ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

Vitamin A loaded Bioadhesive Patches for Oral Mucosal Delivery in Treatment of Potentially Malignant White Lesions: A Placebo-Controlled Study

Dr Vishal Mehrotra , Dr Rahul Srivastava, Dr Kriti Garg

Professor & HOD, Department Oral Medicine and Radiology, Rama Dental College Hospital and Research Centre, Rama University, Kanpur, U.P

Professor, Department Oral Medicine and Radiology, Rama Dental College Hospital and Research Centre, Rama University, Kanpur, U.P

Reader, Department Oral Medicine and Radiology, Rama Dental College Hospital and Research Centre, Rama University, Kanpur, U.P

Abstract

Introduction: This randomized controlled trial aimed to evaluate the efficacy of Vitamin A-loaded bioadhesive patches for the treatment of potentially malignant white lesions of the oral mucosa.

Materials and Methods: A total of 100 participants with clinically diagnosed oral leukoplakia were randomly assigned to receive either Vitamin A-loaded bioadhesive patches (n=50) or placebo patches (n=50) for 8 weeks. The primary outcome was the reduction in lesion size, while secondary outcomes included histopathological improvement, patient-reported pain levels, and adverse effects. Participants were followed up for 36 months to assess long-term efficacy and lesion recurrence.

Results: At the end of the treatment period, the intervention group showed a significantly greater reduction in lesion size (mean 18.6 mm^2) compared to the control group (mean 7.4 mm^2) ($p < 0.001$). Histopathological improvement was observed in 70% of participants in the intervention group versus 30% in the control group ($p < 0.001$). Long-term follow-up revealed that 78% of participants in the intervention group remained lesion-free at 36 months, with no cases of malignant transformation, compared to 46% in the control group ($p < 0.01$).

Conclusion: Vitamin A-loaded bioadhesive patches are an effective and safe treatment for potentially malignant white lesions, offering significant lesion size reduction, histopathological improvement, and sustained long-term benefits with minimal adverse effects. This study

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

supports the use of localized Vitamin A therapy as a promising approach for the management of oral potentially malignant disorders.

Keywords: Vitamin A, bioadhesive patches, oral leukoplakia, randomized controlled trial, potentially malignant lesions, oral mucosal delivery.

Introduction

Potentially malignant white lesions of the oral mucosa, such as Leukoplakia, Erythroplakia, and Oral submucous fibrosis (OSMF), represent a significant clinical challenge due to their unpredictable progression to oral cancer. Leukoplakia, the most common of these lesions, has an estimated malignant transformation rate ranging from 1% to 20%, depending on various factors such as lesion size, site, and histological characteristics.[1] Given the serious implications of these lesions, effective management is crucial to prevent malignant transformation and improve patient outcomes.[2]

Vitamin A, a fat-soluble retinoid, has long been recognized for its role in maintaining epithelial health and modulating cellular differentiation and proliferation.[3] Several studies have investigated the use of retinoids in chemoprevention and treatment of potentially malignant oral lesions, with varying degrees of success.[4] However, systemic administration of Vitamin A and its analogs is often associated with significant side effects, including hepatotoxicity, teratogenicity, and mucocutaneous reactions. This has prompted the exploration of localized delivery methods to enhance efficacy while minimizing systemic toxicity.[5]

Bioadhesive patches represent a promising vehicle for the localized delivery of therapeutic agents to the oral mucosa. These patches adhere to the mucosal surface, allowing for sustained release of the active ingredient directly at the site of the lesion. This targeted approach not only enhances drug bioavailability but also reduces systemic exposure and associated side effects.[6] Recent advances in bioadhesive technology have led to the development of patches that can deliver a range of therapeutic agents, including vitamins, directly to the oral mucosa with high precision and control.[7]

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

In this study, we aim to evaluate the efficacy of Vitamin A-loaded bioadhesive patches in the treatment of potentially malignant white lesions of the oral mucosa. By leveraging the localized delivery system, we hypothesize that these patches will provide a more effective and safer treatment alternative compared to traditional systemic therapies. This randomized controlled trial will assess the clinical and histopathological outcomes of patients treated with Vitamin A-loaded patches versus those receiving a placebo.

Materials and Methods

Study Design

This study was conducted as a double-blind, randomized controlled trial (RCT) to evaluate the efficacy of Vitamin A-loaded bioadhesive patches in treating potentially malignant white lesions of the oral mucosa. Participants were randomly assigned to either the intervention group (Vitamin A-loaded patches) or the control group (placebo patches).

Participants

Inclusion Criteria:

- Adults aged 18-65 years.
- Clinically and histologically confirmed diagnosis of potentially malignant white lesions, including Leukoplakia or Erythroplakia.
- Lesions with no prior treatment or recurrence after treatment.
- Willingness to comply with study procedures and provide written informed consent.

Exclusion Criteria:

- History of hypersensitivity to Vitamin A or any components of the bioadhesive patch.
- Presence of any other oral mucosal diseases unrelated to the study condition.
- Use of retinoids or other treatments that might interfere with study outcomes within the last 6 months.
- Pregnant or lactating women.

Intervention

Intervention Group:

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

Participants in the intervention group received Vitamin A-loaded bioadhesive patches. Each patch was containing 25,000 IU of Vitamin A in a matrix designed to release the vitamin gradually over 8 hours when applied to the oral mucosa. Patches were applied once daily to the lesion site for duration of 8 weeks.

Control Group:

Participants in the control group received placebo patches identical in appearance to the Vitamin A-loaded patches but containing no active ingredient. Patches were applied with the same frequency and duration as in the intervention group.

Randomization and Blinding

Participants were randomly assigned to either the intervention or control group using a computer-generated randomization sequence. Both participants and investigators were blinded to the group assignments to prevent bias in treatment administration and outcome assessment.

Outcome Measures

Primary Outcome:

Reduction in lesion size, measured in square millimeters, from baseline to 8 weeks.

Secondary Outcomes:

Histopathological improvement, assessed through biopsy at baseline and after 8 weeks, including changes in dysplasia grading. Patient-reported outcomes on discomfort, pain, and any adverse effects, measured using a standardized questionnaire at baseline, 4 weeks, and 8 weeks.

Follow-Up and Compliance

Participants were scheduled for follow-up visits during three key periods:

0-3 months: This includes the initial treatment period, with follow-up visits at 4 weeks, 8 weeks, and 12 weeks post-treatment to monitor immediate effects and compliance.

4-24 months: Participants returned for bi-annual visits at 6 months, 12 months, 18 months, and 24 months. These visits were focus on assessing the long-term effects of the treatment, including the persistence of lesion reduction and any late-onset side effects.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

25-36 months: Annual follow-up visits at 30 months and 36 months were conducted to evaluate the sustained efficacy of the treatment and to monitor for any signs of lesion recurrence or progression to malignancy.

Compliance Monitoring: Patch application compliance was monitored using patient diaries and patch return counts during the first 3 months. In subsequent visits, compliance with follow-up schedules and any additional interventions were recorded.

Statistical Analysis

Data was analyzed using SPSS software. The primary and secondary outcomes were compared between the intervention and control groups using appropriate statistical tests, such as the independent t-test or Mann-Whitney U test for continuous variables and chi-square tests for categorical variables.

Longitudinal data across the follow-up periods were analyzed using repeated measures ANOVA or mixed-effects models to account for within-subject correlations over time. A p-value of <0.05 will be considered statistically significant.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the institutional review board (IRB) before the commencement of the trial. Informed consent was obtained from all participants, and their confidentiality was strictly maintained.

Results

Participant Characteristics

A total of 100 participants were enrolled in the study, with 50 participants randomly assigned to the intervention group (Vitamin A-loaded bioadhesive patches) and 50 participants to the control group (placebo patches). The demographic and baseline characteristics of the participants are summarized in Table 1. There were no significant differences between the two groups in terms of age, gender, or baseline lesion size, ensuring comparability between the groups.

Table 1: Demographic and baseline characteristics of the participants

Characteristic	Intervention Group (n = 50)	Control Group (n = 50)	p-value
Mean Age (years)	45.2 ± 10.3	44.8 ± 9.7	0.79

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

Male (%)	30 (60%)	28 (56%)	0.68
Female (%)	20 (40%)	22 (44%)	0.68
Baseline Lesion Size (mm²)	35.4 ± 10.2	34.9 ± 9.8	0.77
Smoking History			
Yes (%)	25 (50%)	27 (54%)	0.70
No (%)	25 (50%)	23 (46%)	0.70
Alcohol Consumption			
Yes (%)	15 (30%)	16 (32%)	0.83
No (%)	35 (70%)	34 (68%)	0.83

Primary Outcome:

Reduction in Lesion Size

At the end of the 8-week treatment period, the mean reduction in lesion size was significantly greater in the intervention group compared to the control group. Participants in the intervention group experienced a mean reduction in lesion size of 18.6 mm² (SD ± 8.2), while those in the control group had a mean reduction of 7.4 mm² (SD ± 6.5). The difference in lesion size reduction between the groups was statistically significant ($p < 0.001$), indicating a clear therapeutic benefit of the Vitamin A-loaded bioadhesive patches.

Table 2: Reduction in Lesion Size

Outcome	Intervention Group (n = 50)	Control Group (n = 50)	p-value
Mean Reduction in Lesion Size (mm²)	18.6 ± 8.2	7.4 ± 6.5	<0.001

Secondary Outcomes

Histopathological Improvement

A significant proportion of participants in the intervention group showed histopathological improvement, with 70% (35 out of 50) of the lesions showing a decrease in dysplasia grading. In contrast, only 30% (15 out of 50) of participants in the control group showed any histopathological improvement ($p < 0.001$).

Patient-Reported Outcomes

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

Participants in the intervention group reported lower levels of discomfort and pain compared to the control group, with a mean pain score of 2.3 ± 1.2 versus 4.1 ± 1.5 on a 10-point scale ($p < 0.001$). The incidence of adverse effects was low in both groups, with no significant difference ($p = 0.68$).

Table 3: Secondary Outcomes

Secondary Outcomes	Intervention Group (n = 50)	Control Group (n = 50)	p-value
Histopathological Improvement (%)	70% (35/50)	30% (15/50)	<0.001
Mean Pain Score (0-10 scale)	2.3 ± 1.2	4.1 ± 1.5	<0.001
Adverse Effects (%)	10% (5/50)		

Long-Term Follow-Up Results

Participants were followed for up to 36 months to assess the long-term efficacy of the treatment.

4 to 24 Months:

During the 4 to 24 months follow-up period, 80% of the participants in the intervention group maintained the reduction in lesion size with no recurrence, compared to 50% in the control group ($p < 0.01$).

Histopathological stability was also significantly higher in the intervention group, with 72% of participants showing no progression in dysplasia grading, versus 40% in the control group ($p < 0.01$).

25 to 36 Months:

By the end of the 36-month follow-up, 78% of participants in the intervention group remained free of lesion recurrence, compared to 46% in the control group ($p < 0.01$).

No new cases of malignant transformation were reported in the intervention group, whereas 6% (3 out of 50) of participants in the control group experienced malignant progression ($p < 0.05$).

Table 4: Long-Term Follow-Up

Long-Term Follow-Up (25-36 Months)	**Intervention Group (n = 50)**	**Control Group (n = 50)**	**p-value**

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

Lesion Recurrence-Free (%)	78% (39/50)	46% (23/50)	<0.01
Malignant Transformation (%)	0% (0/50)	6% (3/50)	<0.05

Discussion

The results of this randomized controlled trial (RCT) provide strong evidence supporting the efficacy of Vitamin A-loaded bioadhesive patches in the treatment of potentially malignant white lesions of the oral mucosa. This novel delivery method not only significantly reduced lesion size and improved histopathological outcomes but also offered a sustained therapeutic effect with minimal adverse reactions over a 36-month follow-up period. These findings contribute to the growing body of literature exploring the benefits of localized therapy for oral potentially malignant disorders (OPMDs).

The use of retinoids, including Vitamin A, in the management of OPMDs has been widely studied, with varying outcomes depending on the mode of delivery and dosage. For example, Hong et al demonstrated that systemic retinoid therapy could reduce the size of oral leukoplakia lesions; however, this approach was associated with significant side effects, such as mucocutaneous dryness and elevated liver enzymes, leading to low patient compliance and frequent discontinuation of therapy. In contrast, our study's localized delivery system via bioadhesive patches not only minimized systemic side effects but also enhanced patient compliance, as evidenced by the high adherence rates reported during the trial.[8]

The findings of this study align with the results of Singh et al. who explored the use of topical Vitamin A in gel form for the treatment of oral leukoplakia.[9] Singh et al. reported a mean lesion size reduction of 12 mm^2 over 6 months, with moderate improvement in dysplasia grading. While these results were promising, the long-term efficacy and patient adherence were not thoroughly addressed.[9] In comparison, our study demonstrated a more substantial reduction in lesion size (mean 18.6 mm^2) within a shorter treatment period (8 weeks) and provided robust long-term follow-up data, showing sustained benefits over 36 months. The bioadhesive patch, by

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

ensuring a consistent and controlled release of Vitamin A directly at the lesion site, likely accounts for the enhanced efficacy observed in our study.

Another relevant study by Lippman et al. investigated the chemo preventive effects of systemic 13-cis-retinoic acid in patients with oral leukoplakia. Although the study showed a reduction in lesion size and some degree of dysplasia regression, it was marred by significant toxicity, including hyperlipidemia, conjunctivitis, and teratogenic risks.[10] our study's localized approach provides a clear advantage by delivering therapeutic effects with minimal systemic exposure, thereby avoiding the serious side effects associated with systemic retinoid therapy.

Moreover, our study contributes to the limited data on the long-term management of OPMDs. A key strength of this study is the extensive follow-up period, which revealed that 78% of participants in the intervention group remained lesion-free at 36 months, with no cases of malignant transformation. In contrast, studies with shorter follow-up periods, such as Epstein et al., often fail to capture the full spectrum of long-term outcomes, including lesion recurrence and progression to malignancy. Our findings underscore the importance of long-term monitoring in the management of OPMDs, especially when assessing the efficacy of chemopreventive interventions.[11]

The superior efficacy of the Vitamin A-loaded bioadhesive patches observed in this study may be attributed to several factors. First, the bioadhesive nature of the patches ensures prolonged contact between the active agent and the lesion site, allowing for sustained release and absorption of Vitamin A into the mucosal tissue. This targeted approach enhances local bioavailability and therapeutic efficacy while reducing the potential for systemic absorption and associated side effects as explained by Song et al.[7]

Second, Vitamin A's role in modulating epithelial differentiation and proliferation is well-documented, with studies showing that it can reverse hyperkeratosis and dysplastic changes by promoting normal cellular turnover and inhibiting abnormal cell proliferation.[3] The concentrated delivery of Vitamin A directly to the lesion site likely amplifies these effects, leading to the significant histopathological improvements observed in our study.

Clinical Implications and Future Research

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

The findings of this study have important clinical implications for the management of OPMDs. The Vitamin A-loaded bioadhesive patch offers a practical and effective treatment option that can be easily administered in a clinical setting or by the patient at home, enhancing treatment accessibility and adherence. Additionally, the localized delivery method reduces the risk of systemic toxicity, making it a safer alternative to traditional systemic therapies.

However, further research is warranted to explore the broader applicability of this treatment approach. Future studies could investigate the efficacy of Vitamin A-loaded bioadhesive patches in other forms of OPMDs, such as oral submucous fibrosis and lichen planus, as well as in different patient populations. Additionally, research into optimizing the formulation and dosage of the patches could further enhance their therapeutic potential and patient compliance.

Limitations

Despite the strengths of this study, there are several limitations that should be acknowledged. First, the study was conducted at a single center, which may limit the generalizability of the findings to other populations and clinical settings. Second, while the long-term follow-up provided valuable insights into the sustained efficacy of the treatment, further studies with even longer follow-up periods are needed to fully assess the risk of malignant transformation over time. Lastly, although the study showed promising results in terms of lesion reduction and histopathological improvement, the mechanisms underlying these effects were not directly investigated and remain speculative based on existing literature.

Conclusion

In conclusion, this study demonstrates that Vitamin A-loaded bioadhesive patches are a highly effective and safe treatment option for potentially malignant white lesions of the oral mucosa. The localized delivery method offers significant advantages over systemic therapies, including enhanced efficacy, reduced side effects, and improved patient compliance. The sustained benefits observed over a 36-month follow-up period suggest that this treatment could play a crucial role

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

in the long-term management of OPMDs, potentially reducing the risk of malignant transformation and improving patient outcomes.

References

1. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. J Oral Pathol Med. 2008 ;37(1):1-10. doi: 10.1111/j.1600-0714.2007.00579.x.
2. 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):575-80. doi: 10.1111/j.1600-0714.2007.00582.x.
3. Lotan, R. Retinoids in cancer chemoprevention. FASEB Journal 1996; 10(9):1031-39.
4. Lippman, S. M., Hong, W. K., & Lazarus, P. Retinoids in cancer prevention and treatment: advances in the biology and clinical management of premalignant lesions. Curr Opin Oncol 2005;17(6):581-86.
5. Shapiro, S. S., & Rosenblum, J. L. The risks and benefits of vitamin A therapy. Am J Public Health 1986;76(11): 1398-1402.
6. Chinna Reddy P, Chaitanya KS, Madhusudan Rao Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. Daru. 2011;19(6):385-403
7. Song, K. H., Chung, S. J., Shim, C. K., & Chung, S. J. Preparation and evaluation of oral bioadhesive films for control of localized infections. J Cont Release 2011; 152(2): 216-22.
8. Hong W. K., Lippman S. M., Itri L. M., Karp D. D., Lee J. S., Byers R. M.et al. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. NEJM 1986;323(12): 795-801.
9. Singh, M., Gupta, A., Chauhan, I., & Tyagi, R. Efficacy of topical Vitamin A in the treatment of oral leukoplakia. J Oral Pathol Med 2010;39(8): 612-17.
10. Lippman, S. M., Hong, W. K., & Hittelman, W. N. Retinoid chemoprevention of oral carcinogenesis: Biologic and clinical studies. JNCI 1993;85(3):187-93.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 12, 2023

11. Epstein, J. B., Gorsky, M., Cabay, R. J., Day, T., & Gonsalves, W. Efficacy of systemic 13-cis-retinoic acid and topical clobetasol in the treatment of oral leukoplakia: Results of a double-blind randomized trial. Oral Surg, Oral Med, Oral Pathol 1994; 77(6), :571-75.