stem-cell therapy and platelet-rich plasma in regenerative medicines: A review on pros and cons of the technologies .Journal of oral and maxillofacial pathology22(3):367.*
33. *Tomoyasu A, Higashio, Kanomata.K, Goto.M, Kodaira.K, Serizawa.H, et al (2007). Platelet-rich plasma stimulates osteoblastic differentiation in the presence of BMPsBiochemical and biophysical research communications.361(1):62-67.*
34. *Efficacy of intralesional injection of autologous platelet-rich plasma versus intralesional injection of corticosteroids on pain relief and ulcer healing in patients with erosive oral lichen planus Randomized clinical trial .AbdelHameed Hamid Mohammad Hijazi M.Sc. of Oral Medicine Faculty of Dentistry Cairo University.*