



Regenerative potential of platelet concentrates in chronic oral mucosal lesions

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ABSTRACT

Chronic oral mucosal diseases (COMDs) represent a significant challenge for clinicians and patients. They are commonly associated with chronic pain and negative effects on healing and patient's quality of life. Regenerative medicine including the use of biological autologous blood-derived substances (e.g., platelet concentrates [PCs]), has been reported to improve healing and reduce pain in orthopedic and maxillofacial surgeries as well as chronic oral mucosal diseases. In this review, we aim to describe the different types of PCs and their applications in the management of COMDs such as lichen planus, mucositis, pemphigus vulgaris, mucous membrane pemphigoid, and plasma cell mucositis, in terms of healing potential, pain control, and quality of life. Overall, PC applications seem to enhance healing and reduce pain in patients with COMDs. However, due to the small sample size and the lack of standardized clinical trials, further research is required to support these findings.

1. Introduction

Chronic oral mucosal diseases (COMDs) are a distinct group of inflammatory and autoimmune diseases that involve the oral soft tissues. These conditions may cause significant patient morbidity.¹ COMDs will often manifest with oral ulceration, which has been classified based on their number and chronological presentation as proposed by Schneider et al., 1998, or based on their etiology and clinical appearance, as proposed by Heerden et al., 2007 which was later modified to be based on number and lesion morphology.²

Many COMDs are recalcitrant to conventional therapeutics (e.g., topical or systemic corticosteroids). They may be associated with severe physical, social, and psychological consequences. COMDs include oral lichen planus, pemphigus vulgaris, oral mucositis, and aphthous stomatitis.³

The management of COMDs varies considerably according to the nature of the disease. It includes the following treatments:

immunomodulating agents (e.g. corticosteroids), topical and systemic analgesics, antivirals, antibiotics, and antifungals.^{3–5} Based on the evolving concepts of tissue regeneration, the use of growth factors has emerged as an alternative treatment option for COMDs including mucositis and oral ulcers.⁶

Platelet concentrates (PCs) are blood derived biological autologous materials that are rich in platelets and plasma proteins.⁷ Platelets are small cell fragments derived from megakaryocytes.⁷ Platelet count in healthy individuals ranges from 150,000 to 450,000 platelets/ μ l. Platelets contain microtubules, alpha-granules, dense granules, and lysosomes.⁸ An alpha granule contains growth factors (GFs), adhesion proteins, and coagulation proteins. A dense granule contains ADP, ATP, histamine, polyphosphate, calcium, and potassium. The main function of platelet is to stop bleeding via platelet adhesion, activation, secretion and aggregation. Furthermore, platelets have a key role in inflammation and tissue healing mainly via regenerative and angiogenic effects of their products.⁹

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The content of the platelet granules is released upon activation. Platelet activation occurs due to tissue injury as the exposed collagen activates platelets, whereas in PCs application, an external activator such as calcium chloride (CaCl₂), thrombin, collagen, or calcium gluconate is added before its application. It has been reported that platelet activation via ADP stimulates the release of vascular endothelial growth factor (VEGF), which promotes capillary formation, whereas platelet activation via thromboxane A₂ stimulated endostatin secretion, which inhibits capillary formation.¹⁰ Platelet activation allows the release of GFs from a-granules. These bioactive GFs and cytokines include VEGF, platelet-derived growth factors AB (PDGF-AB, PDGF-BB), transforming growth factor-beta (TGF-β), fibroblast growth factors (FGF), insulin-like growth factor (IGF), and brain-derived neurotrophic factor (BDNF).⁷ These GF have been reported to enhance chemotaxis, cellular differentiation, angiogenesis, and tissue regeneration.^{7,8}

PCs are capable of inducing adequate pain relief through their anti-inflammatory properties, angiogenic potentials, and tissue perfusion.¹¹ PCs have an anti-inflammatory role via their effects on the canonical nuclear factor κβ signaling pathway. The net outcome of the therapeutic PC application is to improve angiogenesis and tissue healing.¹² Angiogenesis is vital to accelerate healing via carrying nutrients and modulating immune reaction.¹³ Furthermore, PCs contain cannabinoid receptors,¹⁴ which could modulate pain perception.¹⁵

PC have shown beneficial therapeutic effects in chronic ulcers (e.g. diabetic ulcers), vascular ulcers, acute wounds, chronic non-healing lesions, tendinopathy, and chondropathy.¹⁶ Furthermore, PCs have been used to improve soft and bone regeneration in oral and maxillo-facial interventions.¹⁷ However, there is a lack of evidence regarding the applications of PCs in the treatment of COMDs. Therefore, the aim of the present study was to review different types of PCs and their applications in the management of COMDs in regard to healing potential, pain control, and quality of life.

2. Platelet concentrates (PCs)

2.1. Classification of PCs

PC is a plasma concentrate of the patient's whole blood, which comprises of a high concentration of platelets and other plasma products.^{11,18} The first classification of PCs was proposed in 2009.¹⁹ This classification divides PC products based upon two factors; 1) cell content (mainly leukocytes) and 2) the architecture of fibrin.¹⁹ This classification allows one to identify four main types of PC. The first is called Pure Platelet-Rich Plasma (P-PRP). This type has a low-density fibrin network but does not contain leukocytes. It is produced as an injectable liquid or an activated gel.²⁰

The second is Leukocyte-and Platelet-Rich Plasma (L-PRP), which contains leukocytes and has a low-density fibrin network.²¹ The third type is Pure Platelet-Rich Fibrin (P-PRF), which does not contain leukocytes, and has a high-density fibrin.²² Lastly, leukocyte PRF (L-PRF) that contains leukocytes and has a high-density fibrin network. This is only produced in an activated gel form and it is not used as an injectable material¹⁹ (Table 1).

Advancements have been made in PRF preparation methods to

Table 1
Types of platelet concentrates (PCs).¹⁹

Type of PC	Form	Leukocyte	Fibrin network density
P-PRP	Liquid\ gel	No	Low
L-PRP	Liquid\ gel	Yes	Low
P-PRF	Gel\membrane	No	High
L-PRP	Gel\membrane	Yes	High

Abbreviations: P-PRP, Pure Platelet-Rich Plasma; L-PRP, Leukocyte-and Platelet-Rich Plasma; P-PRF, Pure Platelet-Rich Fibrin; L-PRP, Leukocyte-and Platelet-Rich Fibrin.

overcome the restrictions of its clinical applications. These include the use of injectable-PRF, advanced-PRF, and Titanium-PRF. Furthermore, new PCs products have been proposed to enhance the bioavailability of GFs; these include PRF lysate (PRF-ly), lyophilized-PRF (ly-PRF), and albumin-PRF (Alb-PRF).²³

2.2. PC preparation

2.2.1. Platelet rich plasma (PRP)

PRP can be produced via a single or double spin centrifugation protocol. The centrifugation time ranges from 8 to 30 min and the centrifugation force (g) ranges from 100 g to 1000 g. The plasma rich in growth factors preparation protocol (Anitua's PRGF) is the most commonly documented single spin centrifugation protocol.^{18,19,24}

2.2.2. Platelet-Rich Fibrin (PRF)

PRF, the second generation of PCs, was developed by Choukroun J. et al., in 2001.²⁵ Among different types of PRF, L-PRF is more commonly applied than P-PRF. Preparation of PRF is considered a simple process, in which the blood is first collected in a plan tube without anticoagulants and then centrifuged using a one-step centrifugation method [3000 rpm (700 g) for 10 min].²⁵

P-PRF is produced using Fabrinet PRFM kit via two-spin centrifugation method. First, the blood sample is collected in tubes, which contain tri-sodium citrate and a separator gel, followed by centrifugation at 1100 rpm for 6 min. Second, the buffy coat and the platelet poor plasma layers are aspirated, activated, and then centrifuged at 4500 rpm for 15 min.²⁶

2.3. Immune regulatory effect of platelets

In addition to its essential role in hemostasis, platelet is a vital component of the immune system. Recent evidence supported its crucial functions in inflammatory disease, infection, and malignant tumors.^{25,26} Activated platelet releases GFs and forms pseudopods on its surface, which enhances its connection with other cells such as lymphocytes and neutrophils.²⁷ Among these connections, neutrophil induces the thromboinflammatory function of the activated platelet.^{28,29}

3. Clinical application of PC in chronic oral mucosal diseases

3.1. Oral potentially malignant disorders (OPMDs)

OPMDs are a broad category of oral diseases, which are associated with a potential risk of cancer.³⁰ They include oral lichen planus, oral submucous fibrosis, leukoplakia, erythroplakia, and palatal lesions in reverse smokers.³⁰ The management of OPMDs includes pharmacological therapy, surgical excision, or combination of both.³¹

3.1.1. Oral lichen planus (OLP)

OLP is a common chronic mucosal inflammatory lesion of uncertain etiology and with no definitive cure.³² It affects 0.47%–1.74% of the population.³³ Although many treatments are available, none of them is curative.³⁴ Lichen planus, particularly the erosive form, has a 1.14% reported risk of malignant transformation, although there are no long-term studies regarding the risk of malignant transformation.

Many authors have reported beneficial effects of topical and/or intralesional PC application.^{34,35} In a single interventional study, the topical application of PRP once a week in patients with erosive OLP for 8 weeks showed reduced pain and complete healing in 50% of the participants.³⁴ Also, PRP topical rinses for two months, in patients with ulcerative lesions of OLP, showed significant pain reduction.³⁵ Furthermore, applying PRF to cover scalp excised oral lesions, including OLP, has been reported to improve maximum mouth opening (MMO), reduced pain scores, and resulted in a complete epithelization of the wound after 60 days of the intervention.³⁶ Likewise, intralesional

PRP injections in cases with recalcitrant erosive OLP for 4–8 weeks showed a significant reduction in pain, ulcer size, and erythema.^{37–41} In addition, a randomized clinical trial showed that PRF injections in OLP resulted in a significant reduction of lesion size, pain score, and decreased mean values of oral health impact profile scale, which were comparable to corticosteroid injections.^{42–44} Overall, clinical studies suggest that applying PCs either topically or intralesional for an average of eight weeks would be a valid treatment option for recalcitrant OLP lesions.

3.1.2. Oral submucous fibrosis (OSF)

OSF is a potentially malignant oral disorder characterized by fibrosis of the oral mucosa. OSF is associated with mucosal pain, limited mouth opening, and loss of oral tissue elasticity.⁴⁴ The treatment of OSF is challenging with no effective evidence-based medications available.^{43,44} Studies assessing PRF on oral submucous fibrosis are very limited. Only a single article assessed PRF application in OSF, and the results revealed a positive significant reduction in pain scores, maximum mouth opening scores, and all sites showed complete healing at 60 days after treatment.³⁶ However, there are no long-term studies regarding the role of PC on malignant transformation of OSF.

3.2. Treatment-related oral mucositis (OM)

OM is an inflammatory disease of the lining mucosal layer of the oral cavity.⁴⁵ OM is a common side effect of radiotherapy or chemotherapy in cancer patients. Also, graft versus host disease (GVHD), which could affect patients requiring bone marrow transplantation, may present as a lichenoid mucositis.⁴⁵

The topical application of the cord blood platelet gel in chemotherapy-induced OM revealed a considerable enhancement in patient's quality of life and mucosal healing.⁴⁶ In addition, PRP use in patients with OM induced by GVHD resulted in enhanced healing and reduced pain scores.^{47–49} In addition, mucoadhesive gel vehicle mixed with platelet lysate *in vitro* showed optimal mucoadhesive properties and maintained healing properties until 14 days, while *in vivo*, the reported clinical response showed varied results.⁵⁰ These findings would support the beneficial therapeutic potentials of PCs applied to chronic oral ulcers.

3.3. Pemphigus Vulgaris (PV)

PV is an autoimmune mucocutaneous disease characterized by autoantibodies directed against the desmosomal junctions.³ Oral PV manifests with blisters that rapidly rupture to produce chronic painful ulcers.³ The treatment of choice for PV is corticosteroids.⁵¹ PRP injection used as an adjunctive therapy to immunosuppressive medications showed a significant decrease in pemphigus disease area index in cases of recalcitrant PV lesions compared to corticosteroids only.^{52,53} Recently, another study showed that the application of PRP topically for two months with multiple infusions of rituximab resulted in a complete remission of the lesion.⁵⁴ However, as there are few studies addressed the effects of PC in PV oral lesions, more well-established trials are required to confirm these findings.

3.4. Mucous Membrane Pemphigoid (MMP)

MMP is a type of subepithelial blistering diseases commonly affects the oral mucosa.³ The current management of MMP is based on topical and/or systemic immunosuppressant agents (e.g., corticosteroids).³ Two studies described the clinical effects of injectable PRGF or topical application of PRF in patients with resistant oral MMP. Both studies showed favorable results regarding pain scores and WHO mucositis scores.^{6,55}

3.5. Stevens Johnson Syndrome (SJS)

SJS is a potentially life-threatening mucocutaneous blistering disease.³ This presents with widespread blisters on the skin and the lining mucosa.⁵⁶ A single article reported that the use of topical PRF in patients with SJS showed complete healing after 72 h.⁶ Furthermore, the combination of topical application of PRP with biostatic amnion transplantation in toxic epidermal necrolysis (TEN), a severe form of SJS accelerated healing and decreased morbidity.⁵⁷

3.6. Plasma cell mucositis (PCM)

PCM is an uncommon disease of the oropharyngeal region.⁵⁸ It is manifested by intense pain, dysphagia, and reduced quality of life. Hence, the management is aimed at reducing pain and discomfort. It includes local and systemic corticosteroids, antibiotics, and topical cyclosporine, although such treatments associated with questionable results.^{58,59} Evidence on the application of PC in PCM is lacking; only one case report stated that the application of i-PRF resulted in less pain, but not a complete remission of the lesion.⁵⁸

3.7. Behcet's disease (BD)

BD is a chronic inflammatory disease affecting blood vessels and manifesting with recurrent oral and genital aphthous-like ulcers, and ocular lesions.⁶⁰ Despite the genetic and pathophysiologic background of the disease, the goal of treatment is to reduce the release of cytokines. In non-responding cases, biological agents such as TNF- α inhibiting agents and IFN- α and were used.⁶⁰ A recent pilot study investigated the effect of periumbilical subcutaneous injections of P-PRP in the treatment of BD; the authors concluded that a protective effect is suggested due to significant immunological alterations characterized by the increase in Treg cells and the stability anti-inflammatory cytokine pattern.⁶¹

3.8. Recurrent Aphthous Stomatitis (RAS)

RAS is a common ulcerative disease of the oral mucosa. It manifests as recurrent painful oral ulcers.⁶² Different types of RAS, can be identified clinically, including minor, major, and herpetiform types.⁶² As the etiology of this condition is unknown, no curative treatment is currently available. The management of RAS includes topical or intralesional injections of anesthetics, glucocorticosteroids, or antibiotics.⁶³ A recent randomized clinical trial showed a significant improvement in oral clinical manifestation index in patients with RAS treated with a monthly intralesional PRP injections for 6 months compared to triamcinolone acetonide injections,⁶⁴ (Table 2).

4. Discussions

This review presents the available literature regarding the potential therapeutic effects of PCs for COMDs. Overall, topical and intralesional injections of PC showed beneficial results in terms of pain reduction and overall healing potential of COMDs including oral lichen planus, oral mucositis, mucous membrane pemphigoid, plasma cell mucositis and Behcet's disease.

COMDs are heterogeneous group of conditions that can affect the patient's general health. Given the overlapping immune-inflammatory pathophysiology of these conditions, most COMDs are treated with similar pharmacological interventions such as immunosuppressants (e.g., corticosteroids), nonsteroidal anti-inflammatory drugs, analgesics, and antimicrobials. These therapeutic methods may harbor significant side effects⁶⁶; for example the long-term use of corticosteroids is associated with hypertension, adrenocortical suppression, hyperglycemia, and osteoporosis.⁶⁷

The above-mentioned challenges highlight the need for safer and more effective treatments, utilizing tissue regeneration concepts to

Table 2
Effects of PCs in oral lesions.

Lesion	Type of PCs	Effect of PCs	Ref.
Oral lichen planus	PRF	PRF resulted in a decrease in lesions' size within 3 weeks of treatment	36
	membrane Platelet solution	PC improved quality of life and decreased pain	35
	PRP	Complete regression of the lesion after 4 weeks	41
	PRP	90% of patients reported complete resolution of erythema	40
	PRP	Significant reduction in pain, size of the lesion and inflammation	37
	i-PRF	i-PRF reduced the lesion size by 59.8% and reduced the VAS scores by 47.6%	65
	i-PRF	i-PRF reduced pain and lesion's size	44
	PRP	PRP reduced pain and size of the ulcers	39
	i-PRF	i-PRF reduced VAS scores and lesion size by 68.5% and 74%, respectively	42
Oral mucositis	PRP	Significant decrease in lesion size and pain score	38
	Platelet lysate	Healing was good-to-complete in 5 out of 7 cases	50
	Platelet gel	Platelet gel resulted in improvement of oral mucosa, revealing restitutum ad integrum	46
Pemphigus vulgaris	Platelet gel	PC resulted in improved quality of life and pain reduction	49
	PRP	PRP improved clinical scores in 6 out of 7 cases	53
Mucous membrane pemphigoid	PRF	Three patients showed 100% clinical improvement, while one patient showed 50 % improvement	6
	PRGF	Significant reduction in VAS scores and complete healing of the lesion	55
Submucous fibrosis	PRF	Two patients showed 100% clinical improvement after PRF application	6
Steven Johnson Syndrome	PRF	Complete improvement in clinical parameters after 60 days of application	36
Plasma cell mucositis	PRF	100% showed complete healing after 72 h	6
Behcet's disease	i-PRF	Complete pain reduction after the fourth injection, reduced inflammation for 6 months of follow up	58
	P-PRP	P-PRP reduced the time required to heal for oral ulcers	61
Recurrent aphthous stomatitis	PRP	PRP improved lesion's healing	64

Abbreviations: i-PRF, injectable Platelet-Rich Fibrin; PRGF, plasma rich in growth factors; PRP, platelet rich plasma; P-PRP, pure platelet rich plasma.

improve healing. GFs have been reported to enhance tissue healing.^{68,69} However, due to protein instability, high cost, and the need of high doses of GFs, their clinical application is limited. Thus, PCs could be considered as good alternatives to deliver GFs.⁷⁰ Furthermore, PCs have anti-inflammatory effects. For example, they can modulate levels of pro-inflammatory molecules (e.g., lipoxin A4). Lipoxin A4 is a metabolite of arachidonic acid secreted by many cells. The lipoxin A4 prohibits cytokine secretion, and ultimately reduce pain and enhance healing.⁷¹

Despite the growing literature on the use of PCs for the treatment of oral lesions, the available evidence regarding their clinical applications remains limited due to the lack of standardized RCTs, rarity of some oral mucosal diseases, and heterogeneity of PC preparation and application protocols. Thus, further research is required to investigate the efficacy, duration of action, and role of PC in primary management versus complementary to corticosteroids in patients with COMD. Also, assessing the ancillary benefits of PC (e.g. does it reduce risk of carcinoma?) and its immunomodulatory effects requires further investigations.

5. Conclusions

Within the limitations of published literature, the topical or intra-lesional injections of PCs in patients with chronic oral mucosal lesions seem to reduce pain and improve healing. However, due to limited evidence, further RCTs are required to support these findings.

Future directions

Based on the limited level of evidence regarding clinical application of PCs, future research utilizing standardized PCs preparations protocols, as well as new well-designed RCTs are required to better assess the efficacy of PCs in healing of oral lesions. Another suggestion could aim at investigating allogenic PC applications to optimize their effect and to reduce complexity of harvesting autogenous PCs.

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Declaration of competing interest

The authors declare no conflict of interest.

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