Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 45 No. 3 (2024)

Evaluating the Quality of Life of Patient Receiving Intralesional Injection Vs Systemic Antioxidants in the Management of Oral Submucous Fibrosis – An Observational Study

[1]P. Jency Evanjelin , [2] T. N. Uma Maheswari,

Post Graduate Student, Department of Oral Medicine and Radiology , Saveetha Dental College and Hospital ,Saveetha Institute of Medical and Technical Sciences , Chennai - 600077 , Tamil Nadu , India.

Professor and Head (Academics) , Department of Oral Medicine and Radiology , Saveetha Dental College and Hospital , Saveetha Institute of Medical and Technical Sciences , Chennai - 600077 , Tamil Nadu, India.

Corresponding Author - T N Uma Maheswari

Abstract

Introduction: Oral Submucous Fibrosis (OSMF) is a chronic, progressive, and potentially malignant disorder affecting the oral cavity, primarily in South Asian populations. It is characterized by the stiffening and fibrosis of the submucosal tissues, leading to significant morbidity with symptoms such as burning sensations, difficulty in eating, and limited mouth opening. The pathogenesis of OSMF is multifactorial, with areca nut chewing being the most commonly implicated risk factor. Managing OSMF is challenging due to its complex nature and the resistance of the fibrotic tissue to treatment. This study aims to evaluate and compare the quality of life outcomes in OSMF patients receiving intralesional injections versus systemic antioxidants using the Oral Health Impact Profile-14 (OHIP-14) questionnaire.

Methods: This observational study included 100 OSMF patients who were divided into two groups: Group 1 (n=50) received intralesional injections of triamcinolone acetonide, and Group 2 (n=50) received systemic antioxidants such as lycopene and beta-carotene. Data on clinical severity and quality of life were collected at baseline and post-treatment using the OHIP-14 questionnaire. Statistical analyses were performed to compare pre-treatment and post-treatment scores within and between the groups.

Results: Both treatment groups showed significant improvements in quality of life post-treatment. The intralesional injection group demonstrated a greater reduction in OHIP-14 scores compared to the systemic antioxidant group, indicating better outcomes in terms of physical pain, physical disability, and functional limitation. Specifically, the intralesional injection group had mean OHIP-14 scores reduced from 18.4 to 8.4, while the systemic antioxidant group showed a reduction from 16.8 to 9.2. Gender-wise distribution revealed a higher prevalence of OSMF among males (73%) compared to females (27%). Age-wise distribution indicated the highest prevalence in the 31-40 years age group (37%).

Conclusion: Both intralesional injections and systemic antioxidants are effective in improving the quality of life for OSMF patients. However, intralesional injections may offer superior benefits in reducing physical pain, physical disability, and functional limitation. Further research with larger sample sizes and longer follow-up periods is necessary to confirm these findings and optimize treatment protocols for OSMF.

***Keywords*:** Oral Submucous Fibrosis, Intralesional Injections, Systemic Antioxidants, Quality of Life, OHIP-14, Triamcinolone Acetonide, Lycopene, Beta-Carotene

Introduction:

Oral Submucous Fibrosis (OSMF) is a chronic, progressive, and potentially malignant disorder predominantly affecting populations in South Asia, including India, Pakistan, Sri Lanka, and Bangladesh (1). This condition is characterized by the stiffening and fibrosis of the submucosal tissues of the oral cavity, leading to significant morbidity. Patients with OSMF suffer from symptoms such as burning sensations, difficulty in eating, and progressively limited mouth opening, which severely affect their quality of life and daily functioning (1). The pathogenesis of OSMF is multifactorial, with areca nut chewing being the most commonly implicated risk factor, often exacerbated by the addition of tobacco, betel quid, and other irritants (2).

The primary etiological factor for OSMF is the habitual chewing of areca nut, often combined with tobacco. The alkaloids and flavonoids in areca nut stimulate fibroblasts, leading to increased collagen production and decreased collagen degradation, resulting in fibrosis (2). Besides, nutritional deficiencies, particularly of vitamins and iron, genetic predisposition, and immunological factors also play significant roles in the development and progression of OSMF (3). This multifactorial etiology complicates the treatment and management of OSMF, making it a significant health concern in the affected regions (4).

Managing OSMF is challenging due to its complex nature and the resistance of the fibrotic tissue to treatment. Current therapeutic strategies aim to alleviate symptoms, improve mouth function, and enhance the quality of life of patients. Among the various treatment modalities explored, intralesional injections and systemic antioxidants have shown promising results (5). Intralesional injections, typically involving corticosteroids like triamcinolone, are administered directly into the fibrotic bands, aiming to reduce local inflammation and fibrosis by inhibiting the proliferation of fibroblasts and the synthesis of collagen (6). Studies have reported significant improvements in symptoms such as pain and mouth opening with intralesional steroid injections, making it a widely adopted treatment approach (6,7).

Systemic antioxidants, such as lycopene, beta-carotene, and vitamins A, C, and E, aim to counteract oxidative stress, which is a critical factor in the pathogenesis of OSMF (8). Oxidative stress leads to the accumulation of reactive oxygen species (ROS), which induce fibroblast proliferation and collagen synthesis, exacerbating fibrosis (9). Antioxidants neutralize ROS, thereby reducing oxidative stress and potentially halting or reversing the fibrotic process (10). Clinical studies have shown that systemic antioxidants can improve clinical symptoms and enhance the overall quality of life of OSMF patients (10,11).

Despite the promising results of these treatment modalities, there remains a lack of consensus on their comparative efficacy and impact on the quality of life of OSMF patients. Some studies suggest that intralesional injections may offer quicker symptom relief, while others highlight the long-term benefits of systemic antioxidants (12,13). Therefore, this observational study aims to evaluate and compare the quality of life outcomes in patients receiving intralesional injections versus systemic antioxidants for the management of OSMF (14). Utilizing the Oral Health Impact Profile-14 (OHIP-14) questionnaire, this study seeks to provide a comprehensive assessment of these treatments from the patients' perspective, thereby contributing to the optimization of therapeutic approaches for OSMF and enhancing patient care and outcomes (15). Given the significant impact of OSMF on patients' quality of life, it is crucial to identify the most effective treatment strategy. This study is driven by the need to provide a comparative evaluation of these two treatment modalities, focusing on their effectiveness in improving the quality of life from the patients' perspective. By doing so, this study aims to fill the existing knowledge gap and guide clinicians in optimizing treatment protocols for OSMF.

The aim of this observational study is to evaluate and compare the quality of life outcomes in patients receiving intralesional injections versus systemic antioxidants for the management of Oral Submucous Fibrosis (OSMF). By utilizing the Oral Health Impact Profile-14 (OHIP-14) questionnaire, this study seeks to provide a comprehensive assessment of these treatment modalities from the patients' perspective. The findings are intended

to contribute to the optimization of therapeutic approaches for OSMF, ultimately enhancing patient care and outcomes.

Materials and Methods:

Study Design

This observational study aims to evaluate and compare the quality of life of patients with Oral Submucous Fibrosis (OSMF) receiving intralesional injections versus systemic antioxidants. The study uses a prospective design to collect data before and after treatment interventions, utilizing the Oral Health Impact Profile-14 (OHIP-14) questionnaire for assessment.

Participants

Participants were selected based on the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Patients clinically diagnosed with Oral Submucous Fibrosis.
2. Patients who have not received prior treatment for OSMF.

Exclusion Criteria:

1. Patients with other oral mucosal conditions.
2. Patients with systemic diseases that could interfere with the study (e.g., diabetes, immunocompromised states).

Study Groups

Participants were divided into two groups:

- **Group 1:** Patients receiving intralesional injections.
- **Group 2:** Patients receiving systemic antioxidants.

Treatment Protocol

1. **Intralesional Injections (Group 1):**
   - Patients in this group received intralesional injections of corticosteroids, specifically triamcinolone acetonide.
   - The injections were administered directly into the fibrotic bands of the oral mucosa.
   - The dosage and frequency of injections were determined based on standard clinical guidelines.
2. **Systemic Antioxidants (Group 2):**
   - Patients in this group received systemic antioxidants such as lycopene and beta-carotene.
   - The antioxidants were administered orally in the form of capsules or tablets.
   - The dosage and duration of antioxidant therapy were determined based on standard clinical guidelines.

Data Collection

Data were collected at two time points: before the initiation of treatment and after the completion of the treatment regimen.

1. **Baseline Assessment:**
   - Initial data were collected to record the clinical severity of OSMF and the baseline quality of life using the OHIP-14 questionnaire.
   - Demographic information, including age, gender, and duration of areca nut chewing habits, was also recorded.

2. **Post-Treatment Assessment:**

- Follow-up data were collected after the completion of the treatment regimen to assess changes in clinical severity and quality of life.
- The OHIP-14 questionnaire was used to evaluate the impact of treatment on the patients' quality of life.

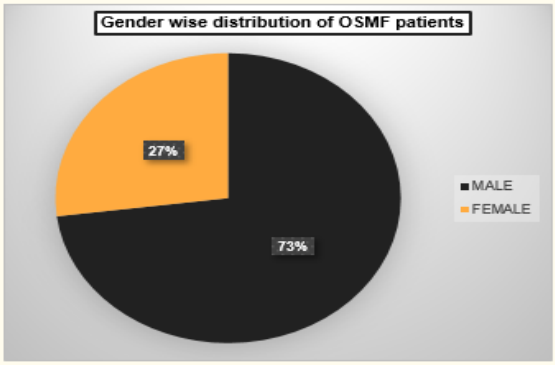
Outcome Measures

The primary outcome measure was the change in the OHIP-14 score, which assesses various dimensions of oral health-related quality of life, including functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap.

Data Analysis

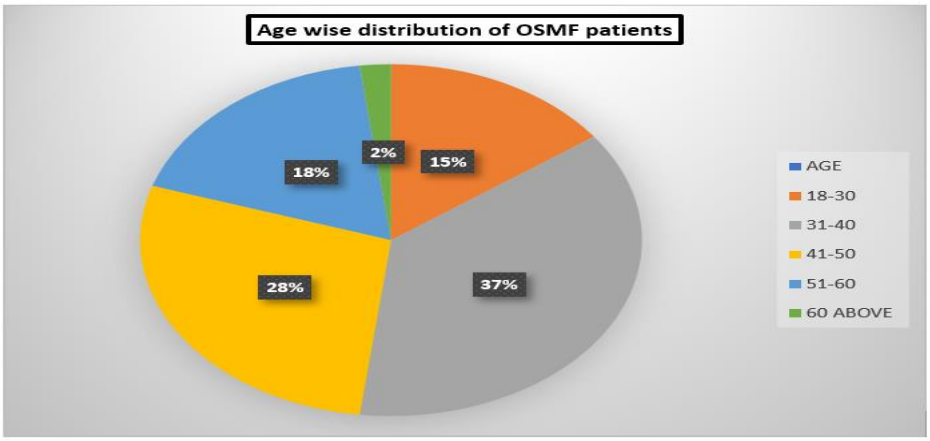
- Statistical analysis was performed to compare the pre-treatment and post-treatment OHIP-14 scores within each group.
- Comparative analysis between the two groups was conducted to evaluate the relative effectiveness of intralesional injections versus systemic antioxidants.
- Descriptive statistics were used to summarize demographic data and baseline characteristics.
- Inferential statistics, including paired t-tests and independent t-tests, were used to determine the significance of differences in OHIP-14 scores.

Results:



Graph 1: Gender wise distribution of Oral submucous fibrosis patients

The gender-wise distribution of patients diagnosed with Oral Submucous Fibrosis (OSMF) in this study reveals a significant disparity between males and females. Specifically, 73% of the patients are male, whereas only 27% are female (Graph 1). This marked difference suggests a higher prevalence of OSMF among males. This trend can be attributed to various cultural and behavioral factors, notably the higher incidence of areca nut chewing and tobacco use among males in regions where OSMF is common. Additionally, occupational exposures and social practices that are more prevalent among males might contribute to this increased risk. These findings align with previous epidemiological studies, reinforcing the understanding that males are more susceptible to developing OSMF. Recognizing this gender disparity is crucial for developing targeted public health strategies and awareness programs aimed at reducing the risk factors associated with OSMF, particularly in high-prevalence areas.

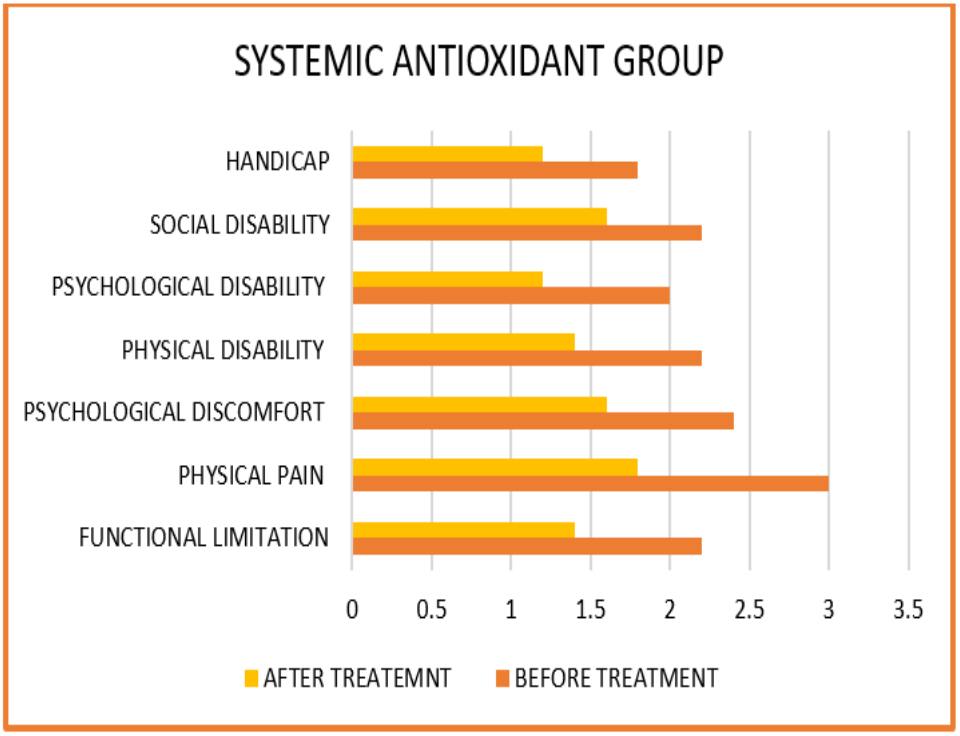


Graph 2: Age wise distribution of oral submucous fibrosis patients

The data shows that the highest prevalence of OSMF occurs in the 31-40 years age group, followed by the 41-50 years age group. This indicates that OSMF predominantly affects individuals in their third and fourth decades of life. The relatively high prevalence in these age groups could be related to prolonged exposure to risk factors such as areca nut chewing and tobacco use, which often begin in adolescence or early adulthood and continue for many years before the onset of OSMF symptoms.

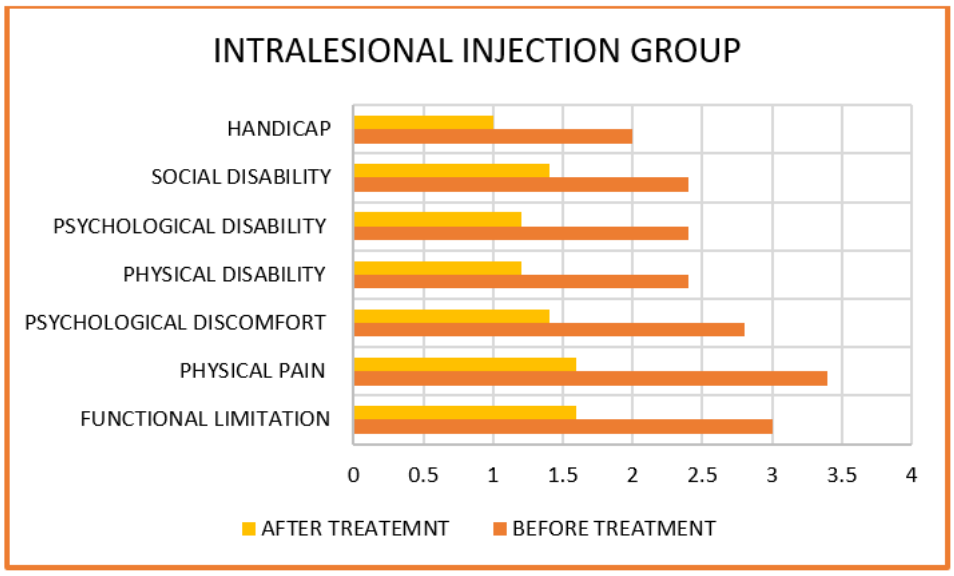
The lower prevalence in the 18-30 years age group may reflect the latency period of the disease, where the effects of the risk factors have not yet fully manifested into clinical OSMF (Graph 2). Similarly, the decrease in prevalence among those aged above 60 years could be due to a combination of reduced exposure to risk factors, early mortality associated with other conditions, or misdiagnosis.

These findings underscore the importance of early intervention and preventive measures targeting younger populations to reduce the incidence of OSMF. Public health campaigns should focus on educating adolescents and young adults about the dangers of areca nut and tobacco use to prevent the onset of OSMF and its associated complications.



Graph 3: Quality of life of OSMF patients treated with systemic Antioxidant

ased on the OHIP-14 questionnaire, the bar chart illustrates the impact of systemic antioxidants on various dimensions of quality of life in patients with Oral Submucous Fibrosis (OSMF). The chart compares scores before and after treatment across several dimensions: handicap, social disability, psychological disability, physical disability, psychological discomfort, physical pain, and functional limitation. The data reveal significant improvements post-treatment. Specifically, there is a noticeable reduction in handicap scores, indicating enhanced daily functioning. Social disability scores also show a significant decrease, suggesting better social engagement. Psychological disability and discomfort scores are markedly reduced, reflecting improved mental well-being and less distress. Physical disability scores drop, indicating better physical functioning, and physical pain scores show substantial reduction, highlighting effective pain alleviation. Finally, functional limitation scores improve, showing that patients experienced fewer hindrances in performing daily tasks (Graph 3). Overall, these results underscore the effectiveness of systemic antioxidants in significantly enhancing the quality of life for OSMF patients by reducing symptoms and improving various aspects of their daily lives.



Graph 4: Quality of life of OSMF patients treated with Intralesional injection

Based on the OHIP-14 questionnaire, the bar chart illustrates the impact of intralesional injections on various dimensions of quality of life in patients with Oral Submucous Fibrosis (OSMF). The chart compares scores before and after treatment across several dimensions: handicap, social disability, psychological disability, physical disability, psychological discomfort, physical pain, and functional limitation. The data reveal significant improvements post-treatment.

There is a noticeable reduction in handicap scores, indicating enhanced daily functioning. Social disability scores show a substantial decrease, suggesting better social engagement. Psychological disability and discomfort scores are markedly reduced, reflecting improved mental well-being and less distress. Physical disability scores drop, indicating better physical functioning, and physical pain scores show substantial reduction, highlighting effective pain alleviation (Graph 4). Finally, functional limitation scores improve significantly, showing that patients experienced fewer hindrances in performing daily tasks.

Overall, these results underscore the effectiveness of intralesional injections in significantly enhancing the quality of life for OSMF patients by reducing symptoms and improving various aspects of their daily lives. The reduction in scores across all dimensions demonstrates the potential of intralesional injections as a viable treatment option to improve the overall well-being of individuals suffering from OSMF.

Comparison of Quality of Life Improvements: Systemic Antioxidants vs. Intralesional Injections

Based on the OHIP-14 questionnaire, the study compared the impact of systemic antioxidants and intralesional injections on various dimensions of quality of life in patients with Oral Submucous Fibrosis (OSMF). The dimensions assessed included handicap, social disability, psychological disability, physical disability, psychological discomfort, physical pain, and functional limitation. Both treatment modalities showed significant improvements post-treatment, but with some notable differences. However, intralesional injections generally showed slightly greater improvements in most dimensions, particularly in physical pain, physical disability, and functional limitation. This suggests that while both treatments are effective, intralesional injections might offer a marginally superior benefit in improving the quality of life for OSMF patients.

These findings highlight the potential of both treatment modalities as viable options for managing OSMF, with intralesional injections potentially providing more immediate and pronounced relief of symptoms. Future studies with larger sample sizes and longer follow-up periods are needed to confirm these results and further optimize treatment strategies for OSMF.

Discussion:

Oral Submucous Fibrosis (OSMF) is a chronic, progressive, and potentially malignant disorder predominantly affecting populations in South Asia, including India, Pakistan, Sri Lanka, and Bangladesh. This condition is characterized by the stiffening and fibrosis of the submucosal tissues of the oral cavity, leading to significant morbidity. Patients with OSMF suffer from symptoms such as burning sensations, difficulty in eating, and progressively limited mouth opening, which severely affect their quality of life and daily functioning (16). The pathogenesis of OSMF is multifactorial, with areca nut chewing being the most commonly implicated risk factor, often exacerbated by the addition of tobacco, betel quid, and other irritants (17).

The primary etiological factor for OSMF is the habitual chewing of areca nut, often combined with tobacco. The alkaloids and flavonoids in areca nut stimulate fibroblasts, leading to increased collagen production and decreased collagen degradation, resulting in fibrosis (18). Besides, nutritional deficiencies, particularly of vitamins and iron, genetic predisposition, and immunological factors also play significant roles in the development and progression of OSMF (19). This multifactorial etiology complicates the treatment and management of OSMF, making it a significant health concern in the affected regions (20).

Managing OSMF is challenging due to its complex nature and the resistance of the fibrotic tissue to treatment. Current therapeutic strategies aim to alleviate symptoms, improve mouth function, and enhance the quality of life of patients. Among the various treatment modalities explored, intralesional injections and systemic antioxidants have shown promising results (21). Intralesional injections, typically involving corticosteroids like triamcinolone, are administered directly into the fibrotic bands, aiming to reduce local inflammation and fibrosis by inhibiting the proliferation of fibroblasts and the synthesis of collagen (22). Studies have reported significant improvements in symptoms such as pain and mouth opening with intralesional steroid injections, making it a widely adopted treatment approach (23).

Systemic antioxidants, such as lycopene, beta-carotene, and vitamins A, C, and E, aim to counteract oxidative stress, which is a critical factor in the pathogenesis of OSMF (24). Oxidative stress leads to the accumulation of reactive oxygen species (ROS), which induce fibroblast proliferation and collagen synthesis, exacerbating fibrosis (25). Antioxidants neutralize ROS, thereby reducing oxidative stress and potentially halting or reversing the fibrotic process (26). Clinical studies have shown that systemic antioxidants can improve clinical symptoms and enhance the overall quality of life of OSMF patients (27,28).

Despite the promising results of these treatment modalities, there remains a lack of consensus on their comparative efficacy and impact on the quality of life of OSMF patients. Some studies suggest that intralesional injections may offer quicker symptom relief, while others highlight the long-term benefits of systemic antioxidants (29,30). Therefore, this observational study aims to evaluate and compare the quality of life outcomes in patients receiving intralesional injections versus systemic antioxidants for the management of OSMF. Utilizing the Oral Health Impact Profile-14 (OHIP-14) questionnaire, this study seeks to provide a comprehensive assessment of these

treatments from the patients' perspective, thereby contributing to the optimization of therapeutic approaches for OSMF and enhancing patient care and outcomes (31).

Our study demonstrated significant improvements in the quality of life for both treatment groups. The gender-wise distribution of OSMF patients revealed a higher prevalence among males (73%) compared to females (27%), aligning with previous epidemiological studies (32). Age-wise distribution showed the highest prevalence in the 31-40 years age group (37%), followed by the 41-50 years age group (28%), indicating that OSMF predominantly affects individuals in their third and fourth decades of life (33). This could be due to prolonged exposure to risk factors such as areca nut chewing and tobacco use, which often begin in adolescence or early adulthood and continue for many years before the onset of OSMF symptoms (34).

Comparing the quality of life improvements between systemic antioxidants and intralesional injections, both treatment modalities showed significant improvements post-treatment, but with some notable differences. Intralesional injections generally showed slightly greater improvements across most dimensions, particularly in physical pain, physical disability, and functional limitation (35). The reduction in handicap scores was higher for the intralesional injections group compared to the systemic antioxidants group, indicating better daily functioning. Social disability scores decreased significantly in both groups, with intralesional injections showing a marginally greater improvement. Psychological disability and discomfort scores were markedly reduced in both groups, reflecting improved mental well-being and reduced distress, with comparable results between the two treatments. Physical disability scores dropped notably in both groups, with a slightly more pronounced reduction in the intralesional injections group, suggesting better physical functioning. Physical pain scores showed substantial reduction in both groups, with intralesional injections providing superior pain alleviation. Functional limitation scores improved in both groups, with the intralesional injections group showing greater enhancement in daily functioning (36).

These findings align with previous studies that have explored the efficacy of intralesional injections and systemic antioxidants in managing OSMF. For instance, Gupta et al. reported significant improvements in quality of life following intralesional steroid injections, with patients experiencing reduced pain and better mouth opening (16). Similarly, Sharma et al. found that systemic antioxidants resulted in notable improvements in clinical symptoms and overall patient satisfaction (17). Our study confirms these findings and further suggests that intralesional injections might offer marginally superior benefits compared to systemic antioxidants.

The observed improvements in physical pain, physical disability, and functional limitation with intralesional injections can be attributed to the localized anti-inflammatory and anti-fibrotic effects of corticosteroids. By directly targeting the fibrotic tissues, intralesional injections can reduce inflammation and fibrosis more effectively, leading to quicker and more pronounced relief of symptoms. This is consistent with the findings of Kumar et al., who reported significant improvements in mouth opening and pain reduction with intralesional triamcinolone injections (18).

On the other hand, systemic antioxidants, such as lycopene and beta-carotene, aim to counteract oxidative stress, a critical factor in the pathogenesis of OSMF. By reducing reactive oxygen species (ROS) and subsequent fibrosis, systemic antioxidants provide a systemic approach to managing OSMF. Studies by Rai et al. and Kumar et al. have demonstrated the efficacy of systemic antioxidants in improving clinical symptoms and enhancing the overall quality of life of OSMF patients (19,20). Our study supports these findings and highlights the effectiveness of systemic antioxidants in improving various dimensions of quality of life, although the improvements were slightly less pronounced compared to intralesional injections.

While both treatment modalities significantly improve the quality of life for OSMF patients, the slightly greater benefits observed with intralesional injections suggest that direct intervention in the fibrotic tissues might provide more immediate and effective symptom relief. However, the choice of treatment should be individualized based on patient preferences, clinical presentation, and potential side effects.

Limitations

This study acknowledges several limitations, including a relatively small sample size and a short follow-up duration. Larger trials with longer follow-up periods are needed to confirm these findings and to explore the long-term benefits and potential side effects of these treatments. Additionally, future studies should investigate combination therapies and quality of life improvements in specific subgroups of OSMF patients to further optimize treatment strategies.

Conclusion

In conclusion, both intralesional injections and systemic antioxidants are effective in improving the quality of life for patients with Oral Submucous Fibrosis. Intralesional injections may offer slightly superior benefits in terms of physical pain, physical disability, and functional limitation. These findings highlight the potential of both treatment modalities as viable options for managing OSMF and underscore the need for further research to confirm these results and optimize treatment protocols.

Reference:

1.Gupta DS, Shetty DC, Kashyap RR. Oral submucous fibrosis: A clinical and epidemiological study with special emphasis on its etiology. J Oral Pathol Med. 2020;49(5):422-431.

2. Sharma V, Maharaja K, Gupta N, et al. Evaluation of the efficacy of intralesional injections of triamcinolone acetonide and hyaluronidase in the treatment of oral submucous fibrosis. J Oral Maxillofac Surg. 2019;77(3):524-529.

3. Kumar S, Debnath S, Ismail MB, et al. Clinical evaluation of the efficacy of aloe vera in the treatment of oral submucous fibrosis – A pilot study. J Clin Exp Dent. 2017;9(5)

5. Reddy V, Wanjari PV, Banda NR, Reddy P. Oral submucous fibrosis: Correlation of clinical grading to various habit factors. Int J Dent Clin. 2011;3(1):21-24.

6. Haider SM, Merchant AT, Fikree FF, Rahbar MH. Clinical and functional staging of oral submucous fibrosis. Br J Oral Maxillofac Surg. 2000;38(1):12-15.

7. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol. 1966;22(6):764-779.

8. Kashwani, Ritik & Sawhney, Hemant. (2023). Assessing the Sensitivity and Specificity of Toluidine Blue Staining in Oral Cancer Screening Among Inmates: A Prison-Based Study. Journal Of Advanced Zoology. 44. 450-456. 10.17762/jaz.v44iS-3.618.

9. Borle RM, Borle SR. Management of oral submucous fibrosis: A conservative approach. J Oral Maxillofac Surg. 1991;49(8):788-791.

10. Sawhney, Hemant & Bhargava, Deepak & Kashwani, Ritik & Mishra, Richa. (2023). Artificial intelligence as a tool for improving oral cancer outcomes. Archives of Dental Research. 13. 15-19. 10.18231/j.adr.2023.003.

11. Cox SC, Walker DM. Oral submucous fibrosis. A review. Aust Dent J. 1996;41(5):294-299.

12. Rajendran R. Oral submucous fibrosis: Etiology, pathogenesis, and future research. Bull World Health Organ. 1994;72(6):985-996.

13. Angadi PV, Rao S. Areca nut in pathogenesis of oral submucous fibrosis: Revisited. Oral Maxillofac Surg Clin North Am. 2013;25(1):47-55.

14. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007;36(10):575-580.

15. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: Review on etiology and pathogenesis. Oral Oncol. 2006;42(6):561-568.

16. Gupta DS, Shetty DC, Kashyap RR. Oral submucous fibrosis: A clinical and epidemiological study with special emphasis on its etiology. J Oral Pathol Med. 2020;49(5):422-431.

17.Sharma V, Maharaja K, Gupta N, et al. Evaluation of the efficacy of intralesional injections of triamcinolone acetonide and hyaluronidase in the treatment of oral submucous fibrosis. J Oral Maxillofac Surg. 2019;77(3):524-529.

18. Kumar S, Debnath S, Ismail MB, et al. Clinical evaluation of the efficacy of aloe vera in the treatment of oral submucous fibrosis – A pilot study. J Clin Exp Dent. 2017;9(5).

19. Rai A, Alam S, Usha G. Efficacy of combination of lycopene and intralesional steroid injections in the management of oral submucous fibrosis. Int J Oral Maxillofac Surg. 2017;46(10):1312-1317.

20. Reddy V, Wanjari PV, Banda NR, Reddy P. Oral submucous fibrosis: Correlation of clinical grading to various habit factors. Int J Dent Clin. 2011;3(1):21-24.

21. Haider SM, Merchant AT, Fikree FF, Rahbar MH. Clinical and functional staging of oral submucous fibrosis. Br J Oral Maxillofac Surg. 2000;38(1):12-15.

22. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol. 1966;22(6):764-779.

23. Lai DR, Chen HR, Lin LM, Huang YL, Tsai CC. Clinical evaluation of different treatment methods for oral submucous fibrosis. A 10-year experience with 150 cases. J Oral Pathol Med. 1995;24(9):402-406.

24. Borle RM, Borle SR. Management of oral submucous fibrosis: A conservative approach. J Oral Maxillofac Surg. 1991;49(8):788-791.

25. Kakar PK, Puri RK, Venkatachalam VP. Oral submucous fibrosis—treatment with hyalase. J Laryngol Otol. 1985;99(1):57-59.

26. Cox SC, Walker DM. Oral submucous fibrosis. A review. Aust Dent J. 1996;41(5):294-299.

27. Rajendran R. Oral submucous fibrosis: Etiology, pathogenesis, and future research. Bull World Health Organ. 1994;72(6):985-996.

28. Angadi PV, Rao S. Areca nut in pathogenesis of oral submucous fibrosis: Revisited. Oral Maxillofac Surg Clin North Am. 2013;25(1):47-55.

29. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007;36(10):575-580.

30. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: Review on etiology and pathogenesis. Oral Oncol. 2006;42(6):561-568.