www.jmscr.igmpublication.org Impact Factor 3.79
ISSN (e)-2347-176x

IGM Publication Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

# Impact of Fluconazole Prophylaxis on Oral Mucositis and Nutrition Status of Head and Neck Cancer Patients Receiving Radiotherapy

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**Abstract**
**Background:** *Oral mucositis is one of the most significant toxicities associated with head and neck radiotherapy. Radiation related mucosal barrier injury allows for microbial colonization and infection, leading, in turn, to amplification of tissue injury.*
**Aim of work***: To evaluate the effect of fluconazole antifungal prophylaxis on the incidence and severity of oral mucositis induced by radiation therapy in patients with head and neck cancer and to determine the impact of this prophylaxis on their nutritional status.*
**Patients and methods***: Eighty patients with head and neck cancer, eligible to receive radiotherapy were categorized into two groups each of 40 patients. Study group received oral fluconazole 100mg/day starting from the sixth irradiation session throughout treatment course as compared to control group with similar radiotherapy characteristics who didn't receive antifungal prophylaxis. Incidence and severity of oral mucositis and impact of oral mucositis on nutritional status (using malnutrition score) of this patient population were evaluated.*
**Results:** *Incidence of clinical oral mucositis wasnon-significantly lower in patients who received fluconazole antifungal prophylaxis at the end of radiation therapy (90% vs 100%). However fluconazole prophylaxis showed a very high significant reduction of the severity of mucositis (P=0.00).High incidence of oral mucositis in both groups negatively affected patient's nutritional status, however less significantly in patients who received fluconazole prophylaxis.*
**Conclusions:** *Although fluconazole prophylaxis showed no significant effect on the prevention of oral mucositis, it significantly reduced its severity and showed significant improvement in patients' nutritional status.*
**Keywords:** *Antifungal prophylaxis; oral/oropharyngeal candidiasis; oral mucositis, radiotherapy; head and neck cancer, malnutrition*

## Introduction

Head and neck cancer (HNC) refers to a group of biologically similar cancers that start in the upper aero-digestive tract, including lips, oral cavity, nasal cavity, para-nasal sinuses, pharynx, and larynx. 90% of HNC are squamous cell carcinomas, originating frommucosal lining of these regions. Each year there are approximately 560,000 new cases diagnosed and about 300,000 deaths [(1)].In Egypt; studies showed that HNC constitutes about 17-20% of malignancie, most of them have metastatic disease at the time of diagnosis [(2)].

Treatment modalities of HNC tumor is either by chemotherapy or radiotherapy or chemo-radiation[(3)].Radiation therapy (RT) causes acute side effects which include mouth sores, dysphagia, taste alteration, pain, and most importantly oral mucositis (OM) due to hypo-salivation secondary to destruction of glandular tissue which encourages candida colonization [(4)].Candida species (especially; albicans), are commensal inhabitants of oral cavity in a large proportion of individuals, which due to mucosal tissue destruction, immunosuppression induced by radiation or disease and imbalance in the oral flora (e.g.,secondary to antibiotic therapy) develop into oral fungal infection in this population with a significantly higher incidence rate than general population. In fact oral candidiasis being superimposed on the radiation-induced mucositis would be anticipated to contribute to the severity of mucositis in this patient population[(5)].

Mucositis in patients with HNC receiving radiation therapy is severe enough so that it may require narcotics for pain, it severely interfere with oral nutrition resulting in weight loss and affecting patient quality of life, also it may delay scheduled treatment, compromising therapeutic efficacy [(6)].

In addition, immunosuppressed cancer patients are at higher risk for oral candidiasis to spread to theoropharyngeal regions and subsequently to systemic circulation and can be fatal However, there is limited information on the prevalence of oral fungal infection in this population and its impact on quality of life and cost of care[(7)].

Fluconazole is the predominant medication utilized to treat oropharyngeal candidiasis. It has also been used effectively to treat this infection in patients receiving head and neck radiation, as the predominant organism is C. albicans, which also has been reported to be colonized in the oral cavity of HNC patients receiving RT[(8)]. Fluconazole is also indicated as a prophylactic therapy to decrease the incidence of candidiasis in HNC patients receiving RT[(9)].

## Aim of work

The aims of current study were; to assess the efficacy of fluconazole prophylactic treatment of mycotic mucositis inpatients with HNC who undergo radiotherapy, to determine the impact of oral mucositis on patients' nutritional status, and to investigate the potential positive effect of fluconazole prophylaxis on patients' nutritional status.

**Patients and Methods**

This is a randomized, prospective, controlled study that was carried out from September 2011 till February 2013 on eighty adult patients, after obtaining an informed consent from each patient. Before starting radiotherapy each patient was given a complete dental examination, detailed oral mucosal and dental hygienic care instructions and any necessary dental restorations.

Study group consisted of 40 patient who received RT plus oral fluconazole 100mg/day starting from the sixth irradiation session throughout treatment course (prophylactic dose) and control group consisted of 40 patient who received RT alone but were given fluconazole 100mg/day, for two week only when mycotic infections appeared (curative dose).

Inclusion criteria:- Histologically confirmed HNC planned to receive radiotherapy, patients Eastern Cooperative Oncology Group Performance Status (0-2)(10), age > 18 and < 65 years, patient willing and reliable for follow-up, hematopoietic criteria (WBC > 3,000/mm³,neutrophil count > 1,500/mm³, hemoglobin > 10 g/dL, platelet count > 100,000/mm³), specific hepatic criteria (AST and ALT ≤ 2.0 ULN, bilirubin < 2.0 mg/dL, alkaline phosphatase ≤ 2 ULN) and renal criteria (creatinine clearance ≥ 60 mL/min).

Exclusion criteria: Previous therapeutic irradiation for HNC, history of prior malignancy, patients with active, uncontrolled bacterial, fungal, or viral infection, which precludes the use of systemic chemotherapy or would interfere with completion of treatment like tuberculosis, any histopathology other than squamous carcinoma, age < 18 or > 65 years, pregnancy or lactating women, severe neurologic disease, or patients currently receiving phenytoin, hydrochlorothiazide, or warfarin.

Radiation protocol: a total dose 60-80 Gray (Gy) was applied by fractionation schedule to 2 Gy/day five days a week for six weeks for each patient using linear accelerator device [(11)].

Measured outcomes included: demographic data (age, sex, weight), incidence of mucositis, World Health Organization Oral Toxicity Score for assessing severity of occurred mucositis [(12)] and malnutrition screening tool according to Ferguson ML et al,[(13)]for assessing patient nutritional status after completion of treatment(patients were considered to be at risk of malnutrition if they score ≥2 that's when they lose weight due to inability of eating as a result of mucositis related to irradiation).

Statistical analysis of results was conducted using SPSS for windows, version 17 (SPSS, Inc., Chicago, IL). Mixed Design analysis of variance (MANOVA) was conducted to compare all disease parameters between both groups in the "pre" and "post" tests and between the "pre" and "post" tests for each variable within each tested groups. As MANOVA revealed significant difference, multiple pair wise comparisons were required to test the significance of these differences where significance level was set at $p<0.05$.

**Results**

As shown in table (1), there was no significant difference regarding patients' age & sex between studied groups.

**Table (1):** demographics data of the studied groups

| Item | Control | Study | p-value |
|---|---|---|---|
| Age(years; (mean± SD) | 57.05±5.75 | 54.35±12.4 | 0.22 |
| Sex, no (%) | | | |
| Male<br><br>Female | 29 (72.5%)<br><br>11 (27.5%) | 26 (65%)<br><br>14 (35%) | 0.217 |

Significant at P<0.05

Mucositis: mucositis incidence was 100 % in control group, while it was 90 % in study group without significant difference between studied groups(*P*=0.05). Regarding mucositis severity (figure 1) ; in control group 7.5% were mild, 30% were moderate and 55% were severe, while in study group 65% were mild, 20% were moderate and 5% were severe respectively. Mean values concerning the post treatment mucositis severity score for both groups showed significantly higher value in control group (*P*= 0.0000) (figure 2).

Malnutrition Screening: 55 % were at risk of malnutrition and 45% were not at risk of malnutrition in control group, while 30% were at risk of malnutrition and 70% were not at risk of malnutrition in study group. Mean values of post treatment malnutrition score (figure 2)was significantly higher in control group (*P*= 0.011).

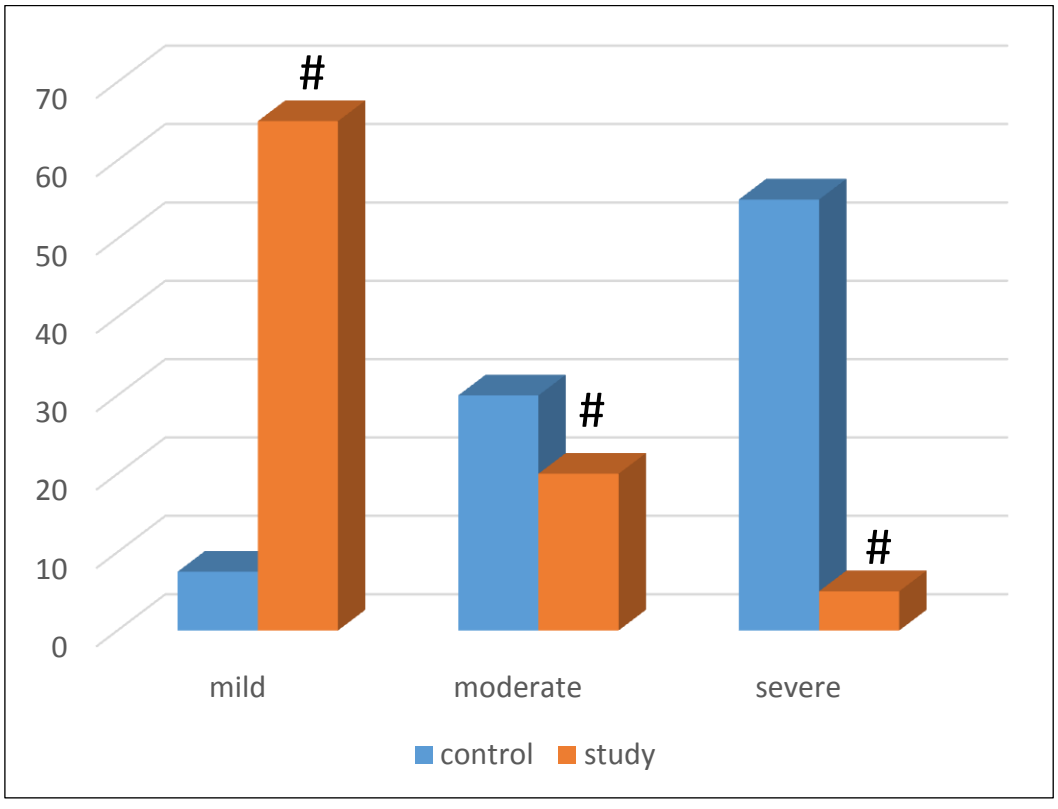


**Fig (1)**: Percentage of different severity grades of mucositis in both groups

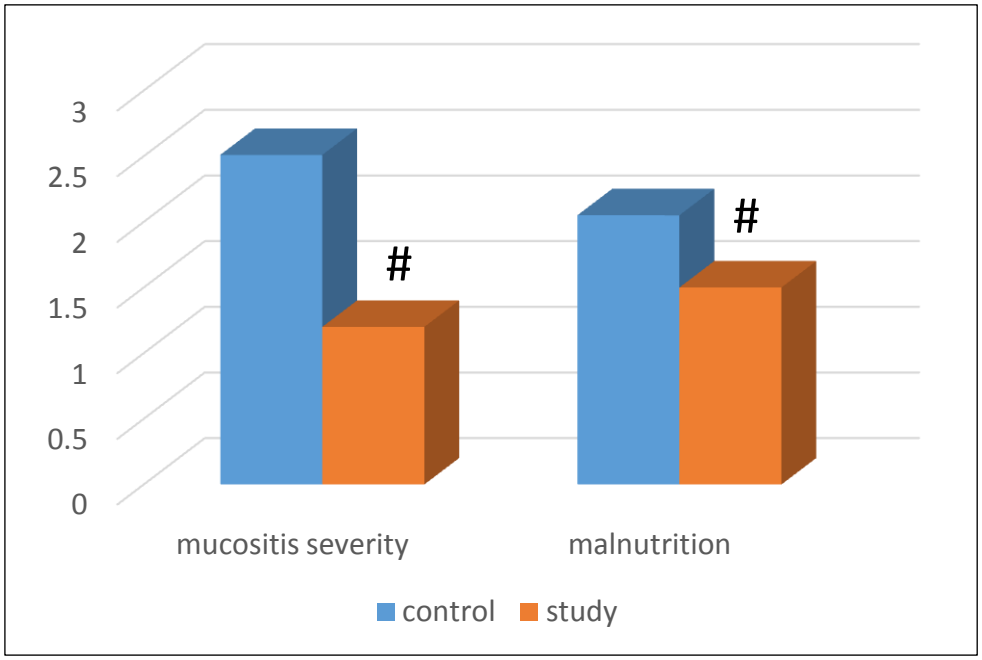


**Fig (2):** Mucositis severity and malnutrition scores in both groups

Weight loss: There was a significant decrease of weight in both groups (*P* =0.000) highly showing that weight loss was more in control group due to malnutrition as result of radiation induced mucositis (figure 3). There was no significant difference between mean values of "post" test between both groups (*P*=0.431).

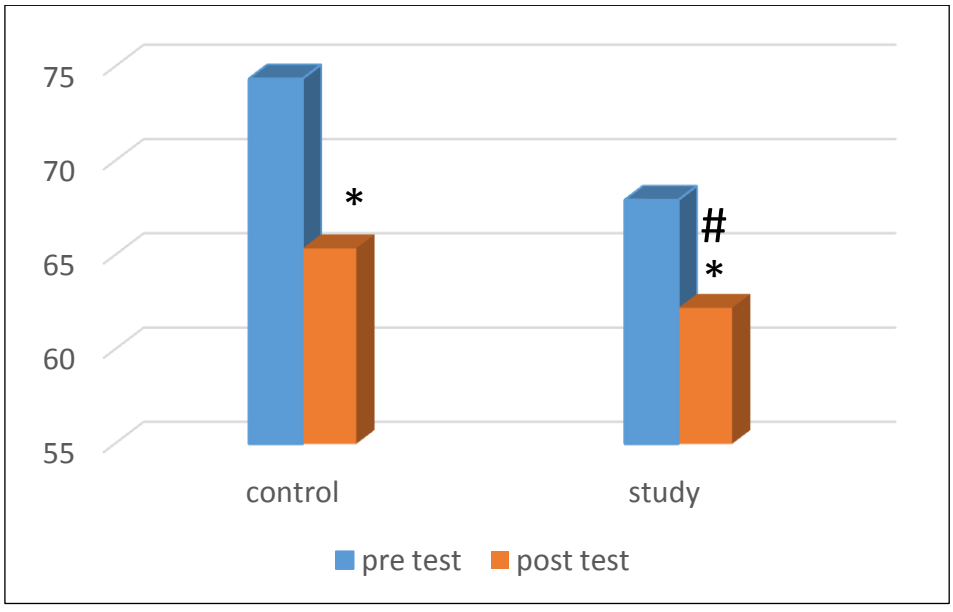


**Fig (3):** Mean weight in both groups pre- and post-treatment

**Discussion**

Previous studies have shown that the frequency of fungal infection especially candida species that colonizes in the oral cavity increases from the beginning to the completion of RT[7].

About 34–43% of patients who receive RT, alone or in combination with chemotherapy, for HNC may experience severe, grade 3 or 4 mucositis characterized by painful ulcerations extending on more than half of the oral mucosa which may lead to RT interruptions in 9–19% of patients[4].

In the present study, incidence of mucositis was 100% in control group while it was 90% in study group with no significant protective effect of fluconazole prophylaxis against the incidence of mucositis. However occurred mucositis was significantly more sever in control group due to absence of prophylactic antifungal treatment as evidenced by significantly higher mucositis severity score in control group ($P$= 0.0000).The beneficial impact of fluconazole prophylaxis on RT in the current study was consistent with other similarly conducted studies[5],[9]. The significant incidence (55 %) of severe mucositis observed in control group without fluconazole prophylaxis in the present study, is even higher than those reported in the systemic review of studies conducted during radiotherapy of HNC (34%)[7][4].

The cellular activities required for chronic tissue repair of mucous membranes injured by daily radiation therapy fundamentally depend upon availability of energy and amino acids [6]. The prevalence of malnutrition is associated with higher mortality and morbidity rates, shorter failure-free survival and poorer quality of life among radiotherapy patients, it is therefore essential to control unintended weight loss/malnutrition and maintain an efficient nutritional status for patients with head and neck cancer [14].

Current results indicate significant improving on malnutrition score in fluconazole prophylaxis group were patients were taking prophylactic fluconazole as compared to those of control group that did not receive this prophylaxis. This finding was inconsistent with similarly conducted studies of head and neck cancer patients undergoing radiotherapy[15][16].The significantly improved nutritional status in the study group can be explained by the concomitant improvement of the degree of severity of OM as compared to control group.

Weight loss during RT for HNC is a well-known occurrence. Altered taste, radiation reactions in the mucosa, decreased appetite[6] and psychological reactions of the patient to the real or feared existence of his tumor[17]can all contribute to poor oral intake and result in weight loss. Individuals who lose weight during radiotherapy tend to have greater severity and longer duration of side effects [18].

Similarly, in the current study, mean values of patient's weight in "pre" and "post" tests showed a significant weight loss in both groups but it was much recognized in control than study group as a result of local symptoms induced by mucositis. These study results are consistent also with similarly conducted studies [19][20].

In conclusions fluconazole prophylaxis showed a significant beneficial effect on reducing the

severity of radiation induced mucositis as well as a significant improvement in nutritional status of patients with head and neck cancer.

Limitations of the study include its inability to address the cost-effectiveness of fluconazole prophylaxis against the needed treatment of oral fungal infection in this patient population, an analysis which is highly valuable and recommended for clinical practice as well as the small sample size.

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