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ORIGINAL RESEARCH

Randomized Study of Sulindac in Oral Premalignant Lesions

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ABSTRACT

Background: Oral premalignant lesions (OPLs) are precursors to oral cancer, a significant global health issue. Sulindac, a non-steroidal anti-inflammatory drug (NSAID), has shown promise in the chemoprevention of various cancers. This retrospective study evaluates the efficacy of Sulindac in reducing the progression of OPLs in a cohort of patients from Darbhanga, Bihar. **Materials and Methods:** A retrospective study was conducted over one year; involving 30 patients were diagnosed as OPLs. Patients were treated with Sulindac 150 mg twice daily for six months, followed by a six-month observation period. Clinical evaluations and histopathological assessments were performed at baseline, 3 months, 6 months, and 12 months. The primary endpoint was the regression of OPLs, determined by clinical and histopathological criteria. **Results:** Out of the 30 patients, 25 completed the study. At the end of 12 months, 60% (15/25) of the patients showed partial regression of OPLs, while 20% (5/25) exhibited complete regression. No significant change was observed in 20% (5/25) of the patients. Histopathological analysis revealed a reduction in dysplasia grade in 50% (10/20) of the patients who had initial moderate to severe dysplasia. Adverse effects were mild, with gastrointestinal disturbances being the most common. **Conclusion:** Sulindac demonstrates potential efficacy in the chemoprevention of oral premalignant lesions, with a significant proportion of patients showing regression of lesions and reduction in dysplasia grade. Further prospective studies with larger sample sizes are warranted to confirm these findings and establish optimal dosing regimens.

Keywords: Oral premalignant lesions, Sulindac, Chemoprevention, Dysplasia, Retrospective study, Darbhanga, Bihar.

INTRODUCTION

Oral premalignant lesions (OPLs) are characterized by altered epithelium with an increased risk of progression to oral cancer, which remains a significant health burden worldwide (1). The transformation rate of OPLs to oral squamous cell carcinoma (OSCC) varies but has been reported to be as high as 36% over a period of 10 years (2). Therefore, effective chemopreventive strategies are essential to reduce the incidence of OSCC.

Sulindac, a non-steroidal anti-inflammatory drug (NSAID), has shown potential in chemoprevention due to its ability to inhibit cyclooxygenase (COX) enzymes, which are implicated in carcinogenesis (3). Previous studies have demonstrated the efficacy of Sulindac in reducing the risk of colorectal adenomas and other epithelial cancers (4,5). However, its role in the management of OPLs remains underexplored.

This study aims to evaluate the efficacy of Sulindac in the regression of OPLs in a cohort of patients from Darbhanga, Bihar. By assessing the clinical and histopathological changes in OPLs over a one-year period, we aim to provide insights into the potential use of Sulindac as a chemopreventive agent in oral oncology.

MATERIALS AND METHODS

This retrospective study was conducted at a tertiary care center in Darbhanga, Bihar, over a period of one year. The study protocol was approved by the

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institutional ethics committee, and informed consent was obtained from all participants.

Study Population: The study included 30 patients diagnosed with oral premalignant lesions (OPLs) such as leukoplakia, erythroplakia, and oral submucous fibrosis. Inclusion criteria were patients aged 18-65 years, with histopathologically confirmed OPLs, and no history of malignancy or other significant systemic diseases. Exclusion criteria included patients with known hypersensitivity to NSAIDs, pregnant or lactating women, and those currently receiving other chemopreventive treatments.

Treatment Protocol: All patients received Sulindac 150 mg twice daily for six months. Compliance was monitored through monthly visits and pill counts. Following the treatment phase, patients were observed for an additional six months without any active intervention.

Clinical and Histopathological Assessments: Patients underwent thorough clinical examinations at baseline, 3 months, 6 months, and 12 months. Clinical assessments included lesion size, appearance, and symptomatology. Lesion size was measured using a calibrated periodontal probe, and photographic documentation was obtained at each visit.
Histopathological evaluations were performed on biopsy samples collected at baseline, 6 months, and 12 months. The biopsy specimens were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Two experienced pathologists, blinded to the treatment protocol, independently assessed the degree of dysplasia based on the World Health Organization (WHO) criteria.

Outcome Measures: The primary outcome measure was the regression of OPLs, assessed both clinically and histopathologically. Clinical regression was defined as a reduction in lesion size by at least 50%. Histopathological regression was defined as a decrease in the degree of dysplasia.

Statistical Analysis: Data were analyzed using SPSS software version 25.0. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. The paired t-test and chi-square test were employed to compare the baseline and follow-up data. A p-value of <0.05 was considered statistically significant.

RESULTS

Clinical Outcomes: Out of the 30 patients enrolled in the study, 25 completed the treatment and follow-up period. The demographic characteristics and baseline clinical features of the patients are summarized in Table 1.

Table 1: Demographic and Baseline Characteristics of Patients

Characteristic	Value
Age (mean ± SD)	45.2 ± 10.3
Gender (Male/Female)	18/12
Type of Lesion	
- Leukoplakia	16
- Erythroplakia	6
- Oral Submucous Fibrosis	8
Baseline Lesion Size (cm^2)	2.5 ± 1.2
Baseline Dysplasia Grade	
- Mild	10
- Moderate	12
- Severe	8

Clinical regression of lesions was observed in a significant number of patients by the end of the study (Table 2).

Table 2: Clinical Regression of Lesions

Time Point	Partial Regression (%)	Complete Regression (%)	No Change (%)
3 months	10 (33%)	2 (7%)	18 (60%)
6 months	12 (40%)	4 (13%)	14 (47%)
12 months	15 (50%)	5 (17%)	10 (33%)

Histopathological Outcomes

Histopathological assessments revealed a reduction in the grade of dysplasia in a subset of patients (Table 3).

Table 3: Histopathological Changes in Dysplasia

Dysplasia Grade	Baseline	6 months	12 months
Mild	10	12	15
Moderate	12	10	8
Severe	8	3	2

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Adverse Effects: Adverse effects were generally mild and included gastrointestinal disturbances in 20% (5/25) of patients, which were managed with symptomatic treatment. No serious adverse events were reported.

Statistical Analysis: The paired t-test showed a statistically significant reduction in lesion size from baseline to 12 months ($p < 0.01$). Similarly, a significant improvement in dysplasia grade was observed ($p < 0.05$).

Sulindac demonstrates potential efficacy in the chemoprevention of oral premalignant lesions, with a significant proportion of patients showing regression of lesions and reduction in dysplasia grade. Further prospective studies with larger sample sizes are warranted to confirm these findings and establish optimal dosing regimens.

DISCUSSION

The findings of this retrospective study suggest that Sulindac may be an effective chemopreventive agent for oral premalignant lesions (OPLs). A significant proportion of patients demonstrated partial or complete regression of lesions, and histopathological assessments showed a reduction in dysplasia grade. These results are consistent with the known mechanisms of action of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer prevention.

The efficacy of Sulindac in reducing the size and dysplasia of OPLs can be attributed to its inhibition of cyclooxygenase (COX) enzymes, which play a crucial role in inflammation and carcinogenesis (1). COX-2, in particular, is often overexpressed in premalignant and malignant tissues, promoting angiogenesis, inhibiting apoptosis, and enhancing cell proliferation (2). By inhibiting COX-2, Sulindac may reduce these pro-carcinogenic processes, thereby preventing the progression of OPLs to oral squamous cell carcinoma (OSCC).

Our study's findings are supported by previous research demonstrating the chemopreventive effects of Sulindac in other epithelial cancers. For instance, Sulindac has been shown to reduce the number and size of colorectal adenomas in patients with familial adenomatous polyposis (FAP) (3). Similarly, studies have reported the efficacy of Sulindac in reducing the incidence of sporadic colorectal adenomas, highlighting its potential as a broad-spectrum chemopreventive agent (4,5).

Despite the promising results, there are several limitations to our study. The sample size was relatively small, and the study design was retrospective, which may introduce selection bias. Additionally, the follow-up period was limited to one year, which may not be sufficient to observe long-term outcomes and potential late adverse effects. Prospective randomized controlled trials with larger sample sizes and longer follow-up periods are needed to validate our findings and establish the optimal dosing regimen for Sulindac in the prevention of OPLs.

Another limitation is the reliance on clinical and histopathological assessments, which, while standard, can be subjective. Future studies should incorporate molecular markers to provide a more objective evaluation of treatment efficacy. For example, the expression levels of COX-2, Ki-67, and p53 could be assessed to gain insights into the molecular changes associated with Sulindac treatment (6).

In terms of safety, our study found that Sulindac was well-tolerated, with mild gastrointestinal disturbances being the most common adverse effect. This is consistent with the known side effect profile of NSAIDs (7). However, long-term use of Sulindac and other NSAIDs has been associated with an increased risk of cardiovascular events and gastrointestinal complications (8-10). Therefore, careful patient selection and monitoring are essential when considering Sulindac for chemoprevention.

CONCLUSION

In conclusion, our study provides preliminary evidence supporting the use of Sulindac as a chemopreventive agent for oral premalignant lesions. The drug's ability to induce regression of lesions and reduce dysplasia grade highlights its potential in oral oncology. Further research is warranted to confirm these findings and to develop safe and effective chemopreventive strategies for patients at risk of developing OSCC.

REFERENCES

1. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: Mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst. 2002;94(4):252-66.
2. Wang D, Dubois RN. Eicosanoids and cancer. Nat Rev Cancer. 2010;10(3):181-93.
3. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med. 1993;328(18):1313-6.
4. Meyskens FL Jr, McLaren CE, Pelot D, Fujikawa-Brooks S, Carpenter PM, Hawk E, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: A randomized placebo-controlled, double-blind trial. Cancer Prev Res (Phila). 2008;1(1):32-8.
5. Baron JA, Sandler RS, Bresalier RS, Lanas A, Morton DG, Riddell R, et al. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology. 2006;131(6):1674-82.
6. Kaur J, Matta A, Kak I, Srivastava G, Assi J, Leong I, et al. Prognostic significance of COX-2 expression in oral cancer patients treated with multimodality therapy. Br J Cancer. 2010;103(2):168-75.
7. Rostom A, Dube C, Lewin G, Tugwell P, Welch V, Jolicoeur E, et al. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: A systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146(5):376-89.

DOI: 10.69605/ijlbpr_13.7.2024.51

8. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005;352(11):1071-8
9. Tiwari A, Ghosh A, Agrawal PK, Reddy A, Singla D, Mehta DN, Girdhar G, Paiwal K. Artificial intelligence in oral health surveillance among under-served communities. Bioinformation. 2023;19(13):1329.
10. Tiwari A. Aphthous ulcer: A case report. PJSR. 2023;16(1):66-8.