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A Randomized Controlled Trial to Evaluate the Efficacy of Topical Application of a Combination of Chlorhexidine, Clotrimazole and Sucralfate in the Prevention of Oral Mucositis During Definitive Concurrent Chemoradiation Therapy for Head and Neck Squamous Cell Cancers.

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ABSTRACT

Background: Oral mucositis is a common adverse event experienced by head neck squamous cell cancer patients undergoing definitive chemoradiation therapy. Aim of this randomised controlled trial is to test the efficacy of topical application of a combination of Chlorhexidine, Clotrimazole, Sucralfate in reducing chemoradiation-induced oral mucositis. **Methods**: Patients were randomised into two arms each consisting of 50 patients. Patients in the study arm were put on prophylactic application of a combination of topical non-alcohol based Chlorhexidine , Clotrimazole , Sucralfate preparation thrice a day along with maintenance of oral hygiene by brushing the teeth twice a day with soft tooth brush. The protocol was started on the day before D1 of concurrent Cisplatin based chemoradiation. The practice was continued upto 1 month following completion of chemoradiation. In control arm, patients were put on standard oral hygiene practice in the form of brushing the teeth twice a day with soft brush. Both the arms received Concurrent chemotherapy with weekly inj. Cisplatin at the dose of 40mg/m2 and radiation therapy is given at a dose of 70Gy in 2Gy per day fractionation 5 days a week by conventional 2 D planning. The endpoint was to notice the grade of oral mucositis and compare between two arms. **Results**: In the study arm 4 patients out of 50 patients (8%) develop grade 3 or more oral mucositis . In the control arm grade 3 or more oral mucositis was seen in 14 out of 50 patients (28%) recorded any time during the study period. It is evident that incidence of grade 3 or mucositis was lower in the study group and the difference is statistically significant with a p value of 0.009. **Conclusion**: Prophylactic application of a combination of Chlorhexidine, Clotrimazole and sucralfate seems to be quite effective in prevention of severe oral mucositis in patients undergoing definitive chemoradiation therapy for head neck squamous cell cancer.

Keywords: Oral mucositis, Chemoradiation, Squamous Cell Carcinoma.

INTRODUCTION

Oral mucositis is one of the most frequently observed adverse events encountered during Cisplatin based concurrent chemoradiation therapy employed in the treatment of head and neck malignancies.[1] It results in pain inside oral cavity, burning sensation causing difficulty in oral feeding.[2] As a consequence, there occurs frequent interruption in the treatment, nutritional deficit – the factors ultimately leading to poor treatment outcome. The pathogenesis of oral mucositis is not fully understood. It is thought to involve direct and indirect mechanisms.[3] Direct mucosal injury by radiation and chemotherapy interfere with the average 5- to 14-day turnover time of the oral epithelium and induce apoptosis.[4] Indirect stomatotoxic effects result from release of inflammatory mediators, loss of protective salivary constituents, and therapy-induced neutropenia. These factors contribute to the development of oral mucositis and also promote the emergence of bacteria, fungi, and viruses on damaged mucosa.[5]

The degree and duration of oral mucositis in patients treated with radiotherapy for head and neck squamous cell carcinoma is related to the radiation dose, the volume of irradiated mucosa, smoking and alcohol consumption habits,[6] and pre-existing oro-dental infection.[7] In conventional 200 centi-Gray (cGy) daily fractioned radiotherapy programs, mucosal erythema occurs within the first week of treatment. Patchy or confluent radiation-induced mucositis peaks during the fourth to fifth week of therapy.[2]

Several mucosa-protective agents are tried and prophylactic elimination of oral pathogenic flora to reduce the severity of oral mucositis in patients undergoing Radiotherapy with or without concomitant chemotherapy has been addressed in several studies with varying success.

Scherlacher A et al,[6] conducted a study on patients undergoing radiotherapy for head neck cancer to see

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the effectiveness of topical Sucralfate in prevention of radiation- mucositis. Mucosal inflammation, oral pain and dysphagia were significantly less in the study group. There were no side-effects from the sucralfate. Allison RR et al,[9] showed that acute mucositis can be effectively reduced by the prophylactic use of combination of topical sucralfate and oral fluconazole in patients undergoing radiation therapy for head neck cancer. The study by Franzen L et al,[10] demonstrated that the incidence of severe mucositis was significantly lower on topical application of sucralfate compared to placebo during and after radical radiotherapy for head-neck cancers. However in another randomized controlled trial Epstein et al,[11] found that prophylactic oral application of sucralfate did not prevent oral ulcerative mucositis in patients undergoing head neck radiotherapy. Sucralfate showed some reduction in oral pain during radiation therapy. Barker et al,[12] compared topical Sucralfate vs. combined application of Diphenhydramine-Kaolin-Pectin in prevention of radiation-induced oropharyngeal mucositis. There was no significant difference among the two groups. In the study by Feretti et al,[5] there was no difference in oral mucositis on topical chlorhexidine application in patients undergoing high-dose radiotherapy. But reduction of oral microflora was evident in patients who received chlorhexidine. Spizkervet et al,[13] did not find any difference in mucositis on application of Chlorhexidine in comparison to placebo in a study containing 2 groups of 15 patients undergoing head neck radiotherapy. Subsequently the same Researchers used lozenges containing 2 mg polymyxin E, 1.8 mg tobramycin, and 10 mg amphotericin B 4 times a day in patients receiving radiotherapy for head and neck cancer as prophylaxis for oropharyngeal mucositis. The results were compared to the previous study containing comparing chlorhexidine mouth wash with placebo. Eradication of gram-negative bacilli and yeasts was achieved within 3 weeks in all patients using lozenges. Mucositis was significantly reduced compared to the previous two groups.[14] An oral rinse consisting of hydrocortisone, nystatin, tetracycline, and diphenhydramine was seen to significantly reduce radiation-induced mucositis in patients receiving definitive radiation therapy for head neck cancer in another study by Rothwell et al.[15]

In the present study we have used combination of Sucralfate, Chlorhexidine, Clotrimazole to evaluate their efficacy in preventing chemoradiation therapy induced oral mucositis. Sucralfate protects ulcerated epithelium by coating, and increases local availability of prostaglandins and other protective factors. In this way the drug may directly interfere with the pathogenesis of radiation induced mucositis.[14] Chlorhexidine is approved for use as an antibacterial agent for topical use at a concentration of 0.12% and 0.2% to prevent and treat orodental sepsis.[15,16] Topical Chlorhexidine may prevent colonisation of microbial agents inside oral cavity. In addition to its broad spectrum of antibacterial activity, minimal systemic absorption, and ability to bind to oral surfaces led to the use of prophylaxis in an attempt to prevent the development of oral mucositis.[16] However, it has some disadvantages like discoloration of teeth and unpleasant taste.[17, 18] Although fungi are not primarily involved in the development of oral mucositis, they account for the most frequent infections of the damaged oral mucosa in immunosuppressed patients.[19-21] In patients undergoing head and neck radiotherapy, Candida colonization tends to increase throughout the course of treatment.[22,23] Randomized trials have provided evidence that prophylactic and therapeutic topical use of imidazole such as clotrimazole and fluconazole significantly reduces the incidence and duration of oropharyngeal candidiasis in patients undergoing radiation therapy with or without chemotherapy.[24,25]

MATERIAL AND METHODS

Cases of squamous cell carcinoma of head and neck to be treated by definitive concurrent chemoradiation therapy are included in the study. Inclusion Criteria were - adult patients (Age 18 to 70 years); cytologically / histologically confirmed patients of squamous cell carcinoma of head and neck stage III, IVA; ECOG Performance Status 0 – 2; Normal baseline complete blood counts, liver function test, renal functions test; Signed informed consent to participate in the study. Exclusion criteria were – Carcinoma of oral cavity; Carcinoma arising from paranasal sinuses; Previously irradiated patients.

Patients of head neck squamous cell carcinoma requiring concurrent chemoradiation therapy were randomized into two arms each containing 50 patients. In Study arm (Arm A) patients were instructed to apply topical non-ethanol based Chlorhexidine 2% , Clotrimazole 1% mouth paint mixed with Sucralfate 1000mg/10 ml oral suspension thrice a day thoroughly over entire mucosa of oral cavity along with maintenance of oral hygiene by brushing the teeth twice a day with soft tooth brush. The protocol was started on the day before D1 of concurrent Cisplatin based chemoradiation. The practice is continued upto 1 month following completion of chemoradiation. In Control arm (Arm B) patients were put on standard oral hygiene practice in the form of brushing the teeth twice a day with soft tooth brush.

Both the arms received Concurrent chemotherapy with weekly inj. Cisplatin at a dose of 40mg/m2 26 and radiation therapy is given at a dose of 70Gy in 2Gy per day fractionation 5 days a week by conventional 2D planning using Bhabatron II Telecobalt machine.

Patients were followed up every week following start of chemoradiation therapy. Patients were evaluated by history taking enquiring burning sensation inside mouth, oral pain, pain during chewing, bleeding or ulceration of oral cavity. Clinical examination were undertaken in the form of inspection of oral cavity. Grade of oral mucositis was the parameter to be noted. Oral mucositis grading was done using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.27 Statistical analysis was done using SPSS Statistics version 24.

RESULTS

In this study the population in each arm was subdivided in terms of age distribution, stage of disease, and subsite of disease to assess comparability of the two groups. The results, as shown in [Table 1], show that the differences between composition of the two groups are not statistically significant. Therefore, the groups are comparable.

Table 1: Baseline characteristics of Study (Arm A) and Control Arm (Arm B)

Parameter		Arm A	Arm B	P value
Mean age (in years)		62.8 (SD 7.4)	59.6 (SD 9.5)	0.08
Gender	Male	47 (94%)	49 (98%)	0.60
	Female	3 (6%)	1 (2%)	
Stage	Stage III	28	32	0.71
	Stage IVA	22	18	
Subsites	Nasopharynx	3	2	0.68
	Oropharynx	14	17	
	Hypopharynx	12	15	
	Larynx	21	16	

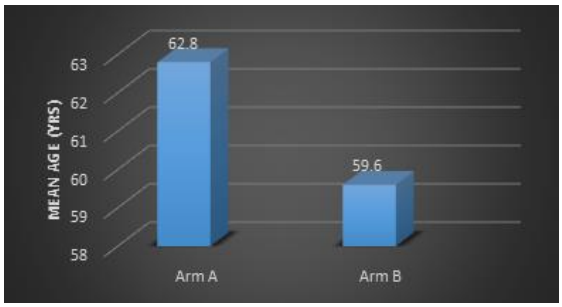

Figure 1: comparing distribution of mean age between two arms

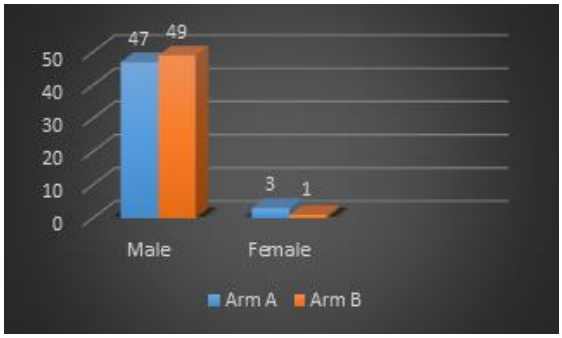

Figure 2: Comparing distribution of gender between two arms

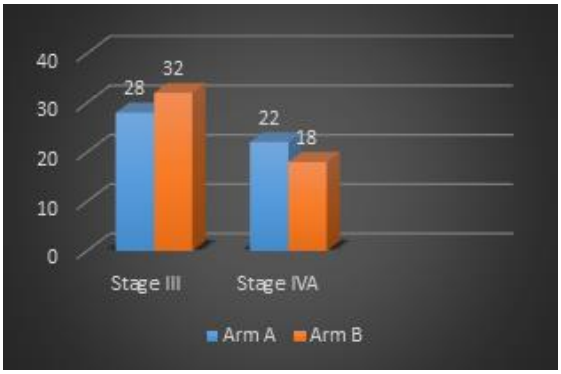

Figure 3: Comparing stage distribution between two arms

Figure 4: Comparing subsite distribution between two arms

In the study arm 4 patients out of 50 patients (8%) develop grade 3 or more oral mucositis. In the control arm grade 3 or more oral mucositis was seen in 14 out of 50 patients (28%) recorded any time during the study period. It is evident that incidence of grade 3 or mucositis was lower in the study group and the difference is statistically significant with a p value of 0.009.

Table 2: Comparing grades of mucositis between two arms

Grade of mucositis	Arm A	Arm B	P value
Grade <3	46	36	0.009
Grade >/=3	4	14	

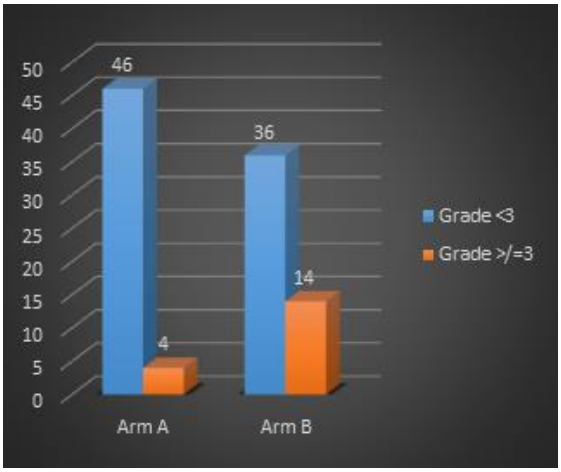

Figure 5: Comparing grades of mucositis between two arms

DISCUSSION

Rising incidence of head and neck cancer worldwide has posed an important public health concern. Radiotherapy with or without chemotherapy has been the primary option in most of the treatment of head and neck cancer. However, chemo-radiotherapy is universally associated with short- and long-term side effects because of the cytotoxic effect. Oropharyngeal mucositis is considered as one of the most common and problematic adverse effect of head and neck irradiation. Mucositis-associated pain significantly impairs oral functions such as deglutition resulting in the nutritional deficit and may cause treatment interruptions which in turn may influence the outcome.[28] Besides, severe oropharyngeal mucositis also increases the risk of infections and the hospitalization.[29] In this study we tried to evaluate the efficacy of combining mucosal protectant with antimicrobial agents in preventing oral mucositis in patients undergoing concurrent chemoradiation therapy for radical treatment of head neck squamous cell cancer. There were a number of studies which used varied agents either topically or systemically for prevention of chemoradiation therapy induced oral mucositis. But none of these studies employed the combination of Sucralfate, Chlorhexidine and Clotrimazole topically. We have chosen these agents for topical application over oral mucosa because they are relatively safe, easy to use and are cheaper. Studies with the aforementioned three agents used individually gave varying and inconsistent results. A study by Diaz-Sanchez R.M. et al,[30] has not shown effectiveness of Chlorhexidine bio-adhesive gel in the prevention of radiation therapy induced oral mucositis. Another study by Kin-Fong Cheng K et al,[31] shown Chlorhexidine mouth wash with Benzydamine to be effective in prevention and treatment of irradiation mucositis in patients with head and neck cancer. this present study the prophylactic application of combination of these three agents has shown statistically significant lowered incidence of severe grade oral mucositis. In the study by Feretti et al,[5] Chlorhexidine mouth rinses significantly reduced the occurrence and severity of oral mucositis in patients undergoing chemotherapy but there was no such benefit in patients undergoing radiotherapy. A placebo controlled study by Cengiz et al,[32] evaluating Sucralfate in the prevention of radiation-induced oral mucositis shown that patients in the sucralfate group experienced significantly lower degree of mucositis than placebo group. Another study by Makkonen et al,[33] however, did not find the efficacy of Sucralfate in prevention of radiation mucositis, but its use was associated with lesser oral pain. Aviles et al in a randomized controlled trial shown lower incidence of oral mucosal complications on using Clotrimazole prophylaxis in patient receiving chemotherapy. In our study prophylactic application of Sucralfate, Chliorhexidine, Clotrimazole has shown lower incidence of severe degrees of oral mucositis and the result is statistically significant. Although some degree of oral mucositis is universal to all ptients belonging to both study and control groups, most patients in the study group experienced halt of the mucositis in grade 1 or grade 2 unlike the control group, where significantly more number of patients landed up at grade 3 or grade 4 oral mucositis. These findings suggest that the aforementioned three pharmaceutical agents are quite effective in preventing severe degrees of radiation induced oral mucositis. However, low sample size in the present study is its limitation. Hence, further larger studies on this topic is all that needed.

CONCLUSION

Prophylactic application of a combination of Chlorhexidine, Clotrimazole and Sucralfate seems to be quite effective in prevention of severe oral mucositis in patients undergoing definitive chemoradiation therapy for head neck squamous cell cancer.

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