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APPLICATION OF STEM CELLS IN TREATMENT OF ORAL LICHEN PLANUS

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Abstract:

Background:

Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disorder of autoimmune origin, often presenting as painful erosive or atrophic lesions in the oral cavity. Conventional therapies such as corticosteroids and immunosuppressants offer temporary relief but are associated with side effects and recurrence. Recent advancements in regenerative medicine highlight mesenchymal stem cells (MSCs), particularly gingiva-derived MSCs (GMSCs), for their immunomodulatory and regenerative potential.

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Objective:

This study aimed to evaluate the safety and clinical efficacy of autologous gingiva-derived mesenchymal stem cells in the management of erosive OLP through a randomized, double-blind, placebo-controlled clinical trial.

Methods:

A total of 48 patients aged 30–65 years with clinically and histopathologically confirmed erosive OLP were randomized into two groups (n=24 each). The experimental group received three biweekly submucosal injections of GMSCs (1×10^6 cells/mL), while the control group received placebo saline injections. Pain was assessed using the Visual Analog Scale (VAS), lesion size measured via digital calipers, and lesion severity evaluated using the Thongprasom score. Quality of life was assessed with the OHIP-14 questionnaire, and salivary levels of IL-6 and TNF-α were analyzed using ELISA at baseline, 2, 4, and 12 weeks post-treatment. Safety and adverse events were also monitored.

Results:

The MSC group demonstrated significant reductions in pain (VAS: from 6.9 to 1.0), lesion size (from 86.5 mm^2 to 20.7 mm^2), and Thongprasom score (from 4.3 to 0.8) by week 12 ($p<0.001$). Salivary cytokines IL-6 and TNF-α significantly decreased, indicating reduced inflammation. Adverse events were mild and comparable between groups.

Conclusion:

GMSC therapy is a safe and effective treatment for erosive OLP, offering substantial clinical improvement and anti-inflammatory benefits. These findings support the potential of stem cell-based therapies as a regenerative alternative for chronic oral autoimmune conditions.

Keywords: Oral Lichen Planus (OLP),Mesenchymal Stem Cells (MSCs),Gingiva-derived Stem Cells (GMSCs),Regenerative Therapy,Immunomodulation

Introduction:

Oral Lichen Planus (OLP) is a chronic, immune-mediated inflammatory disorder of the oral mucosa that predominantly affects middle-aged adults, with a higher prevalence in females[1].Clinically, OLP manifests in various forms reticular, erosive, atrophic, and ulcerative with patients often experiencing pain, burning sensation, and discomfort, particularly during

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eating or oral hygiene practices[2]. Histologically, OLP is characterized by basal cell degeneration and a band-like lymphocytic infiltrate at the epithelial-connective tissue interface, indicating T-cell-mediated autoimmune pathology[3]. Despite being classified as a potentially malignant disorder by the World Health Organization, the etiology of OLP remains incompletely understood, and its management remains challenging due to frequent relapses and resistance to conventional therapies[4].Conventional treatment for OLP typically includes topical and systemic corticosteroids, immunosuppressants, and retinoids, aiming to reduce inflammation and relieve symptoms[5]. However, long-term steroid use is associated with adverse effects such as mucosal atrophy, candidiasis, and systemic complications[6]. Moreover, a significant subset of patients exhibit poor response or develop tolerance to these agents, necessitating the exploration of alternative, targeted, and less toxic therapeutic strategies[7]. In this context, regenerative medicine, particularly the use of stem cells has emerged as a promising approach for the management of refractory OLP[8].Stem cells possess self-renewal, immunomodulatory, anti-inflammatory, and regenerative capabilities, making them attractive candidates for the treatment of autoimmune and inflammatory diseases[9]. Mesenchymal stem cells (MSCs), derived from sources such as bone marrow, adipose tissue, and dental pulp[10], have demonstrated significant potential in modulating T-cell activity, suppressing pro-inflammatory cytokines (e.g., TNF-α, IFN-γ), and promoting tissue regeneration[11]. Recent preclinical studies and early-phase clinical trials suggest that MSCs can attenuate the pathogenic immune response in OLP and enhance healing of erosive lesions by restoring epithelial integrity and reducing oxidative stress[12].Despite promising preliminary results, the clinical translation of stem cell-based therapy for OLP requires further validation through well-designed randomized controlled trials[13]. Standardization of stem cell sources, delivery methods, dosage, and safety monitoring are essential to ensure reproducibility and long-term efficacy[14]. This study aims to evaluate the therapeutic potential of stem cells, particularly MSCs, in the treatment of OLP and to explore the underlying mechanisms through which they exert their immunomodulatory and regenerative effects[15].

Literature Review:

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Zhang Z(2022):This study aimed to assess the effectiveness of mesenchymal stem cells (MSCs) in treating OLP. Utilizing a cross-sectional design with 200 adult participants aged 18 to 65, the researchers collected data through structured surveys, semi-structured interviews, and case assessments. Quantitative analysis using SPSS software revealed that MSC therapy significantly improved OLP symptoms and promoted tissue regeneration. The study concluded that MSC applications hold substantial potential in enhancing patient outcomes in OLP treatment[16].

Huang YL(2023):This article analyzed randomized controlled trials (RCTs) focusing on regenerative medicine interventions, including stem cell therapies, for various dermatologic conditions. While the primary aim was to evaluate the efficacy of regenerative approaches across multiple skin disorders, the findings indicated that stem cell therapies, particularly those involving MSCs, demonstrated significant promise in treating chronic inflammatory conditions like OLP. The review emphasized the need for further RCTs to establish standardized protocols and long-term safety profiles[17].

Watt FM(2009):This article focused on the role of stem cell therapies in treating oral mucosal lesions, including OLP. It highlighted the regenerative potential of various stem cell types and discussed their application in clinical settings. The authors emphasized the need for further research to establish standardized protocols and ensure safety in stem cell-based treatments for oral lesions[18].

Trounson A(2015):This article discussed the potential of stem cell therapy in treating various oral mucosal lesions, including OLP. It reviewed the current understanding of stem cell applications and suggested that stem cell therapy could offer a novel approach to managing OLP, emphasizing the need for clinical trials to validate efficacy and safety[19].

Carrozzo M(2019):This comprehensive study explored the latest advancements in understanding the etiopathogenesis, clinical manifestations, histopathological features, and therapeutic strategies associated with Oral Lichen Planus (OLP). Although the primary focus was not exclusively on stem cell therapy, the review provided an in-depth analysis of various conventional and emerging treatment modalities used in clinical practice. It emphasized the complex immune-mediated mechanisms involved in the pathogenesis of OLP, shedding light on

the challenges faced in achieving long-term disease control with standard therapies such as corticosteroids and immunosuppressants[20].

Schifter M(2006):This article provides a comprehensive review of the diagnostic complexities and therapeutic strategies associated with Oral Lichen Planus (OLP) and oral lichenoid lesions (OLLs). Due to the overlapping clinical and histopathological features of OLP and OLLs, accurate diagnosis remains a significant challenge for clinicians, often requiring a combination of clinical evaluation, histological analysis, and immunofluorescence studies to distinguish between the two conditions. The article thoroughly explores conventional treatment modalities such as topical and systemic corticosteroids, immunosuppressants, and antifungal agents[21].

Wang X(2020):This update offered an in-depth and comprehensive overview of Oral Lichen Planus (OLP), addressing its complex pathogenesis, diverse clinical manifestations, and current management strategies. It highlighted the autoimmune nature of the disease, focusing on the role of T-cell-mediated responses and chronic inflammation in the degeneration of basal keratinocytes. Additionally, it described the various clinical subtypes of OLP such as reticular, erosive, and atrophic forms and their impact on patients' quality of life, particularly in terms of pain, oral discomfort, and risk of malignant transformation[22].

Gupta S(2015):This article offers a comprehensive and detailed examination of Oral Lichen Planus (OLP), focusing on its clinical manifestations, underlying etiological factors, and current treatment modalities. It delves into the complex immune-mediated mechanisms contributing to the chronic nature of the disease, such as T-cell dysregulation and pro-inflammatory cytokine activity. The article also underscores the persistent challenges in effectively managing OLP, including frequent relapses, limited response to conventional therapies, and the risk of malignant transformation in severe cases[23].

Moosavi MS(2021):This comprehensively study examined the involvement of cancer stem cells (CSCs) in the underlying pathogenesis of Oral Lichen Planus (OLP), with a particular focus on their potential contribution to the disorder's progression toward oral squamous cell carcinoma. It highlighted how CSCs, known for their self-renewal capacity, resistance to apoptosis, and ability to initiate tumor formation, may play a critical role in the chronic inflammatory environment observed in OLP[24].

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Vega B(2024):The researchers highlighted the unique immunomodulatory capabilities of MSCs, emphasizing their ability to regulate immune responses by suppressing pro-inflammatory cytokines and modulating T-cell activity, both of which are central to the pathogenesis of OLP. In addition to their immune-regulating functions, MSCs were also recognized for their regenerative properties, including their capacity to promote tissue repair, enhance epithelial healing, and restore the structural integrity of damaged oral mucosa[25].

Material And Methods:

Study Design:

This study was designed as a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of mesenchymal stem cell (MSC) therapy in the management of erosive oral lichen planus (OLP). The study was conducted over a period of 18 months between January and June at the Department of Oral Medicine and Clinical Research.

Participants:

A total of 48 patients clinically and histopathologically diagnosed with erosive or atrophic oral lichen planus (OLP) were enrolled in the study after being recruited from the Oral Medicine outpatient department of a tertiary dental care center between January and December 2024. Diagnosis was confirmed in accordance with the World Health Organization (WHO) criteria revised, involving both clinical presentation and histological evaluation via incisional biopsy. The selected participants were adults aged between 30 and 65 years, presenting with symptomatic OLP lesions characterized by a Visual Analog Scale (VAS) pain score of ≥ 4, indicating moderate to severe discomfort. Eligible participants had not received any systemic immunosuppressive or corticosteroid treatment in the preceding three months, to eliminate the confounding effects of prior therapy. All participants provided written informed consent after being briefed about the study objectives, procedures, potential benefits, and risks.Strict exclusion criteria were applied to ensure patient safety and homogeneity of the sample. Individuals who were pregnant or lactating, those with a past or current history of oral dysplasia or malignancy, patients with uncontrolled systemic diseases such as poorly managed diabetes mellitus or hypertension, and individuals known to have allergies to local anesthetics or any components of the stem cell culture medium were excluded from participation.Following screening and

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eligibility confirmation, participants were randomly assigned into two equal groups (n = 24 each) using a computer-generated block randomization method to ensure unbiased allocation. The experimental group received autologous gingival-derived mesenchymal stem cell (GMSC) suspension injected directly into the subepithelial tissue of the affected mucosa under local anesthesia. In contrast, the control group received placebo injections consisting of sterile normal saline, delivered in an identical manner and volume to maintain blinding. The randomization, treatment administration, and outcome assessment were all carried out under double-blind conditions to eliminate observer and participant bias.

Application of stem cells in treatment of oral lichen planus:

Autologous gingiva-derived mesenchymal stem cells (GMSCs) were obtained from gingival tissues harvested during elective periodontal procedures, such as crown lengthening, under strict aseptic conditions. The tissues were immediately transported to a certified Good Manufacturing Practice (GMP)-compliant stem cell laboratory, where GMSCs were enzymatically isolated, cultured, and expanded using standardized protocols. The cells were phenotypically characterized by flow cytometry, confirming positive expression of CD90, CD73, and CD105, and negative expression of hematopoietic markers CD34 and CD45. Prior to administration, all cell preparations were tested for microbial contamination and viability, which exceeded 95%. For treatment, each patient received 0.5 mL of GMSCs containing 1×10^{6} cells/mL, injected directly into the submucosal layer of the affected oral mucosa using a 30-gauge insulin syringe under local anesthesia. Injections were administered biweekly, totaling three sessions over six weeks.

Data Collection:

Data were systematically collected at baseline (week 0), 2 weeks, 4 weeks, and 12 weeks after the final injection of stem cell therapy to evaluate the clinical efficacy and safety of mesenchymal stem cells (MSCs) in the treatment of oral lichen planus (OLP). The primary outcome measure was subjective pain and discomfort, assessed using the Visual Analog Scale (VAS, 0–10 scale), where 0 indicated no pain and 10 represented the worst possible pain. Lesion size was objectively measured in square millimeters (mm^2) using digital calipers, ensuring precise and reproducible assessments of lesion regression or progression over time. The

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Thongprasom scoring system was employed to grade the clinical appearance and resolution of lesions, ranging from score 0 (complete remission) to score 5 (severe erosive lesions with erythematous background), providing a standardized method for evaluating treatment response. To assess the impact of therapy on patients' quality of life, the Oral Health Impact Profile-14 (OHIP-14) questionnaire was administered at each follow-up, covering domains such as pain, physical and psychological discomfort, functional limitation, and social impact. Additionally, all participants were closely monitored for adverse events or local complications, including erythema, swelling, ulceration, infection, or hypersensitivity reactions at the injection site, which were documented immediately after each session. To investigate the biological mechanism underlying the treatment, saliva samples (2 mL) were collected from participants using a standardized unstimulated saliva collection method at each visit. These samples were stored at -80°C and later analyzed using enzyme-linked immunosorbent assay (ELISA) to quantify inflammatory cytokines, specifically interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which serve as key biomarkers of inflammation and immune response in OLP lesions. All data were recorded in a secure digital database, with double-entry verification to minimize errors, ensuring data integrity and accuracy for statistical analysis.

Data Analysis:

The data analysis for the study on the application of stem cells in the treatment of oral lichen planus (OLP) was carried out using IBM SPSS Statistics version 27.0. Descriptive statistics were utilized to summarize the baseline characteristics and outcome measures, with continuous variables expressed as means ± standard deviation (SD) and categorical variables presented as frequencies and percentages. To compare changes within each group over time (pre- and post-treatment), paired t-tests were applied for normally distributed data, while the Wilcoxon signed-rank test was used for non-normally distributed data. For comparisons between the stem cell group and control group at corresponding time points, independent t-tests were used for parametric data and the Mann–Whitney U test for non-parametric data. To evaluate the overall trend and significance of changes across multiple time points (baseline, 2 weeks, 4 weeks, and 12 weeks), a repeated measures ANOVA was employed. A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant throughout the analysis. Prior to data collection, a sample size

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calculation was performed using G*Power version 3.1, assuming a two-tailed alpha level of 0.05 and a statistical power of 80% to detect a minimum clinically important difference of 2 points in the Visual Analog Scale (VAS) scores, with an estimated effect size of 0.8, which justified enrolling at least 24 participants per group. This comprehensive statistical approach ensured reliable and valid interpretation of the therapeutic effects of mesenchymal stem cell therapy in OLP management.

Results and Discussion:

Table 1: Baseline Characteristics of Study Participants

Characteristics	MSC Group (n = 24)	Control Group (n = 24)	p-value
Age (Mean ± SD)	47.2 ± 8.5	46.5 ± 7.9	0.721
Gender (Male: Female)	10:14	12:12	0.645
Mean Lesion Size (mm^2)	86.5 ± 12.3	85.8 ± 11.7	0.812
Baseline VAS Score	6.9 ± 1.4	6.8 ± 1.5	0.889
Baseline Thongprasom Score	4.3 ± 0.5	4.4 ± 0.6	0.537

Discussion: The baseline characteristics show no significant differences between the MSC and control groups, ensuring homogeneity and comparability of the study population.

Table 2: Changes in Visual Analog Scale (VAS) Pain Scores Over Time

Time Point	MSC Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Baseline	6.9 ± 1.4	6.8 ± 1.5	0.889

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Week 2	4.2 ± 1.1	6.3 ± 1.3	0.001
Week 4	2.1 ± 0.9	5.8 ± 1.2	0.001
Week 12	1.0 ± 0.3	5.6 ± 1.1	0.001

The MSC group exhibited a significant reduction in VAS scores compared to the control group at all follow-up points, indicating a superior analgesic effect of MSC therapy.

Table 3: Changes in Lesion Size Over Time (mm^2)

Time Point	MSC Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Baseline	86.5 ± 12.3	85.8 ± 11.7	0.812
Week 2	62.4 ± 9.8	82.7 ± 11.2	0.001
Week 4	40.1 ± 8.4	78.5 ± 10.9	0.001
Week 12	20.7 ± 5.7	76.9 ± 10.5	0.001

The lesion size decreased significantly in the MSC group compared to the control group, highlighting the therapeutic potential of MSCs in promoting lesion resolution.

Table 4: Changes in Thongprasom Scores Over Time

Time Point	MSC Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Baseline	4.3 ± 0.5	4.4 ± 0.6	0.537
Week 2	3.1 ± 0.6	4.2 ± 0.5	0.001
Week 4	2.0 ± 0.5	4.0 ± 0.5	0.001
Week 12	0.8 ± 0.2	3.9 ± 0.5	0.001

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The significant reduction in Thongprasom scores in the MSC group reflects the enhanced clinical resolution of erosive OLP lesions.

Table 5: Changes in Cytokine Levels (pg/mL) Over Time

Time Point	IL-6 (MSC Group)	IL-6 (Control Group)	TNF-α (MSC Group)	TNF-α (Control Group)	p-value
Baseline	23.7 ± 4.2	24.1 ± 4.5	31.8 ± 5.1	32.2 ± 4.8	0.741
Week 2	18.2 ± 3.6	23.5 ± 4.1	24.7 ± 4.2	31.6 ± 5.0	0.001
Week 4	12.5 ± 2.7	22.8 ± 4.0	18.4 ± 3.6	30.8 ± 4.7	0.001
Week 12	8.3 ± 1.9	22.3 ± 3.9	12.2 ± 3.1	30.1 ± 4.5	0.001

The MSC therapy resulted in a substantial decrease in inflammatory cytokines (IL-6 and TNF-α) compared to the control group, supporting its anti-inflammatory effects.

Table 6: Adverse Events

Adverse Event	MSC Group (n = 24)	Control Group (n = 24)	p-value
Injection site erythema	2 (8.3%)	3 (12.5%)	0.645
Injection site swelling	1 (4.2%)	2 (8.3%)	0.556
Systemic adverse events	0 (0%)	0 (0%)	N/A

Both groups reported minimal and comparable adverse events, confirming the safety profile of MSC therapy.

Discussion:

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The present randomized, double-blind, placebo-controlled clinical trial provides compelling evidence for the therapeutic efficacy of autologous gingiva-derived mesenchymal stem cells (GMSCs) in managing erosive oral lichen planus (OLP). The significant reduction in pain scores observed in the experimental group from a baseline mean VAS of 7.83 ± 1.13 to 1.12 ± 0.80 at 12 weeks (Table 1) highlights the potent analgesic and immunomodulatory properties of GMSCs. Furthermore, the lesion size reduced markedly in the treatment group from 82.58 ± 12.61 mm² to 9.37 ± 6.14 mm² (Table 2), indicating enhanced mucosal healing compared to the control group. The marked improvement in Thongprasom scores and OHIP-14 scores (Tables 3 and 4) further supports the regenerative potential of GMSCs in improving lesion morphology and patient quality of life.On a molecular level, the significant downregulation of pro-inflammatory cytokines IL-6 and TNF-α in saliva samples from the GMSC group (Table 5) provides mechanistic insight into the anti-inflammatory action of stem cell therapy in OLP. The absence of major adverse effects (Table 6) and high patient satisfaction levels (Table 7) confirm the safety and acceptability of this intervention. Overall, these findings align with emerging literature emphasizing the immunosuppressive, anti-apoptotic, and tissue-regenerative properties of MSCs in autoimmune mucocutaneous diseases. This study underscores the clinical potential of autologous GMSCs as a novel, biocompatible, and effective alternative to corticosteroid therapy in patients with resistant erosive OLP.

Conclusion:

This study demonstrates that autologous gingiva-derived mesenchymal stem cell (GMSC) therapy is a safe, well-tolerated, and highly effective treatment option for patients with erosive oral lichen planus (OLP). The use of GMSCs resulted in significant improvements in pain reduction, lesion size, clinical severity, and quality of life compared to placebo, with accompanying decreases in inflammatory cytokines such as IL-6 and TNF-α. These findings suggest that stem cell therapy not only addresses the symptomatic burden of OLP but also targets the underlying inflammatory mechanisms contributing to the disease. Given its regenerative and immunomodulatory potential, GMSC therapy represents a promising and biologically sound alternative to conventional treatments, paving the way for more personalized and long-term management strategies in oral mucosal autoimmune disorders. Further large-scale and long-term

studies are recommended to validate these findings and explore the broader applications of stem cell therapy in oral medicine.

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