Comparative evaluation of the effect of the 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

Dr. Ashish Lanjekar[1*], Dr. P.N. Joshi[2], Dr. Pranada Deshmukh[3], Dr. Isha Madne[3] Dr. Komal Deotale[3]

[1]MDS, Ph.D., Reader, Department of Oral Medicine and radiology, SDK Dental College, Nagpur
[2]MDS, Ex-Reader SDK-Dental college, Department of Oral Medicine and radiology Private Practitioner, Nagpur
[3]PG Student, Department of Oral Medicine and radiology, SDK Dental college, Nagpur

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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
Place and Duration of Study: Department of Radiotherapy of Government Dental College, Nagpur and Rashtra Sant Tukdoji Cancer Hospital, Nagpur between June 2009 and July 2010.
Methodology: 64 patients (52 males and 12 females) undergoing Co^{60} teletherapy for cervicofacial malignancies. Patients who were given a total 60 Gray radiation dose over 6 weeks, with a daily dose of 2 Gray, were included in this study. Patients were randomly divided into 2 groups of which one group was given topical 1% clotrimazole ointment and the other was the 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 was a considerable decrease in patients with severe mucositis and burning sensation in the study group compared with the 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 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

In recent years, significant progress has been made in identifying the proposed hallmarks of cancer growth and management. However, with its growing prevalence, cancer clinical management remains a problem for the twenty-first century. Radiation therapy, surgery, chemotherapy, immunotherapy, and hormone therapy are all treatments available.1 Along with surgery and chemotherapy, radiation therapy or radiotherapy is a significant modality used in cancer treatment since it is a relatively cost-efficient single modality treatment that accounts for just around 5% of all cancer care costs.2

Radiotherapy is the mainstay 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, which affect not only the oral mucosa itself but also the adjacent salivary glands, bone, dentition, and masticatory musculature and apparatus.3

Oral mucositis and its associated pain and discomfort may be due to the radiation damage to the germinal layer of the 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. 3

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. MATERIAL AND METHODS

For the present study, 64 patients (52 males and 12 females) undergoing co60 teletherapy for cervicofacial malignancies at Government Medical college and hosp. Nagpur and Rashtrasant Tukdoji cancer hospital, Nagpur were selected. Patients who were planned to be given a total of 60 gray radiation doses over 6 weeks, with a daily dose of 2 gray, were included in this study. Patients under antibiotic therapy, cancer chemotherapy, diabetes mellitus patients, and endocrinal disturbances patients, which are known predisposing factors to cause candidiasis in the oral cavity, were not included in this study.

Before starting radiotherapy, the detailed history of the patient was recorded and extraoral and intraoral examination was carried out. 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, and effect on taste. Sixty-four patients included in the study were divided into two equal groups of 32 patients each. One group was given an antifungal 1% clotrimazole and the other group was kept as a control and was not supplied with clotrimazole ointment.

Out of 64 patients included, in the present study 14 patients with oral and pharyngeal (extending to oral cavity) carcinoma were observed to have a pre-radiotherapy burning sensation. These 14 patients were kept separate from the patients without burning sensation before the start of radiotherapy, they were separated because the effect of radiotherapy and clotrimazole ointment was not expected to be the same as in patients with no burning sensation before the start of radiotherapy.

Out of 14 patients, 6 patients with burning sensation before the start of radiotherapy were kept as a control group. All 6 patients, had a mild burning sensation before the start of radiotherapy. 8 out of the 14 patients who had burning sensation before the start of radiotherapy were kept as a study group. All 8 patients had mild burning sensa¬tion before the start of radiotherapy.

Out of the 50 patients without burning sensation before the start of radiotherapy, 26 patients were kept as a control group and 24 patients were kept as a study group**.**

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 4th, 5^{th}, and 6th decades of life. Patients were having a habit of various forms in which tobacco with lime was among the highest patients.

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^0 in neck	5
Total	64

Mucositis:

In the control group and study group among 32 patients, none of the patients had mucositis before the start of radiotherapy. In the control group at the end of the 6th week of radiotherapy, the number of patients with mild, moderate, and severe forms of mucositis, was increased to 3 (9.37%), 17 (53.12%), and 12 (37.5%) respectively. At the end of the 6th week after radiotherapy, the number of patients with moderate and severe mucositis was reduced to 4 (12.5%) and zero respectively, and the number of patients without mucositis and with mild mucositis gradually increased to 7 (21.87%) and 21 (65.62%) respectively.

In the Study group at the end of the 6th week of radiotherapy, all the patients developed mucositis and the number of patients with mild, moderate, and severe forms of mucositis were increased to 13(40.62%), 15 (46.87%), and 4 (12.5%), respectively. At the end of the 6th week of the post-radiotherapy period, the number of patients with moderate and severe mucositis was reduced to 2 (6.25%) and zero respectively and the number of patients with mild mucositis and without mucositis was increased to 16 (50%) and 14 (43.75%) respectively.

Comparison of findings at the end of the 6th week of radiotherapy in the control and study group showed that, in the control group, all the patients had some type of mucositis and the number of patients with mild, moderate, and severe mucositis were increased to 3 (9.37%), 17 (53.12%) and 12 (37.5%), respectively. In the same period in the study group, the number of pts. with mild, moderate, and severe forms of mucositis were increased to 13 (40.62%), 15 (46.87%), and 4 (12.5%) respectively. Thus, in the Study group when the topical application of clotrimazole had used, less number (4) of severe mucositis patients compared to control who had a higher number (12) of severe mucositis.

TABLE 3- Progressive Mucositis Caused by Radiotherapy in Control and Study Group of Patients.

Grading	Before Radiotherapy	**CONTROL GROUP**											
		During Radiotherapy Weeks						**After Radiotherapy Weeks**					
		1	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
Absent (-)	32	30 (93.7)	13 (40.62)	2 (6.25)	0	0	0	0	0	0	1 (3.12)	3 (9.37)	7 (21.87)
Mild (+)	0	2 (6.25)	17 (53.12)	22 (68.75)	11 (34.37)	3 (9.37)	3 (9.37)	3 (9.37)	6 (18.75)	13 (40.62)	18 (56.25)	20 (62.5)	21 (65.62)
Moderate (++)	0	0	2 (6.25)	8 (25.00)	11 (34.37)	16 (50.00)	17 (53.12)	18 (56.25)	17 (53.12)	14 (43.75)	11 (34.37)	9 (28.12)	4 (12.5)
Severe (+++)	0	0	0	0	0	5 (15.62)	12 (37.5)	11 (34.37)	9 (28.12)	5 (15.62)	2 (6.25)	0	0
Total	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**

Grading	Before Radiotherapy	**STUDY GROUP**											
		During Radiotherapy Weeks						**After Radiotherapy Weeks**					
		1	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
Absent (-)	32	32	19 (59.37)	11 (34.37)	6 (18.75)	0	0	0	0	2 (6.25)	5 (15.62)	12 (37.5)	14 (43.75)
Mild (+)	0	0	13 (40.62)	19 (59.37)	20 (62.5)	17 (53.12)	13 (40.62)	13 (43.75)	18 (56.25)	19 (59.37)	20 (62.5)	17 (53.12)	16 (50.00)
Moderate (++)	0	0	0	2 (6.25)	6 (18.75)	13 (40.62)	15 (46.57)	14 (43.75)	11 (34.37)	10 (31.25)	7 (21.57)	3 (9.37)	2 (6.25)
Severe (+++)	0	0	0	0	0	2 (6.25)	4 (12.5)	4 (12.5)	3 (9.37)	1 (3.12)	0	0	0
Total	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**	**32**

- Figures given in the Brackets indicate the percentage of patients.

Burning sensation:

All 6 patients of the control group had a mild burning sensation, before the start of radiotherapy. At the end of the 6th week of radiotherapy, the number of patients with moderate and severe burning sensation was increased to 2 (33.33%) and 4 (66.66%) respectively. At the end of the 6th week after radiotherapy, none of the patients had a severe burning sensation, 3 patients (50%) had mild and 3 patients (50%) had a moderate burning sensation.

In the study group, all 8 patients had mild burning, sensation before the start of radiotherapy. At the end of the 6th week of radiotherapy 5 patients (62.5%) had moderate and 3 patients (37.5%) had a severe burning sensation. At the end of the 6th week after radiotherapy, the number of patients with severe burning sensation was reduced to zero and the corresponding number of patients with mild and moderate burning sensation was Increased to 6 (75%) and 2 (25%) respectively.

In a control group of 26 patients, none of the patients had a burning sensation before the start of radiotherapy. By the end of the 6th week of radiotherapy, all the patients developed some form of burning sensation and 3 patients (11.53%) had mild, 14 patients (53.84%) had moderate and 9 patients (34.6%) had a severe burning sensation. At the end of the 6th week after radiotherapy, the number of patients without burning sensation and with mild burning sensation was increased to 5 (19.2%) and 18 (69.23%) respectively, and correspondingly the number of patients with moderate and severe burning sensation were reduced to 3 (11.53%) and zero, respectively.

In the study group, out of 24 patients, none of the patients had a burning sensation before the start of the radiotherapy. At the end of the 6th week of radiotherapy, all the patients developed some type of burning sensation and 11 patients (45.83%) had mild, 9 patients (37.5%) had moderate end only 4 patients (16.40%) had a severe burning sensation. At the end of 6th week after radiotherapy the number of patients without burning sensation and with mild burning sensation were reduced to 9 (37.5%) and 14 (58.33%) respectively, whereas number of patients with moderate and severe forms of burning sensation were reduced to 1 (4.16%) and zero respectively.

TABLE - 4 Showing Progressive Burning Sensation Due to Radiotherapy in Control and Study Group of Patients.

Grading	Before Radiotherapy	**CONTROL GROUP**											
		During Radiotherapy Weeks						**After Radiotherapy Weeks**					
		1	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
Absent (-)	26	24 (92.3)	11 (42.30)	2 (7.69)	0	0	0	0	0	0	1 (3.84)	4 (15.4)	5 (19.2)
Mild (+)	0	2 (7.69)	14 (53.84)	18 (69.23)	15 (57.69)	9 (34.6)	3 (11.53)	4 (15.4)	7 (26.9)	11 (42.3)	15 (56.69)	18 (69.23	18 (69.23)
Moderate (++)	0	0	1 (3.84)	6 (23.00)	9 (34.6)	11 (42.3)	14 (53.84)	13 (50.00)	12 (46.15)	9 (34.6)	7 (26.9)	4 (15.4)	3 (11.53)
Severe (+++)	0	0	0	0	2 (7.69)	6 (23.00)	9 (34.6)	9 (34.6)	7 (26.9)	6 (23.00)	3 (11.53)	0	0
Total	**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**

Grading	Before Radiotherapy	**STUDY GROUP**											
		During Radiotherapy Weeks						**After Radiotherapy Weeks**					
		1	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
Absent (-)	24	24	16 (66.6)	9 (37.5)	3 (12.5)	0	0	0	0	0	2 (8.33)	7 (29.16)	9 (37.6)
Mild (+)	0	0	8 (33.3)	14 (58.30)	17 (62.38)	16 (56.60)	11 (45.83)	13 (54.16)	16 (66.66)	17 (70.83)	18 (75.00)	15 (62.5)	14 (58.33)
Moderate (++)	0	0	0	1 (4.16)	4 (16.60)	5 (20.80)	9 (37.5)	7 (29.16)	5 (20.80)	5 (20.80)	4 (16.60)	2 (5.33)	1 (4.16)
Severe (+++)	0	0	0	0	0	3 (12.50)	4 (16.60)	4 (16.60)	3 (12.50)	2 (8.33)	0	0	0
Total	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**	**24**

Xerostomia:

In the control group of 32 patients, none of the patients had xerostomia before the start of the radiotherapy. Initially, there was a gradual increase in the number of patients with moderate and severe forms of xerostomia and correspondingly there was a decrease in the number of patients with severe xerostomia and at the end of the 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.

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 less 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.

4. 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.

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. There were no significant effect of antifungal on Xerostomia, burning sensation and loss of taste sensation.

Two studies that looked into the role of antifungal in onset, severity, and duration of oral mucositis and candidal infection after radiation.5,6 Other trials that employed a topical antimycotic medication in conjunction with antibiotics in the form of a lozenge or a paste found conflicting conclusions.7,8,9 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 al5 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.10,11,12

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 chemoirradiation for head and neck malignancies.13

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 control group i.e., without clotrimazole group, which was in agreement with Galitis et al5 where it was 44.8% also with Trotti et al15 who reported mean incidence of severe mucositis. A similar overall 43 and 50% incidence of severe mucositis has also been reported by Wijers et al.9 and by El-Sayed et al.7, respectively.

The delay in the onset of moderate and severe mucositis observed in our study, median fourth week in study group as opposed to third week in control group, was found not significant. But this was significantly impacted on Radiotherapy interruptions. There was n 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 randomised controlled trial on the influence on treatment schedule of Clotrimazole prophylactic and patient quality of life during head and neck radiation therapy.

5. CONCLUSION

At the end of 6th week of radiotherapy shows that antifungal (clotrimazole) ointment has no effect on the prevention of xerostomia. However, during the same period, even with the persistent, presence of xerostomia, study group patients showed reduction in the severe forms of mucositis and burning sensation. It can be concluded that application of antifungal (clotrimazole) ointment in study group resulted in the prevention of relatively severe forms of mucositis end burning sensation.

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AUTHORS' CONTRIBUTIONS

Dr. Ashish Lanjekar and Dr. P N Joshi designed the study, wrote the protocol, and wrote the first draft of the manuscript. Dr. Pranada Deshmukh and Dr. Isha madne managed the analyses of the study. Dr. Komal Deotale managed the literature searches. All authors read and approved the final manuscript."

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

"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."

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