ROLE OF FLUCONAZOLE IN THE PREVENTION OF RADIATION-INDUCED MUCOSITIS IN HEAD AND NECK CANCER PATIENTS

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ABSTRACT

BACKGROUND

This study is aimed to evaluate the effect of fluconazole on prevention of oral candidacies and in reduction of severity of oral mucositis induced by radiotherapy.

METHODS

The study was conducted on 48 head and neck cancers patients. Cases were randomised into study (22/48) and control groups (26/48). Both groups received radiotherapy with or without chemotherapy. Oral swabs were collected before start of radiation three weeks later and at the end of radiation. Oral swabs were cultured for candidial growth. Study group patients received oral fluconazole 50 mg/day throughout the course of radiation and control group patients received no fluconazole prophylaxis. Patients were examined weekly for oral mucositis and were graded according to CTC version 2.0.

RESULTS

Oral swabs were taken from all patients before start of radiotherapy showed candidial growth in 22.9% (11/48). During the course of radiation treatment, oral candidial culture was positive in 42.3% (11/26) of control group patients and 40.9% (9/22) of study group (p=0.644). There was statistically significant reduction in the severity of mucositis in the study arm (p=0.021). In the study arm, there was grade 0 in 27.2% (6/22), grade 1 in 27.2% (6/22), grade 2 in 31.8% (7/22), grade 3 in 22.7% (5/22), and no grade 4. In the control arm, there was no grade 0 noted, grade 1 was seen in 19.2% (5/26), grade 2 in 61.5% (16/26), grade 3 in 15.3% (4/26), and no grade 4. Patients in whom candidial culture was negative had less severe mucositis as compared to patients with positive candidial culture (p=0.029).

CONCLUSION

Prophylactic use of oral fluconazole is effective in reducing the severity of oral mucositis by reducing oral candidiasis.

KEYWORDS

Radiotherapy, Mucositis, Fluconazole, Cancer.

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INTRODUCTION: Head and neck cancers are the most common cancers seen especially in the developing countries like India.[1] About 65% of them present with locally advanced stage requiring combined modality of treatment.[1-3] Radiotherapy is one of the main treatment modality in the treatment of head and neck cancers necessitating administration of relatively high doses of radiation resulting in high grades of oral mucositis.[4-7] Mucositis leads to mucosal barrier injury, which allows microbial colonization, especially candida, which results in the amplification of mucosal injury.

Radiotherapy-induced hyposalivation also encourages oral candidiasis. One out of three patients develop oral candidiasis during course of radiotherapy. The infection is marked by oral pain, burning sensation, and worsening of mucositis.[8] This may lead to unplanned radiotherapy interruption with adverse effect on treatment outcome[9] resulting in significant patient morbidity and compromising patient's quality of life.[9] Patients on chemotherapy experience more severe mucositis, which may result in unplanned treatment interruptions.[10] Therefore, use of suitable antifungal agent like fluconazole for the prevention of oral candidiasis to reduce the severity of oral mucositis during radiotherapy of head and neck cancers has become a necessity. Hence, this study was undertaken to evaluate the effect of fluconazole on prevention of oral candidiasis and to determine whether fluconazole prophylaxis will reduce the severity of oral mucositis.

AIMS AND OBJECTIVES: This study was undertaken to evaluate the efficacy of fluconazole in the prevention of oral candidiasis and to determine whether fluconazole prophylaxis will reduce the severity of oral mucositis.

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MATERIALS AND METHODS: The study was conducted on 48 patients with histopathologically proven head and neck cancers attending the Department of Radiation Oncology. Institutional ethics committee's approval was taken before start of this study.

Inclusion Criteria:

1. Patients above the age of 18 years and both sexes.
2. Patients receiving radiotherapy with or without chemotherapy for head and neck cancer to a dose of 50 Gy or more.

Exclusion Criteria: Allergy to azole antifungal agents.

Informed consent was taken from all patients. Eligible patients were recruited and randomised by open label method (Randomisation was done using computer generated tables) into two groups: Study and control groups. Study group had 22 patients and control group had 26 patients. Basic investigations required for starting radiotherapy was done like Chest X-ray, Ultrasound Abdomen, Blood counts, and Renal function test. Each patient underwent thorough dental prophylaxis before start of radiation. Oral swabs were collected from both groups.

Maximum of three swabs were collected, one before the start of radiotherapy, second one at the end of third week of radiotherapy, and last one after completion of radiotherapy. Oral swab were cultured on Sabouraud's dextrose agar for candidial growth. All patients in the study received radiotherapy with or without chemotherapy depending on the site and stage of tumour. Patients in study group received oral fluconazole 50 mg/day after food from the first day of radiotherapy till the completion of radiotherapy treatment. Patients in control group did not receive fluconazole as prophylactic therapy. Patients in both groups were examined weekly for oral mucositis and were graded according to common toxicity criteria version 2.0.

Patients received radiation treatment either on telecobalt-60 or 6 MV linear accelerator. The total dose ranged from 50 to 70 Gy in 25-35 fractions depending upon the stage and intent of treatment. Patients received radiation treatment either on telecobalt-60 with 80 cms SSD or on 6 MV LINAC with 100 cms SSD. Various techniques were used. Most common was two parallel opposing lateral facial fields, sometimes if required, and an anterior neck field was used. The total dose ranged from 5000 to 7000 cGy in 25-35 fractions depending upon the stage and intent of treatment.

The spinal cord was shielded usually after 4000 cGy. However, if the field length was less than 10 cms, it was shielded after 5000 cGy. Apart from spinal cord shielding, shielding blocks were placed individually if necessary. The treated area included more than half the parotids, the submandibular, sublingual, and minor salivary glands in most of the cases. The data collected was tabulated using Microsoft excel work sheets.

STATISTICAL METHODS: Descriptive statistical analysis was carried out. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%). Chi-square test, Fisher's exact, and multivariate logistic regression tests were used for analysing the data. The statistical software SPSS 15.0, Stata 8.0, MedCalc 9.0.1, and Systat 11.0 was used for the analysis of the data and Microsoft word and excel have been used to generate graphs and tables.

RESULTS: A total of 48 patients were recruited in the study. The characteristics of patients described in Table 1. Oral swabs was taken from all the patients before the start of radiotherapy and tested for oral candidiasis. The pre-treatment Candida was present in 22.9% (11/48). In the control arm, Candida was seen in 23.0% (6/26) of cases and in the treatment arm, it was seen in 22.7% (5/22) of cases. It was almost equally present in both the arms. Oral swabs taken during third week of radiotherapy showed positive candidial culture in 30.7% (8/26) of control arm and in 31.8% (7/22) of the treatment arm. It was almost equally present in the both the arm (p=0.989). At the end of radiotherapy, candida was positive in 26.9% (7/26) of the control arm versus 22.7% (5/22) in the treatment arm. There was a difference of about 4% though statistically not significant.

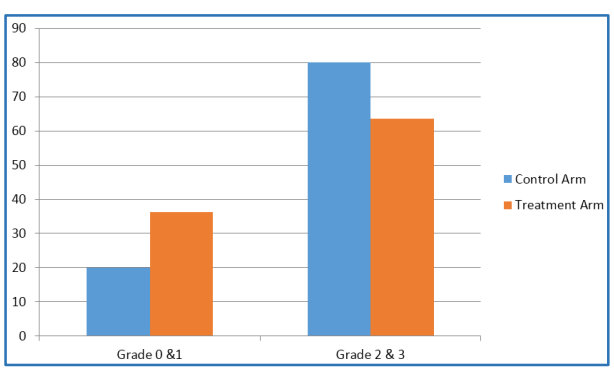
When mucositis and candidiasis was studied in the study arm, there was grade 0 in 27.2% (6/22), grade 1 in 27.2% (6/22), grade 2 in 31.8% (7/22), grade 3 in 22.7% (5/22), and no grade 4. In the control arm, there was no grade 0 noted, grade 1 was seen in 19.2% (5/26), grade 2 in 61.5% (16/26), grade 3 in 15.3% (4/26), and no grade 4. When the grades of mucositis (Gr0 and 1) was combined, it was noted that in the control arm the incidence of grade 0 and 1 mucositis was 19.2% (5/26) as opposed to 36.3% (8/22) in the study arm. The incidence of grade 2 and 3 mucositis was seen in 76.9% (20/26) of the control and 63.6% (14/22) in the study arm. The difference is about 13% favouring the study arm (p=0.005, odds ratio 0.43).

There was no cases with grade 4 mucositis in the both the arms. Graph 1 showing grade of mucositis. In multivariate logistic regression model, it was analysed whether candidiasis, radiation dose, and chemotherapy is likely to increase the severity of mucositis. It was noted that radiation dose had an effect on the severity of mucositis (p=0.041), but candidiasis was not found to be statistically significant (p=0.302). The use of chemotherapy (p=0.039) was found to be associated with increase in the severity of mucositis. Concurrent chemotherapy was given in nine patients. Cisplatin 40 mg/m2 weekly schedule, which was given in 6 cases and one patient received 3 weekly schedule of cisplatin 75 mg/m2. Carboplatin was used in one patient and cetuximab 200 mg/m2 weekly was used in one patient. With the respect to the use of fluconazole, none of the patients developed any side effects related to the tablet.

	Numbers (Percentage)
Age	31 to 82 years
Male	35 (74.5%)
Female	13 (25.5%)
Site	
Oral Cavity	19 (39.6%)
Oropharynx	10 (20.8%)
Hypopharynx	8 (16.7%)
Larynx	4 (8.3%)
Paranasal sinus	4 (8.3%)
Parotid	3 (4.2%)
Intent of Treatment	
Radical Radiation	24 (50%)
RT*following surgery	13 (27%)
Neoadjuvant CT** then RT*	2 (4.2%)
Concurrent chemoradiation	9 (18.7%)
Histopathology	
Squamous cell carcinoma	45 (93.7%)
Adenosquamous	1 (2.1%)
Adenoid cystic	1 (2.1%)
Pleomorphic Adenoma	1 (2.1%)
Stage of Disease	
Stage II	7 (14.6%)
Stage III	17 (35.4%)
Stage IV	20 (14.6%)
Recurrent	4 (8.3%)

Table 1: Patient's Characteristics

*RT=Radiotherapy, **CT=Chemotherapy



Graph 1: Severity of Mucositis

DISCUSSION: Radiation-induced oral mucositis is the most significant morbidity seen with head and neck cancers. Radiation-related mucosal barrier injury allows for microbial colonization and Candidial infection leading in turn to amplification of tissue injury.[7-9] One out of three patients is anticipated to develop oral pseudomembranous candidiasis during the course of RT, which in turn worsens the mucositis.[10] The infection is marked by oral pain, burning sensation, and worsening of mucositis. This may lead to unplanned radiotherapy interruption with adverse effect on treatment outcome. Mucositis is difficult to assess because it occurs not only in the oral cavity, but also in areas that cannot be easily observed such as the oesophagus and hypopharynx.

The secondary acute effects of oral mucositis include acute and chronic aspiration, weight loss, infection, and severe pain. These lead to significant morbidity requiring treatment interruptions.[9] Candida is present in the oral cavity in 40% to 60% of healthy individuals as a normal commensal.[11] However, oropharyngeal candidiasis, which is a common infection in cancer patients especially those receiving radiotherapy and chemotherapy can be troublesome.

It results in oral discomfort, worsening of mucositis, increases pain, dysphagia, anorexia, altered taste, and it contributes toward reduction in food and liquid consumption and this leads to poor nutritional status and strongly deteriorates quality of life.[12] Oral mucosal colonization (up to 93%) and infection (ranging from 17 to 29%) with Candida are particularly common in patients receiving radiation therapy for head and neck cancer.[13] Compromised salivary function secondary to destruction of glandular tissue by radiation and it is thought to be a major factor leading to Candida infection.[13] The epidemiology of C. albicans and other yeasts from the oropharynx of patients receiving radiation for head and neck cancer is as follows. C. albicans is the predominant organism (85%) associated with symptomatic infection seen up to other species like C. dubliniensis, Candida glabrata, Candida krusei, Candida tropicalis, and Candida kefyr have also been associated with oropharyngeal candidiasis.[14,15]

In this study, the presence of oral candidiasis was studied, but the type of species was not studied. It was seen that before starting radiotherapy all 48 patients were tested for oral candidiasis by doing culture and 22% of them were positive, 24% in the control group, and 20% in study group. These findings are similar to 25% of control group and 27.5% of treatment group reported by Mehmet Koc et al.[16] During the course of radiotherapy, the occurrence of candidiasis increased in the control group increased to 44%, whereas there was a reduction in the treatment group by 6.5%. This value was however not statistically significant (p=0.644). According to Mehmet Koc et al., during the course of radiotherapy, the occurrence of candidial carriage increased in the control group (64.8%) as compared to treatment group (21.6%).[16] Presence of oral candidiasis is known to worsen the radiation-induced mucositis by inducing inflammation and mucosal damage.

So, by prevention of oral candidiasis by prophylactic use of fluconazole, the severity of mucositis can be reduced. This study showed similar results. All the patients in the control arm developed mucositis whereas in the treatment arm only 73% of them developed mucositis. This shows by preventing development of oral candidiasis, mucositis can be prevented. The incidence of grade 2 and 3 mucositis was seen in 76.9% (20/26) of the control and 63.6% (14/22) in the study arm. The difference is about 13% favouring the study arm (p=0.005, odds ratio 0.43). These results are in agreement with the data reported by Ourania et al. who showed significant reduction in the incidence of oral mucositis of grade 2 and 3.

This study had sixty three patients with head and neck cancer. Thirty four patients (Group A) received 100 mg/day of fluconazole prophylaxis during radiotherapy and were compared with 29 patients who received radiotherapy alone (group B). A significant reduction of severe mucositis at the end of radiotherapy (14.7 vs. 44.8%, p=0.018) and of interruptions (0 vs. 17.2%, p=0.017) was observed in group A. Candidiasis was prevented (0 vs. 34.5%, p=0.001) with a significant reduction of candida carriage of 40.7% (p=0.001).[17]

Correlating the incidence of oral mucositis with presence of candidial carriage, it was seen that patients with candidial carriage had high incidence of oral mucositis as compared to patients with candidial carriage being negative. This difference was found to be statistically significant (p=0.029). This finding confirms the fact that presence of oral candidiasis worsens mucositis and validates the benefit of prophylactic antifungal agents like fluconazole. This study could not draw conclusions on the treatment interruptions due to oral mucositis and the benefit of prophylactic fluconazole in either the prevention or reduction of unplanned treatment interruptions. This study however is limited by small number of patients and hence to obtain a firm conclusion regarding the role of fluconazole a larger study with more number of patients has to be done.

CONCLUSION: Prophylactic use of fluconazole during radiotherapy reduces the severity of mucositis by reducing oral candidiasis. This could be one of the options in reducing the radiation-induced oral mucositis and candidial infections. Though, this study showed some benefit, it is limited by small number of patients. Further larger studies are required.

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