Review Article

Platelet-rich plasma protein as a therapeutic regimen for oral lichen planus: An evidence-based systematic review

ABSTRACT

Oral Lichen Planus (OLP), an autoimmune disorder of unclear pathogenesis affects quality of life of affected individual. Intervention regimens are multiple and still evolving due to its resistance to recover and ability to recur. Platelet rich Plasma (PRP) is a newer, promising treatment modality tested by researchers because of its low cost and negligible adverse effects. Articles were retrieved from search engines of PubMed / Medline, Scopus and Web of Science which fulfilled the eligibility criteria. Cochrane risk of bias tool assessed quality of clinical studies and Joanna Briggs Institute for case reports. A total of 4 articles were included for the systematic review, of which 2 are clinical trials and 2 case reports. All cases were of erosive nature. PRP in case reports were administered when patients did not respond to conventional therapy. PRP demonstrated effective therapeutic benefit in regards to outcome of pain and lesion appearance. PRP can be considered as a potential alternative therapy in treating non-responsive OLP. Further studies are recommended to arrive at a definitive conclusion.

Keywords: Erythema, mucocutaneous, oral lichen planus, pain, platelet-rich plasma

INTRODUCTION

Oral lichen planus, a mucocutaneous disease of autoimmune origin has a prevalence of 0.5–2.2%. It shows a definite female predilection affecting women in middle age.[1,2] Lichen planus in the human body affects skin, scalp, esophagus, nails, and genitals. In the oral cavity, it is seen in buccal mucosa, tongue, palate, and tongue.[3] OLP is generally seen as bilateral, symmetrical lesion with multifocal involvement in oral cavity, with intermittent periods of recovery and recurrence.[4]

Oral lichen planus has six clinical variants, such as reticular, plaque – type, atrophic, erosive/ulcerative, papular, and bullous types.[5] Most commonly seen are reticular, popular, and plaque kind which are painless and is similar to other white lesions. Atrophic and erosive forms are painful and are associated with discomfort and burning sensation. Chronic standing erosive lichen planus is significantly associated for potential malignant transformation, with a risk of 0.5 – 2%.[6]

The pathogenesis of oral lichen planus remains unclear. Literature documents infiltration of lymphocyte triggering inflammatory reaction of lamina propria and epithelial layer. This results in apoptosis of keratinocyte in mucosal epithelium causing development of oral lichen planus. Though etiology is yet not known, a definite association is noted with autoimmune reaction, infection, hypersensitivity and mental oppression.

Newer treatment modalities for treating OLP include the use of Platelet-Rich Protein, a plasma concentrate of individual's

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Nisha Maddheshiya, Adit Srivastava, Varun Rastogi[1], Amlendu Shekhar, Neha Sah[2], Ajay Kumar

Department of Oral Medicine and Radiology, Faculty of Dental Sciences, I.M.S, B.H.U, [2]Department of Oral and Maxillofacial Surgery, Dental College, Azamgarh, Uttar Pradesh, India, [1]Department of Oral and Maxillofacial Pathology, University College of Medical Sciences, Bhairawa, Nepal

Address for correspondence: Dr. Nisha Maddheshiya, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
E-mail: nishagpt0211@gmail.com

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blood containing platelets predominantly. Various growth factors are released by the activated platelets which results in cell migration, proliferation, differentiation, angiogenesis, debris removal, and regeneration of tissues.[7] Transfusion medicine is an emerging discipline of medicine with many researchers working on it. Studies regarding the effect of plasma-rich protein on oral lichen planus is scant. Hence this review was undertaken to answer the research question "Does Plasma Rich Protein have any therapeutic effect on Oral Lichen Planus?"

METHODOLOGY

Protocol

The review followed the PRISMA protocol checklist enlisted for systematic reviews and meta-analysis.

Eligibility criteria

Only articles published in English language reporting the effect of platelet-rich plasma (PRP) protein on oral lichen planus was included. No time frame was set. Conference proceedings, editorials, and other grey literature were excluded. Study design of any type, with patients intervened for OLP with PRP irrespective of age and gender were chosen. Trials with different doses of PRP intervention, comparative trials between PRP and other drugs, PRP versus placebo or no treatment trials were included. Patient in the case reports included were confirmed histopathologically.

Information sources

A comprehensive search was conducted through search engines of PubMed/MEDLINE, Scopus, and Web of Science which identified those articles meeting the eligibility criteria.

Search strategy

Search limits

No time frame for the article search was included due to scant literature availability.

Study identification

Duplicate studies were removed employing endnote software.

Reviewers

Data extraction was performed by two reviewers separately. If any difference of opinion arose, it was mutually sorted through consultation. The references of the included articles were also looked for to any further relevant articles.

Data items

Data included were study ID, sample, location, clinical presentation, presenting symptoms, outcome assessed, intervention, and results.

Risk of bias

Quality assessment of the included studies was evaluated separately for clinical trials and case reports. Cochrane risk of bias tool[8] graded clinical studies while JBI critical appraisal[9] checklist assessed case reports.

RESULTS

Search results

PubMed, Scopus, and Web of Science search retrieved a total of 14 records. After excluding studies not fitting under eligibility criteria and duplicate removal, 8 articles were identified. Hand search from the reference list did not yield any additional articles. The details of the article inclusion, as per PRISMA format is presented as Figure 1. Two reviewers conducted the reviews independently.

Summative assessment

Of the eight articles screened, four studies were included for the final assessment, two of which were clinical trials and two case studies. Tables 1 and 2 elaborate data characteristics of studies included.

The principal outcome measured in all was pain, which was assessed using Visual Analogue scale. While the study of Mowafey B *et al.*[11] did not employ a control group, Ahuja US *et al.*[10] had a control group treated with steroid. The cases can act as their own controls, from baseline to end of study period in the earlier study.

In case reports, PRP intervention was given after the other therapies failed to bring in any improvement i.e., OLP non-responsive to other intervention. Intralesional PRP significantly reduced pain scores in clinical trials as represented by the study results and definite

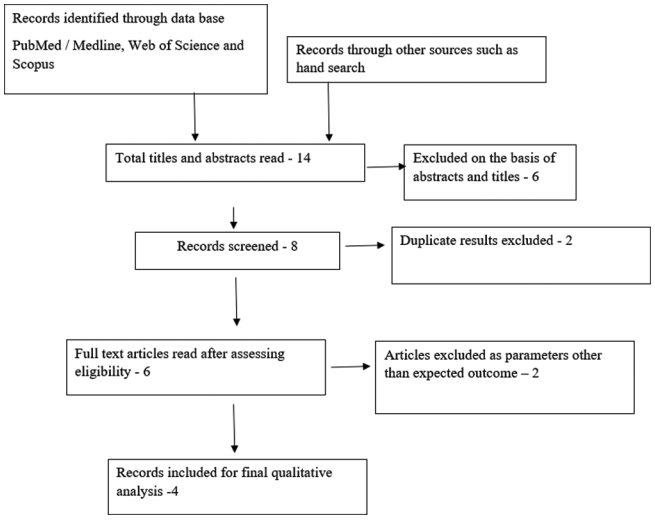

Figure 1: Flow chart diagram for article inclusion

Table 1: Study characteristics of included clinical studies

Study ID	Sample	Location	Clinical presentation	Presenting symptoms	Outcome assessed	Intervention	Results
Mowafey B, 2021[10]	10 patients of erosive OLP; 7 Females: 3 Males; Age range – 50 -65 years	Oral Medicine and Periodontology Department, Faculty of Dentistry, Mansoura University, Egypt	Grayish white lesion with reticular pattern and presenting with differing intensity of ulceration on buccal mucosa, tongue (dorsal surface) and lips	Pain, difficulty in eating and rough sensation	Pain assessed by Visual Analogue Scale (VAS) and healing	0.5 ml of autologous PRP was injected every week for 4 weeks. The patients were followed for 2 months	VAS score significantly decreased from baseline to 4th week (Baseline mean; 9.80+0.42 to 4th week mean; 1.30 + 0.48)
Ahuja US *et al*, 2020[11]	20 patients with erosive lichen planus divided into 2 groups; Group 1 – treated with triamcinolone Group 2 – intervened with PRP	OPD of a dental college in India	Not mentioned	Pain, burning feeling, ulceration and erythema	Pain evaluated by VAS. Scores of erythema and ulceration	Group 2 was injected with 0.5 ml of PRP per 1 cm 2 via 25-gauge needle. The treatment period was for 8 weeks with once-a-week intralesional injection and followed up for 2 months	93.5% reduction in pain was noted at the end of study period. Erythema score reduction was 93.33% at 4th month. A significant difference was noted between group 1 and group 2. Pain percentage reduction was

Table 2: Study characteristics of included case reports

Study ID	Patient characteristic	Predisposition	Hematological or laboratory investigations	Treatment protocol	Outcome evaluate
Merigo E *et al*. 2018[12]	73-year-old male patient	Presented with positive anamnesis for HTN	HCV (Hepatitis C) positive; No other altercations in blood cell count, hepatic values and antitumor markers	Patient was treated in the following sequence a. 0.05% clobetasol ointment in combination with nystatin thrice daily for 5 weeks b. Hydrochloroquinone sulfate 200–400 mg daily for 3 months c. Laser biomodulation with 808 nm diode laser d. Autologous platelet solution from patient's blood administered daily for a month's time	Pain and improvement in ulcerative lesion
Shaik S *et al*., 2020[13]	19 year old female patient	Burning sensation since 1 year in both right and left buccal mucosa	Hematological and biochemical parameters were negative	0.1% of Triamcinolone acetonide was administered four times a day for a month. On reappearance of lesion, 40 mg of systemic prednisolone was given daily, with no improvement in the condition Intralesional PRP was then given along with anesthetic block once a week for a month	Pain evaluated by VAS score and appearance of the lesion

improvement in pain and ulcerative lesion was noted in case reports.

Risk of bias assessment

Quality of studies included was good as assessed by the tools. Overall, low risk of bias was noted in Mowafey B and Ahuja US *et al*.[10,11] The case reports of Merigo *et al*. and Shaik *et al*.[13] also scaled to be of good quality as it followed the proposed protocol of reporting [Tables 3 and 4].

DISCUSSION

The use of PRP as an adjunctive therapy in OLP is gaining wide attention in recent years. Literature reports are very scant and to the best of our knowledge, this is the first systematic review on OLP and PRP.

OLP seems as an incurable condition, with major focus of treatment concentrated on control and reduction of inflammation. Multiple interventional modalities have been employed such as steroids both topical and systemic, retinoids, calcineurin inhibitors, phototherapy, lasers, immunosuppressant, curcumin, and aloe vera. But somehow OLP cases appear to be resistant. A permanent cure is yet to be found. Furthermore, these interventional modalities are linked with adverse effects, limiting their use. PLP in the autologous does not induce any immune response or allergy and literature does not report any serious adverse effects.[14]

The case of Merigo E *et al*.[12] was detected HCV positive. Literature does document the association of OLP with chronic liver disorder, in particular the geographic areas of Japan and Southern Europe.[15] Risk of developing OLP in HCV patients

Table 3: Cochrane risk of bias tool for clinical trials

Study ID	Selection bias		Reporting bias	Other sources of bias	Performance bias	Detection bias	Attrition bias	Other bias
	Random Sequence Generation	Allocation concealment	Selective reporting	Insufficient information	Blinding (participants and personnel)	Blinding (outcome)		
Mowafey B, 2021	*	NA	*	*	**	*	*	*
Ahuja US *et al.*, 2020	?	?	*	?	**	*	*	*

*=Low risk; **=High risk; ?=Uncertain risk

Table 4: Joanna Briggs Institute tool to assess quality in case reports

Components	Merigo E *et al.* 2018	Shaik S *et al.* 2020
1. Were patient's demographic characteristics clearly described?	Yes	Yes
2. Was the patient's history clearly described and presented as a timeline?	Yes	Yes
3. Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes
4. Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes
5. Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes
6. Was the post-intervention clinical condition clearly described?	Yes	Yes
7. Were adverse events (harms) or unanticipated events identified and described?	Yes	Yes
8. Does the case report provide takeaway lessons?	Yes	Yes

is two times greater than the general population. Gerayli *et al.*[16] demonstrated 2.23% of OLP cases were tested positive to HCV antibodies.

All studies had cases with erosive form of lichen planus. This form presents erythema due to inflammation or thinning of epithelium along with Wickham striae. Erosive OLP seems obstinate to presently accessible therapies and hence the need for newer therapeutic agents arises requiring assessment.

Steroids are regarded as the first choice in treating OLP. A switch from topical to systemic is noted in severe cases, but prolonged usage can result in side effects such as candidiasis, mucosal atrophy, adrenal suppression, gastrointestinal disturbances, elevated blood sugar, and blood pressure levels. They can affect progression and severity of OLP and could even activate malignant transformation. The use of natural agents such as aloe vera and curcumin is not able to tackle the issues of resistance and recurrence.[17,18] Hence, PRP intervention with its low cost and effectiveness seems to be a viable alternative in treating OLP.

Mechanism of action of platelet-rich plasma

PRP is a natural source of signaling molecules, and upon activation of platelets in PRP, the P-granules are degranulated and release the Growth Factors (GFs) and cytokines that will modify the pericellular microenvironment which results in cell migration, proliferation, differentiation, angiogenesis, debris removal, and regeneration of tissues. Some of the most important GFs released by platelets in PRP include vascular endothelial GF, fibroblast GF (FGF), platelet-derived GF, epidermal GF, hepatocyte GF, insulin-like GF 1, 2 (IGF-1, IGF-2), matrix metalloproteinases 2, 9, and interleukin 8.[7,19]

Pain reduced significantly among all cases treated with PRP. Ahuja US *et al.* showed that pain percentage reduction in PRP group outweighed the steroid group (82.55% versus 93.5%). Visual Analogue Scale (VAS) was used to measure pain in all the studies included. This scale is widely employed by researchers as the reliability is high. Evidence shows that within 9 mm, 90% of the pain readings were reproducible.[20]

The review ranks better in quality assessment as all cases of OLP in both clinical trial study design and case reports were OLP which was confirmed clinically and histopathologically, thus eliminating the element of selection bias.

Overall, PRP is the treatment of choice in cases non-responsive to conventional therapy without any emergence of adverse in our study. But the evidence is not sufficiently robust to establish the effectiveness as they are not many studies done in this regard. We strongly recommend a greater number of prospective studies conducted in a larger sample with long-term follow-up to arrive at a definitive conclusion to consider PRP as a standard or alternative treatment regimen for OLP.

CONCLUSION

Plasma-rich protein exhibited appreciable effectiveness in alleviating clinical signs and symptoms associated with oral lichen planus, which seemed resistant to conventional treatment. No adverse reaction was noted in any of the patients intervened with PRP.

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Conflicts of interest

There are no conflicts of interest.

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