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Original Article

Effects of Sucralfate in the Control of Oral Mucositis in Patients with Head and Neck Cancers Undergoing Radiotherapy

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ABSTRACT

Introduction: *Head and neck cancers (HNC) are common in our country. The patients with locally advanced disease are treated with combined modality approaches. Oral mucositis is one of the most common complications of radiotherapy in HNC which can lead to chronic sequelae and interrupt radiation treatment.* ***Objectives:*** *The aim of this study was to evaluate the effects of sucralfate in the control of radiation induced mucositis.* ***Methods and materials:*** *This quasi-experimental study was carried out among 60 locally advanced head and neck cancer patients. Every alternate patient was assigned in two groups of 30 patients. One group was treated with basic oral care and other group was treated with sucralfate in addition to basic oral care. Patients were examined weekly. Grade of mucositis was evaluated according to WHO grading scale.* ***Results:*** *It was found that addition of sucralfate significantly delayed the onset of mucositis. The overall percentage of mucositis (grade 1 to 4) in group without sucralfate and in group with sucralfate was 100% and 86.67% respectively. This study also revealed that addition of sucralfate significantly reduced the occurrence of weight loss in patients during radiation (p value = o.o36). 26.7% of patients in group without sucralfate required minimum 3 days of gap due to illness, whereas, 6.7% in patients of sucralfate group required that type of gap (p value = 0.037).* ***Conclusion:*** *This study demonstrated that sucralfate is of beneficial value in minimizing radiation induced oral mucositis.*

Key words: *Head and neck cancers, Radiotherapy, Neo-adjuvant chemotherapy, Mucositis, Sucralfate.*

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INTRODUCTION

Cancers that are known collectively as head and neck cancers (HNC) usually begin in the squamous cells that line the moist, mucosal surfaces inside the head and neck [1]. These area includes oral cavity, pharynx, larynx, paranasal sinuses and nasal cavity and ear [2].

Head and neck squamous cell cancer (HNSCC) is the sixth leading cancer by incidence worldwide [3]. These cancers account for approximately three percent of all cancers in the United States [2]. Cancer of the oral cavity and oropharynx are the second most common cancers in male in all indoor patients presented at NICRH, Dhaka in the year of 2007 [4]. According to Cancer Registry Report of NICRH (2008-2010), approximately 2901(10.6%) patients were registered with HNC. According to JAMA oncology report on The Global Burden of Cancer 2013, published online on May 28, 2015, lip and oral cavity cancer was ranked number 1 of incident cases in both sexes in Bangladesh. Overall, HNC accounts for more than 550,000 cases annually worldwide. Males are affected significantly more than females with a ratio ranging from 2:1 to 4:1. This is mainly attributed to tobacco, areca nut, alcohol etc. In India the age-adjusted rates among females is the highest [5].

Cigarette smoking and alcohol consumption are the main reasons of HNCs in the western population, whereas the use of smokeless tobacco and betel nut is the most common cause in Southeast Asia. The various forms of smokeless tobacco used in Asia-Pacific region like India, Pakistan, Bangladesh, Srilanka etc. include paan, zarda, caustic lime and betel nut (betel quid)[5]. Oral cancer is much commoner in India, probably related to chewing betel quid[2].

The majority of patients (more than 60%) present with locoregionally advanced disease and are managed with combined modality approaches. Treatment of HNC generally consists of a combination of surgery and radiotherapy and more recently concomitant chemotherapy which cause a plethora of short-term and long-term oropharyngeal sequelae, which impair quality of life [6].

Radiation induced mucositis (RIM) is a common toxicity for HNC patients. The frequency has increased because of the use of concurrent chemotherapy regimen [7]. Oral mucositis can affect up to 100% of patients undergoing radiation and/or chemotherapy treatment for HNC [8].

Mucositis is the inflammation of the mucosal surfaces. Since mucous membrane proliferates rapidly, the effects of radiation are expressed at an early stage. Rapidly dividing basal cell of the oral mucosa are vulnerable to damage by chemotherapy and radiation therapy. The occurrence of breakdown in mucosal barriers may occur concurrent with neutropenia, thereby putting the patient at risk of infection through lesions in the oral cavity [9].

The consequences of mucositis include pain, dysphagia including feeding tube dependency, dehydration, micronutrient deficiency, weight loss and potentially life-threatening aspiration that interferes significantly with patient functioning and tolerance for cancer therapy.

Currently, there is no FDA approved cytoprotective agent that reliably prevent radiation induced mucositis for HNCs, but several are under investigation.

Strategies to limit the extent of mucositis and to manage its symptoms include basic oral care and supportive medications [7]. Supportive medications include cleansing agents, mucosal-coating drugs, lubricants, emollients and analgesics. Systemically delivered treatments such as antioxidants, immunomodulating drugs, anticholenergic drugs, pentoxifylline, cytokines, antiviral

drugs, glutamic acid and growth factors are being used with varying success [6,7]. Sucralfate, prostaglandins, NSAIDs, corticosteroids, cryotherapy, laser, vitamins and antioxidants belong to the direct cytoprotectants. Haemopoietic growth factors, antimicrobial agents and pharmacologic regulators are example of indirect cytoprotectants [10].Amifostine is FDA approved drug to decrease the rate and severity of both acute and chronic xerostomia [7].

METHODS AND MATERIALS

It is a quasi-experimental study conducted at Department of Oncology, Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Sirajgonj from January 2016 to December 2016. Patients with locally advanced head and neck cancers who had neoadjuvant chemotherapy and got radiation were enrolled in the study. Prior to commencement of the study, research protocol was approved by the ethical committee. The sampling technique was non probability, convenient and purposive sampling. A structured data collection form was the research instrument which includes a questionnaire and a check list. Total study population was 60, among which 30 were in Arm A and 30 were in Arm B. Every alternate patient was allocated in either arm randomly. Arm A: one group was treated with only basic oral care and Arm B: other group was treated with sucralfate in addition to basic oral care. After competing neoadjuvant chemotherapy all patient received radiotherapy after proper simulation and planning. Dose and energy was 66 to 70 Gy in 33 to 35 fractions over 6.5 to 7 weeks with 6 MV photon energy. For the control of oral mucositis, arm A received only basic oral care as usual practice to prevent infections and potentially help alleviate mucosal symptoms. It involves maintenance of oral hygiene, periodic dental evaluations, avoidance of spicy, acidic and hot foods and beverages brushing in a non-traumatic fashion with soft brush or with fingers using mild-flavored toothpastes and frequent rinsing with bland solutions such as 1 Litre of water with ½ teaspoon of baking soda and 1 teaspoon of table salt. Arm B: received Tab. Sucralfate 500 mg, 2 tablets dissolved in 2 tea spoon of water, was taken 3 times daily before meal, which was added to basic oral care. During treatment, patients were assessed weekly and mucositis grading was recorded based on WHO grading system. After completion of treatment all patients were asked every weekly up to 6 weeks over mobile phone about any oral mucosal symptoms. The first follow up examination was done at 6th week.

The data were tabulated in separate tables for both Arm-A and Arm-B and were checked, edited, coded manually and entered into computer. Data analysis was done according to the objectives of the study by using the SPSS.

RESULTS

Table 1: Distribution of the patients by sex (n=60)

Sex	Frequency	Percentage
Male	42	70.00
Female	18	30.00
Total	**60**	**100**

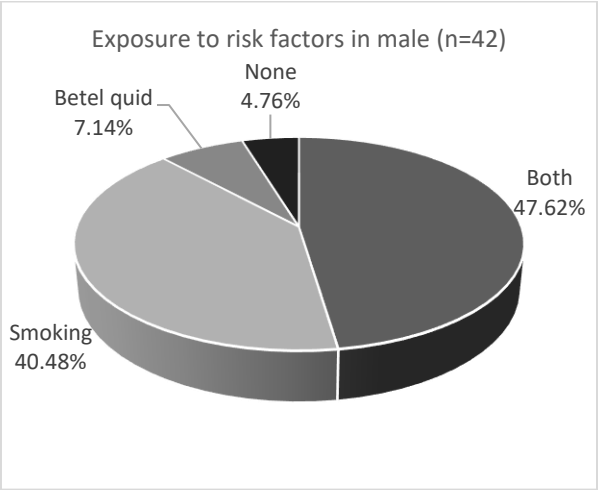

Figure 01: Exposure to risk factors in Male

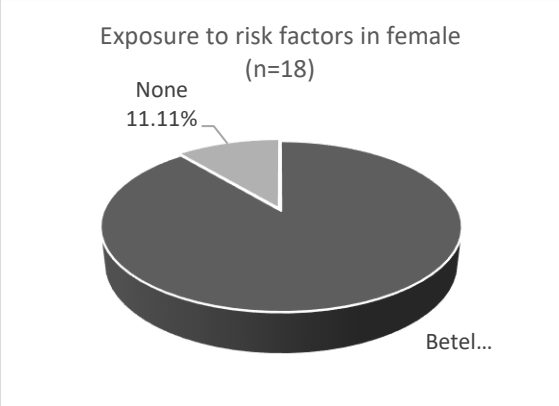

Figure 02: Exposure to risk factors in female

Table 2: Comparison of onset of mucositis between group A and group B in weeks1-4

Week	Group A (n=30)		Group B (n=30)		P value
	N	%	N	%	
Week 1	15	50.0	02	6.7	0.001[s]
Week 2	1	36.7	06	20.0	0.152[ns]
Week 3	04	13.3	14	46.7	0.004[s]
Week 4	00	0.0	08	26.7	0.002[s]

s=significant; ns=not significant

In group A, in 50% of patients, mucositis started in first week, whereas in group B, only in 6.7% of patients, mucositis started in first week which is significant (p value = 0.001).

Table 3: Frequency of grade 3 mucositis in week 1 to 6 (n=60)

Frequency of grade 3 mucositis	Group A (n=30)		Group B (n=30)	
	N	%	N	%
Present	5	16.7	2	6.7
Absent	25	83.3	28	93.3

In group A, 16.7% of patients suffered from grade 3 mucositis, and 6.7% of patients in group B suffered from grade 3 mucositis.

Table 4: Weight loss in patients during treatment (minimum 1 kg)

Weight loss	Group A (n=30)		Group B (n=30)		P value
	N	%	N	%	
Weight loss	26	86.7	19	63.3	0.036[s]
No weight loss	04	13.3	11	36.7	

s = significant

Table 5: Gap of radiation treatment (minimum 3 days) due to illness

Gap of radiation treatment	Group A (n=30)		Group B (n=30)		P value
	N	%	N	%	
Gap of radiation	08	26.7	02	6.7	0.037[s]
No gap of radiation	22	73.3	28	93.3	

s=significant

DISCUSSION

During treatment of tumours in the head and neck region the oral cavity is usually included in the treatment volume. Mucositis is one of the most common complications of radiotherapy in head and neck cancers. Mucositis appears in form of painful lesions with dysphagia and odynophagia in a severe way that negatively affects quality of life in patients and also causes malnutrition and weight loss and even termination of the therapy is a necessary [11].

Studies showed that 80% of patients under radiotherapy with or without chemotherapy suffer from mucositis. Severe mucositis (grade 3-4) occurs in 34% of patients receiving standard RT and in over 56% of patients receiving accelerated RT [12].

Patients may be inclined to discontinue oral care due to discomfort or discontinuation of brushing results in an increased microbial load and risk of gingival inflammation [13].

In our study, the percentage of male patient was 70 % and of female was 30% with a male to female ratio 2.33: 1 which is 1.7:1 in hospital-based cancer registry report 2014 of NICRH. In our study, we found that 47.62% of male patients had a habit of taking both smoked tobacco and betel quid and 40.48% had habit of taking only smoked tobacco. In female patients 88.89% were habituated to take betel quid. A study carried out in Rangpur Medical College Hospital from July 2010 to 2013 showed that 77.96% of all head and neck cancer patients had personal habit of smoking and chewing betel leaf with different ingredients [14].

The specific end point of the study was to evaluate the effects sucralfate in addition to basic oral care to control the radiation induced oral mucositis. In the recent years coating agents like sucralfate were suggested for the prevention and treatment of mucosal reactions. Since sucralfate protects ulcerated epithelium by coating, liberates protective prostaglandinds and increases the local availability of protective factors, this drug might directly interact with the pathogenesis of radiation induced mucositis [15]. A randomized, double-blind, placebo-controlled study using clinical and histopathological evaluation of oral mucositis suggested that sucralfate might be recommended in the prevention of oral mucositis induced by radiation therapy in patients head and neck malignancies [16]. In another study, decrease in the salivary lactoferrin and albumin levels suggested that sucralfate has a slight protective effect on the oral mucosa [17].

The study demonstrated that in group A, in 50% of patient, mucositis started in first week, whereas in group B, only in 6.7% of patient, mucositis started in first week which is significant (p value = 0.001). It indicates that the addition of sucralfate delays the onset of mucositis in the patients of group B. According to the study findings of Hamid Emami et al on the role of sucralfate oral suspension in prevention of radiation induced mucositis [18], the time between the beginning of radiotherapy and the appearance of mucositis was not statistically different in two groups (p=0.9). In our study, frequency of grade 3 mucositis was not statistically different in two groups (p=0.227) which was found significant (p=0.0001) in the study of Hamid Emami et al. It is found that in the overall incidence of mucositis at 4th week of radiation treatment, 70% of group A patients developed high grade (2-3) mucositis which is 20% in group B patients. The study also shows that during the 4th week of radiotherapy most of the patients (66.67%) of group B had grade 1 mucositis, and could continue treatment up to the end without any interruptions. No one in group B had grade 4 mucositis, while 3.33% of group A had grade 4 mucositis. The overall percentage of mucositis (grade 1 to 4) in group A and group B was 100% and 86.67% respectively. If we compare this result with Emami et al., we found that this percentage was 100% and 92.3% respectively in their study. So, in our study, sucralfate showed a slight more protective effect in radiation induced mucositis. In our study, we also found that, sucralfate cannot prevent the development of radiation induced mucositis, but can reduce the grade of mucositis.

A study shows that, as a consequence of mucositis, eating can become difficult, with an average weight loss of 5 kg during treatment [11]. In this study, the percentage of minimum 1 kg of weight loss during radiation treatment was 86.7% and 63.3% in group A and group B respectively (p value = 0.036) which indicates that addition of sucralfate significantly reduce the occurrence of weight loss during radiation treatment.

During radiation treatment 26.7% of patient in group A required minimum 3 days of gap due to illness, whereas, 6.7% of patient in group B required that type of gap during treatment (p value = 0.037). Minimum 3 days of gap during radiation may require some extra dose for gap correction which lengthen the duration of treatment and may cause extra stay in hospital. This study revealed that addition of sucralfate significantly reduce the occurrence of gap in radiation treatment.

Our study revealed that addition of sucralfate reduced high grade mucositis (grade 3 or above) after completion of radiotherapy.

CONCLUSION

The study demonstrated that sucralfate can be of beneficial value in minimizing the radiation induced oral mucositis of HNC patients in terms of delaying onset of mucositis, reducing overall percentage of mucositis and reducing occurrence of weight loss in patients undergoing radiation. Many options are there for minimizing radiation induced mucositis, but the advantages of sucralfate are its simplicity, low cost and minimum adverse effects. It may increase the possibility of uninterrupted radiation treatment which is very much important to achieve a good result.

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