



# **Comparative Evaluation of Effect of use of Antifungal (Clotrimazole) Drug in Preventing and Reducing the Severity of Oral Discomforts Like Mucositis, Burning Sensation, Xerostomia and Loss of Taste Sensation in Cervicofacial Radiotherapy**

**Ashish Lanjekar<sup>a\*#†</sup>, P. N. Joshi<sup>b=†</sup>, Pranada Deshmukh<sup>bω†</sup>,  
Romita Gaikwad<sup>a€†</sup>, Monal Kukde<sup>c¥†</sup>, Isha Madne<sup>bω†</sup> and Komal Deotale<sup>bω†</sup>**

<sup>a</sup> Department of Oral Medicine and radiology, SDK Dental College, Nagpur, India.

<sup>b</sup> Department of Oral Medicine and radiology Private Practitioner, SDK-Dental College, Nagpur, India.

<sup>c</sup> Department of Oral Medicine and Radiology, Dr. RRK Dental College, Akola, India.

## **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors AL and PNJ designed the study, MK wrote the protocol, PD and RG wrote the first draft of the manuscript. Authors PD and IM managed the analyses of the study. Author KD managed the literature searches. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Aims:** To evaluate the effect of Topical antifungal Clotrimazole in Radiotherapy induced mucositis, burning sensation, xerostomia and loss of taste sensation.

**Study Design:** Randomised Controlled Trial.

**Methodology:** 64 patients (52 males and 12 females) undergoing Co<sup>60</sup> teletherapy for cervicofacial malignancies. Patients who received a total 60 Gray radiation dose over a period of 6 weeks, with a

<sup>#</sup>Reader;

<sup>=</sup>Ex-Reader;

<sup>€</sup>Senior Lecturer;

<sup>¥</sup>Reader, HOD;

<sup>ω</sup>PG Student;

<sup>†</sup>Dr.;

\*Corresponding author: E-mail: ashish.lanjekar@sdk-dentalcollege.edu.in;

daily dose of 2 Gray, were included in this study. Patients were randomly divided into 2 groups out of which one group was given topical 1% clotrimazole ointment and the other was control group. During the radiotherapy and 6 weeks after the completion of radiotherapy, patients were examined every week for possible oral changes such as mucositis, xerostomia, burning sensation, candidiasis and effect on taste.

**Results:** There were considerable decrease in patients with severe mucositis and burning sensation in study group compared with control group whereas there was not any significant effect on xerostomia and loss of taste sensation.

**Conclusion:** Simple topical application of antifungal Clotrimazole can be very effective in reducing the oral discomforts such as mucositis and burning sensation and improved the patient compliance to the treatment.

*Keywords: Radiotherapy; oral mucositis; xerostomia; antifungal; topical clotrimazole.*

## 1. INTRODUCTION

Cancer is still the biggest cause of mortality worldwide. The International Agency for Research on Cancer (IARC) recently estimated that cancer was responsible for 7.6 million deaths globally, with 12.7 million new cases recorded each year. Emerging nations bear a substantial share of this burden; 63 percent of cancer fatalities are reported to originate from developing countries [1,2,3].

The last decade has seen significant progress in the treatment and understanding of the previously proposed hallmarks of cancer, [4] and with advances in early detection and treatment modalities, many cancers have become curable [5]. Following the discovery of X-rays in 1895 by Wilhelm Conrad Röntgen of Germany, their therapeutic relevance as a method of cancer therapy was first recognised. It was also one hundred years ago that Marie Curie was awarded a second Nobel Prize for her radium research, establishing her as a pioneer in the field of radiation treatment. To commemorate this, the United Kingdom has declared 2011 as the Year of Radiation Therapy, commemorating a century of progress.

Radiation treatment has now evolved into a recognised medical specialty, with Radiation Oncology being a subject in which many health and scientific specialists from diverse disciplines collaborate [6]. Along with surgery and chemotherapy, radiation therapy or radiotherapy is an essential modality utilised in cancer treatment since it is a very cost-efficient single modality treatment that accounts for just around 5% of overall cancer care costs [7].

Radiotherapy is the main stay in the management of oropharyngeal malignancies

because unlike surgery it preserves the structures and thus helps in maintaining the function and esthetics with limited morbidity. Oral complications of radiotherapy in the head and neck region are the result of the deleterious effects of radiation [8]. Oral mucositis and its associated pain and discomfort is due to the radiation damage to the germinal layer of oral epithelium. Radiotherapy produces many undesirable side effects like xerostomia, mucositis, dysgeusia, edema and fibrosis of soft tissues, decreased resistance to infections, ulcers in the oral cavity and candidiasis [8].

The main objectives behind this study are to know the effect of progressive dose of cervicofacial radiotherapy and the development of oral discomforts like mucositis and burning sensation, xerostomia and loss of taste sensation.

## 2. MATERIALS AND METHODS

### 2.1 Study Design and Participants

The present randomized double-blind trial was done at Rashtra Sant Tukdoji Cancer Hospital, Nagpur. The Institutional Ethical Committee gave their approval to the project. Before enrollment, each patient gave written informed permission after receiving all necessary information about the study's purpose, in accordance with the Declaration of Helsinki's principles. Patients had received a total of 60 Gray of radiation over the course of six weeks, with a daily dosage of 2 Gray. Inclusion criteria were patients diagnosed with oral cancer with >16 yrs. of age and prepared to receive Radiotherapy for the first time. Exclusion criteria was patients with previous Chemo or Radiotherapy, presence of other malignancy within the last 5 years, presence of serious infection, Patients under antibiotic therapy, cancer chemotherapy.

## 2.2 Recruitment and Randomization

A total of 64 patients (52 men and 12 women) were eligible for Co60 teletherapy for cervicofacial radiotherapy. All 64 participants signed written informed consent forms and were randomised into two groups at random. The control group consisted of 32 individuals (28 males and 4 females) who were not given any antifungal medicines. Antifungal medication was given to the remaining 32 patients (24 males and 8 females) in the study group from the first week of radiation and maintained for 6 weeks after radiotherapy was completed. The allocation sequence is carried out by a subject who was not engaged in the recruiting, data collection, or analysis. Surfaz ointment, containing 1 % clotrimazole cream U.S.P., was given to each patient in the study group in 5 gm. collapsible tubes. Out of 64 patients included, in the present study 14 patients had pre-radiotherapy burning sensation. These 14 patients were separated from the patients without burning sensation before the start of radiotherapy, they were separated because of the fact that, the effect of radiotherapy and clotrimazole ointment were not expected to be the same as in patients with no burning sensation before the start of radiotherapy. Out of those 14 patients, 6 patients were kept as control group and 8 were kept in study group. All 14 patients had mild burning sensation before the start of radiotherapy. Out of remaining 50 patients without burning sensation before the start of radiotherapy, 26 patients were kept as control group and 24 patients were kept as study group.

## 2.3 Outcome Measurement and Data Collection

### 2.3.1 Assessment of mucositis

All the oral mucosal sites were checked every week for 6 weeks during radiotherapy and after radiotherapy. Mucositis was assessed as follows- Absent (-), Mild (+)- Erythema, Moderate (++)- patches of mucositis, severe (+++) - Ulceration.

### 2.3.2 Assessment of burning sensation

It was Assessed as subjective symptoms presented by patients as follows: Absent (-), Mild (+) - with spicy food, Moderate (++) - while taking semisolid foods, severe (+++)- Persistent burning sensation.

### 2.3.3 Assessment of Xerostomia

It was also evaluated as subjective symptoms as follows, Absent (-), Mild (+) - Reduced flow and viscous saliva. Moderate (++) - Thick, ropy saliva, severe (+++) - dry mouth, frothy saliva.

### 2.3.4 Assessment of loss of taste sensation

Absent (-), Mild (+) - slight reduction in taste, Moderate (++) - marked. Reduction in taste, Severe (+++) - total Loss.

## 2.4 Statistical Analysis

Chi-squared test was employed to compare the two groups of interest with respect to baseline characteristics, the incidence of mucositis, burning sensation, xerostomia and loss of taste sensation. Differences of mucositis free distribution curves between groups A and B were investigated by log-rank statistic. All tests were two-sided, and the level of statistical significance was set at 5%.

## 3. RESULTS AND DISCUSSION

Out of 64 patients included in this study, 52 were males and 12 were females, with the age range of 16 years to 80 years. Most of the patients belonged to the 4<sup>th</sup>, 5<sup>th</sup>, and 6<sup>th</sup> decades of life. Patients were having a habit of various forms in which bidi smoking was more prevalent.

**Table 1. Showing distribution of patients with different habits undergoing Cervical Radiotherapy**

Habit	Number of Patients
Betel Nut chewing	15
Fennel eating	26
Pan Chewing	25
Tobacco with Lime	31
Bidi smoking	40
Consuming Alcohol	19

The anatomical distribution of the sites of malignancy in the cervicofacial region, in the patients which were selected for this study, is given in the tabulated form (Table 2). The numbers of patients belonging to the category of laryngeal carcinoma were found to be highest, as compared with the malignancies at other sites.

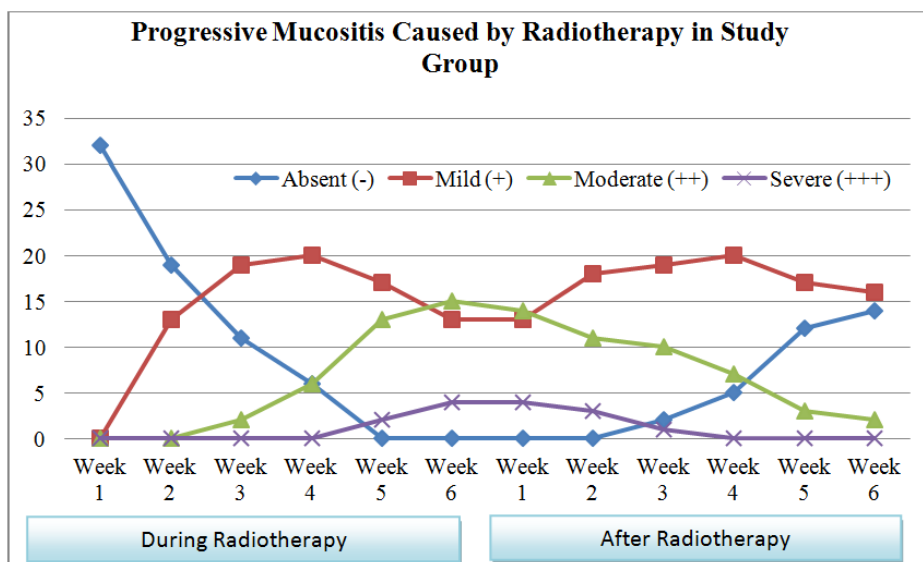
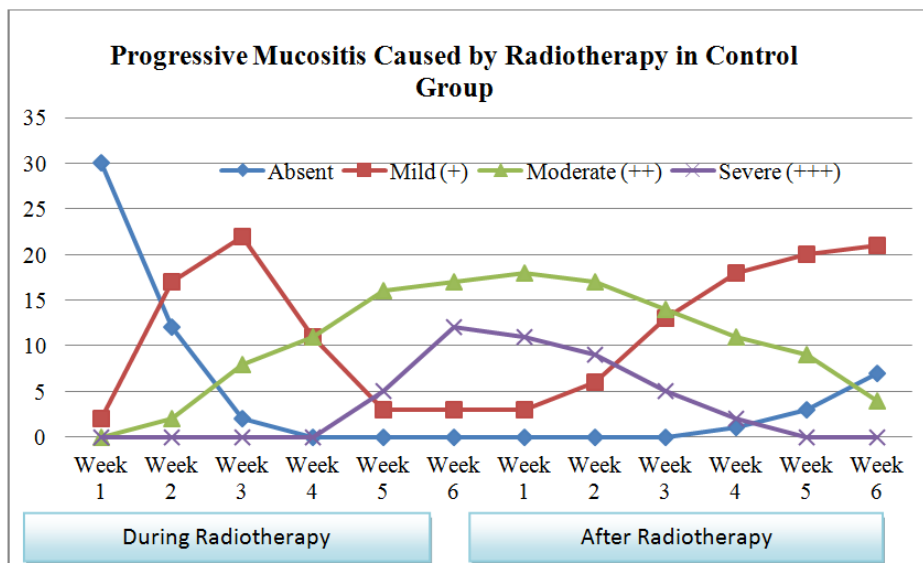
**Table 2. Showing Anatomical Distribution of the Sites of Malignancy in the 64 Patients Undergoing Cervicofacial Radiation**

Location	No. of Patients
Tongue	4
Base of tongue	14
Larynx	28
Pharynx	4
Cheek	4
Lip	1
Tonsil	3
Soft palate	1
II <sup>0</sup> in neck	5
Total	64

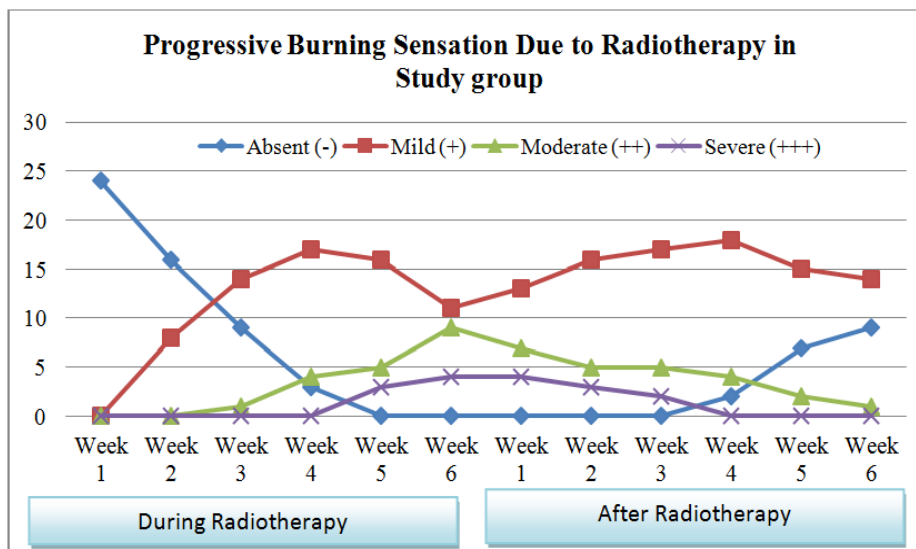
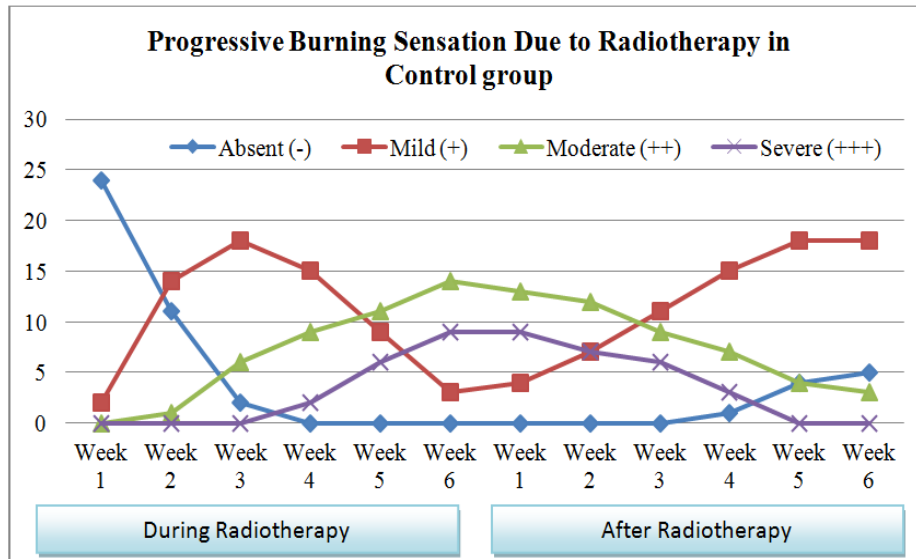
**Mucositis:** In the control group and study group, none of the patients had mucositis before the

start of radiotherapy. The peak of patients with severe mucositis was at last week of radiotherapy in both the groups, but control group had maximum number of patients with severe mucositis compared to study group. The peak of severe mucositis reached to zero in 4<sup>th</sup> week post radiotherapy in study group, whereas in 5<sup>th</sup> week in Control group.

But at the end of 6-week radiotherapy there was significant decrease in subject with severe mucositis in study group ( $p=0.005$ ). However, at 6 weeks of post radiation therapy there was no statistically significant difference between study and control group ( $p=0.15$ ). Thus, clotrimazole helped in reducing the severity of mucositis during radiotherapy and helping in reducing the patient drop outs during treatment.



**Burning sensation:** There was decrease in number of patients during and after radiotherapy with burning sensation in study group comparatively but was not statistically significant with  $p= 0.0233$  and  $p= 0.753$  respectively.



**Xerostomia:** In the control group of 32 patients, none of the patients had xerostomia before start of the radiotherapy. Initially there was gradual increase in the number of patients with moderate and severe forms of xerostomia and correspondingly there was decrease in the number of patients with severe xerostomia and at the end of 6th week of post radiotherapy period.

Comparison of the findings at the end of 6th week after post-radiotherapy period, in control and study group showed that, in the control group, all the patients had some type of xerostomia and 2 patients (6.25%) had mild, 26 patients (81.25%) had moderate and 4 patients

(12.5%) had severe xerostomia. In the study group, during the same period 27 patients (64.37%) had moderate and 5 patients (15.62%) had severe xerostomia. None of the patients had mild xerostomia.

### 3.1 Loss of Taste Sensation

In Control and Study Group, none of the patients had defective taste sensation before start of the radiotherapy. At the end of 6th week of radiotherapy, In Control group 6 patients (18.75%) had mild, 8 patients (25%) had moderate and 18 patients (56.25%) had severe loss of taste sensation. In study Group 12

patients (37.5%) had mild, 13 patients (40.62%) had moderate and 7 patients (21.87%) had severe loss of taste sensation.

Comparison of the findings at the end of 6th week of post-radiotherapy period, in control and study group showed that, in the control group 12 patients (37.5%) had mild, 13 patients (40.62%) had moderate and 7 patients (21.87%) had severe loss of taste sensation. Whereas, in the study group during the same period 14 patients (43.75%) had mild, 12 patients (37.5%) had moderate and 6 patients (16.75%) had severe loss of taste sensation.

### 3.2 Discussion

One of the most serious side effects of head and neck radiation is oral mucositis. Radiation-induced mucosal barrier damage allows for microbial colonization and infection, which leads to tissue harm amplification. Along with this candidal infection, xerostomia, burning sensation, loss of taste sensation are other side effects following radiation therapy. Candidiasis-related mucosal inflammation, when combined with mucositis, would aggravate radiation-related mucosal damage [9].

In the present study, the severity of oral mucositis, xerostomia, burning sensation and loss of taste sensation were evaluated using daily local application of 1% Clotrimazole antifungal prophylaxis during and until 6 weeks post radiation therapy. There was significant reduction in grade 3 and 4 mucositis in patients having prophylactic antifungal as compared to control group.

Only two studies have looked into the role of antifungal in onset, severity, and duration of oral mucositis and candidal infection after radiation [10,11]. Other trials that employed a topical antimycotic medication in conjunction with antibiotics in the form of a lozenge or a paste found conflicting conclusions [12,13,14]. In none of the three investigations, the incidence of pseudomembranous candidiasis, which can occur during RT and coexist with mucositis, was recorded.

Nicolatou-Galitis, O., Velegraki, A., Sotiropoulou-Lontou, A. et al. [10] used Fluconazole as an antifungal and found that, there was a substantial reduction in severe mucositis at the completion of radiation (14.7 vs 44.8 %,  $p=0.018$ ) and interruptions (0 vs 17.2 %,  $p=0.017$ ). Candidiasis

was minimized (0 versus 34.5%,  $p=0.001$ ), with a 40.7% drop in Candida carriage.

A clinical study has shown that systemic fluconazole prophylaxis caused a significant beneficial effect on the severity of OM and on radiotherapy interruptions [15,16,17].

A Clinical study by Srinivasan V. et al evaluated effect of Clotrimazole lozenges in patients receiving head and neck chemoradiation and radiation. There was an additional benefit of adding clotrimazole lozenges to soda bicarbonate mouthwash in controlling radiation-induced oral mucositis in patients undergoing radiation or chemoradiation for head and neck malignancies [18].

A significant reduction in the incidence of severe, grade 3 or 4 mucositis at the end of RT in study group, which received clotrimazole prophylaxis, was observed, pointing to a beneficial effect of clotrimazole on the severity of mucositis. 34.6% of incidence of severe mucositis was observed in present study for the control group i.e., without clotrimazole group, which was in agreement with Galitis et al. [10] where it was 44.8% also with Trotti et al. [19] who reported a mean incidence of severe mucositis. A similar overall 43% and 50% incidence of severe mucositis has also been reported by Wijers et al. [14] and by El-Sayed et al. [12], respectively.

The delay in the onset of moderate and severe mucositis observed in our study at median fourth week in study group as opposed to the third week in control group, was found not significant. But this was significantly impacted on Radiotherapy interruptions. There was a significant effect on Xerostomia and Loss on Taste sensation in both the groups. But the significant effect on mucositis and burning sensation has led to increase in patient compliance for radiotherapy.

The comparatively small size of each treatment arm may be taken into account as a limitation of the study. However, post-hoc power tests found that the power to declare present results significant at 5 percent is 75 percent, based on the incidence of severity of mucositis in the two groups. Given this, we believe the current study offers data on the construction of a randomized controlled trial on the influence on treatment schedule of Clotrimazole prophylactic and patient quality of life during head and neck radiation therapy.

#### 4. CONCLUSION

At the end of 6th week of radiotherapy, even with the persistent, presence of xerostomia, study group patients showed a reduction in the severe forms of mucositis and burning sensation. It can be concluded that application of antifungal (clotrimazole) ointment in the study group resulted in the prevention of relatively severe forms of mucositis and burning sensation.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the Institutional ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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