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The Effect of Chlorhexidine Mouthwash on Chemoradiotherapy Induced Mucositis in Patients of Head and Neck Cancer

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Abstract: *Aim: To assess the effectiveness of chlorhexidine mouthwash in the prevention or amelioration of mucositis among patients undergoing chemoradiotherapy therapy. Patients and Methods: A total of 60 patients (n=30 in each arm) were assigned to receive either Conventional fractionation or Concomitant boost radiotherapy along with concurrent cisplatin. Toxicities were analyzed weekly during the treatment, and one and three month after treatment completion. The radiation therapy oncology group acute radiation morbidity scoring system was used to document the severity.The patients were planned to receive Chlorhexidine mouthwash 5ml, 3 times a day during and after 3 months of completion of the radiation therapy. Results: Acute mucosal toxicity was assessed as per the RTOG Acute Radiation Morbidity Scoring System. Among both the groups, grade I mucosal toxicity was seen in 18 (60%) patients. Grade II mucosal toxicity was seen in 12 (40%) patients in group A and 10 (33.33%) patients in group B. Grade III mucosal toxicity was seen in 2 (6.66%) patients in group B and in none in group A. Conclusion: The severity of mucositis was less intense in both the treatment group. Chlorhexidine mouthwash might provide benefit for the patients receiving chemoradiotherapy.*
Keywords: *Chlorhexidine mouthwash, Head and Neck Cancers,Mucositis,Quality of life[QOL]*

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I. Introduction

Head and neck cancer (HNC) is the sixth most common type of cancer in the world, representing about 6% of all cancer cases [1] .Oral cancer is the most common type in India amongst men, and the third most frequently occurring cancer in India amongst both men and women [2] .Overall, 57.5% of global HNC occur in Asia, especially in India with over 200,000 new cases and over 100,000 deaths occurring each year [3]**.** Patients with HNC are usually treated with surgery, radiotherapy or a combination of both. The most common side effect of Radiotherapy (RT)is mucositis[4].It is defined as an inflammatory change of the oral mucosa resulting from direct effect of RT[5].

Ninety per cent of patients with head and neck cancer receiving standard radiotherapy and chemoradiotherapy will develop oropharyngeal mucositis [6]**,** varying in incidence according to the oncology treatment schedule [7].

Different techniques have been described like intensive oral care protocol, antimicrobial agents, anti-inflammatory agents, cytoprotective agents, nutritional supplements, biostimulants, or natural and homeopathic agents. Although all of these treatment options exist to prevent and treat mucositis, there is no gold-standard protocol that is prominently better than the rest because there is no sufficient evidence describing a treatment with proven efficiency to surpass the other treatments for this condition [8-16]**.**

Chlorhexidine is approved for use as an antibacterial mouthwash at a concentration of 0.12% and 0.2% to prevent the build-up of dental plaque and to prevent gingivitis [10,16].Chlorhexidine is a disinfectant and antiseptic often used as an active ingredient in mouthwash and is designed to reduce dental plaque and oral bacteria.The aim of this study was to evaluate, in an initialway, the effectiveness of 0.2% chlorhexidineMouthwashas a preventive and therapeutic intervention therapy for oral mucositis induced by chemoradiotherapy in patients diagnosed with head and neck cancer.

II. Patients And Method

Between August 2016 – June 2017, 60 patients at our institute were assigned randomly in this study. Prior approval was taken from the institutional ethical board. Patients aged <70 years (both sexes) with histologically proven locally advanced oral cavity/oropharyngeal squamous cell cancers (SCC), with Karnofsky performance score ≥ 70, normal baseline haematological investigations and chest X-ray were included**.**

Patients were treated on Cobalt-60 Theratron 780 machine. A total dose of 7000 centigray (cGy)/35 fraction @ 200 cGy/ fraction /day, five days a week over 7 weeks were prescribed in Group A (CF arm) and a

dose of 6900cGy @ 180 cGy/ fraction five days a week for 6 weeks, and 150 cGy (as a boost dose field -in-field) in the last 10 fractions with an inter fraction gap of 4-6 hours was prescribed in Group B (CBT arm). Concurrent cisplatin 40mg/m2 was administered every fifth day of radiation therapy.Toxicities were analysed weekly as per the radiation therapy oncology group acute radiation morbidity scoring system. Separate assessment of mucosal reactions was made. Statistical analysis was done using the online graph pad software using chi square test. A value of $p<0.05$ was considered significant. RTOG scoring system as depicted in Table 1.

III. Results

A Total of 60 patients were enrolled in the study, mean age was 50 years. The patient and disease characteristics are shown in Table 2&3. As per the anatomical sub site distribution, in group A, 4 patients (13.33%) and in group B, 5 patients(16.66%) had tumor in the alveolus. In group A, 8 (26.66%) patients and 15 (50%) patients in group B had tumor in buccal mucosa (BM). In group A, 10 (33.33%) and in group B, 7 (23.33%) patients had tumor in tongue. In group A, 2 (6.66%) patients and in group B, none had tumor in the floor of mouth (FOM).In group A, 1 (3.33%) and in group B, 2(6.66%) patients had tumor in base of tongue (BOT). In group A, 1 (3.33%) patient and in group B none had tumor on lips.In group A, 3(10%) patients and in group B,none had tumor in the tonsillar fossa. In group A, 1 (3.33%) and in group B 1(3.33%) patients had tumor in hard palate.

The incidence of mucositis after radiotherapy was found in patients of both group and results revealed that maximum no. of patients in both group A and B, 18 patients out of 30 (60%) suffered from grade I toxicity and12 patients out of 30 (40%) patients in group A and10 patients out of 30 (33.33%) patients in group B had grade II toxicity and 2 patients out of 30 (6.66%) patients in group B had grade III toxicity. No incidence of grade III toxicity was observed in group A.

The results of weekly assessment of mucosal toxicity indicates that the incidence of mucositis was gradually increased to 18 patients out of 30 (60% grade I) and 12 patients out of 30 (40% grade II) in group A at the end of 5th week of treatment but this trend was significantly reduced to 8 patients out of 30 (26.6%) at the end of 1st month after treatment completion.

The incidence of mucositis was gradually increased to 18 patients out of 30 (60%grade I), 8 patients out of 30 (26% grade II) and 2 patients out of 30 (6.66%grade III) in group B at the endof 5th week of treatment but this trend was significantly reduced to 4 patients out of 30 (13.3% grade I) at the end of 1st month after treatment completion.

IV. Figures And Tables

RTOG SCORING OF MUCOSITIS-Table 1

Grade 0	No change over baseline.
Grade 1	Irritation ,may experience slight pain, not requiring analgesic
Grade2	Patchy mucositis that may produce inflammatory serosanguinitis discharge, may experience moderate pain requiring analgesic narcotic.
Grade3	Confluent, fibrinious mucositis, may include severe pain requiring narcotic.
Grade4	Ulceration, haemorrahage or necrosis.

AGE WISE DISRTIBUTION-Table 2

S. No.	Age Group Years	Group A		Group B	
		No. Of pt.	%	No. Of pt.	%
1	21-30	0	0	3	10%
2	31-40	7	23.33%	8	26.66%
3	41-50	9	30%	11	36.66%
4	51-60	10	33.33%	6	20%
5	61-70	4	13.33%	2	6.66%

ANATOMICAL DISTRIBUTION –Table 3

S. No.	Site	Group A		Group B	
		No. Of pt.	%	No. Of pt.	%
1	Alveolus	4	13.33%	5	16.66%
2	BM	8	26.66%	15	50%
3	Tongue	10	33.33%	7	23.33%
4	FOM	2	6.66%	0	0
5	BOT	1	3.33%	2	6.66%

6	Lips	1	3.33%	0	0
7	Tonsillar Fossa	3	10%	0	0
8	Hard Palate	1	3.33%	1	3.33%

MUCOSAL TOXICITY AFTER EBRT (OVER ALL) -Table 4

S. No.	Grade	Group A		Group B	
		No. Of pt.	%	No. Of pt.	%
1	I	18	60%	18	60%
2	II	12	40%	10	33.33%
3	III	0	0	2	6.66%

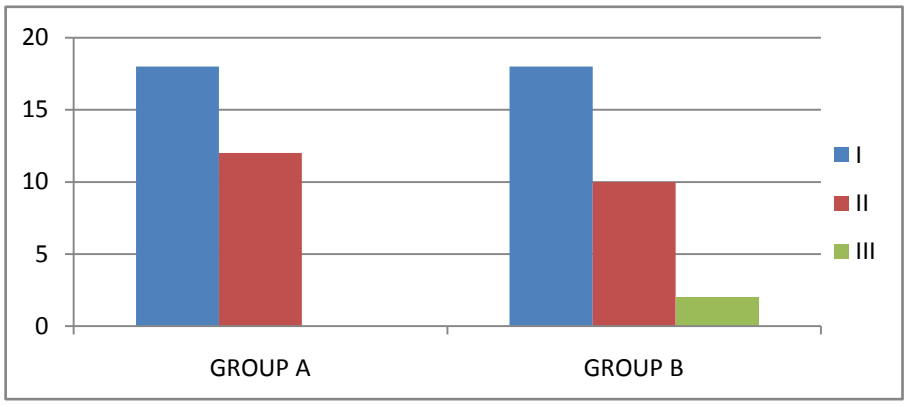
(WEEKLY ASSESSMENT)- Table 5
Mucosal Toxicity Group A

Mucositis Grade	During RT weekly							Post RT (1&3 month)	
	1	2	3	4	5	6	7	1	3
I	-	6 [20%]	14 [46%]	16 [53.3%]	18 60%]	10 [33.33%]	12 [40%]	8 [26.66%]	-
II	-	-	10 [33.3%]	2 [6.66%]	12 [40%]	10 [33.33%]	10 [30.3%]	-	-
III	-	-	-	-	-	-	-	-	-
IV	-	-	-	-	-	-	-	-	-

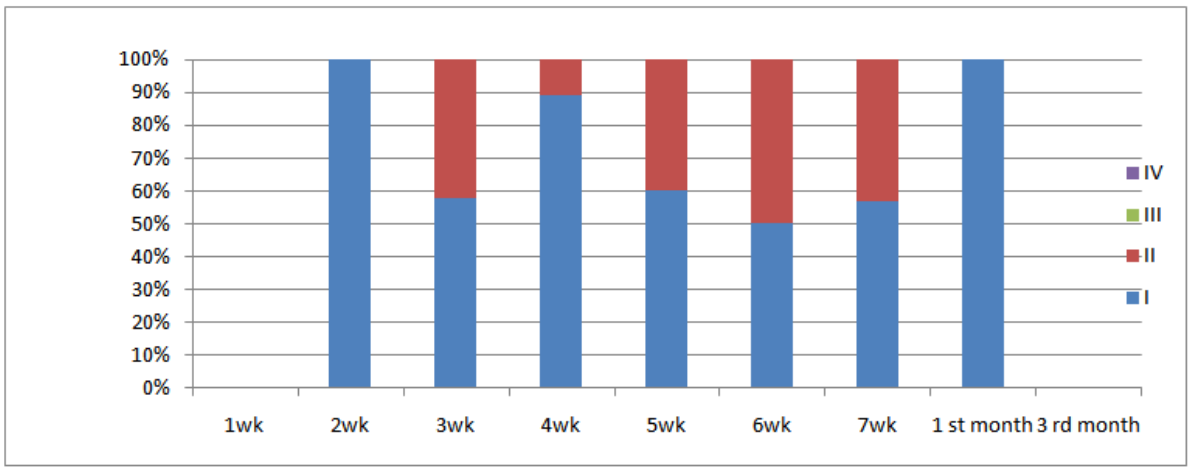
(WEEKLY ASSESMENT)–Table 6
Mucosal toxicity Group B

Mucositis Grade	During RT weekly							Post RT (1&3 month)	
	1	2	3	4	5	6	7	1	3
I	-	4 [13.3%	8 [26.6%]	15 [50%]	18 [60%]	15 [50%]	10 [33.3%]	4 [13.3%]	-
II	-	-	2[6.6%]	10[33.3%]	8[26.6%]	8[26.6%]	5[16.6%]	-	-
III	-	-	-	-	2[6.6%]	-	-	-	-
IV	-	-	-	-	-	-	-	-	-

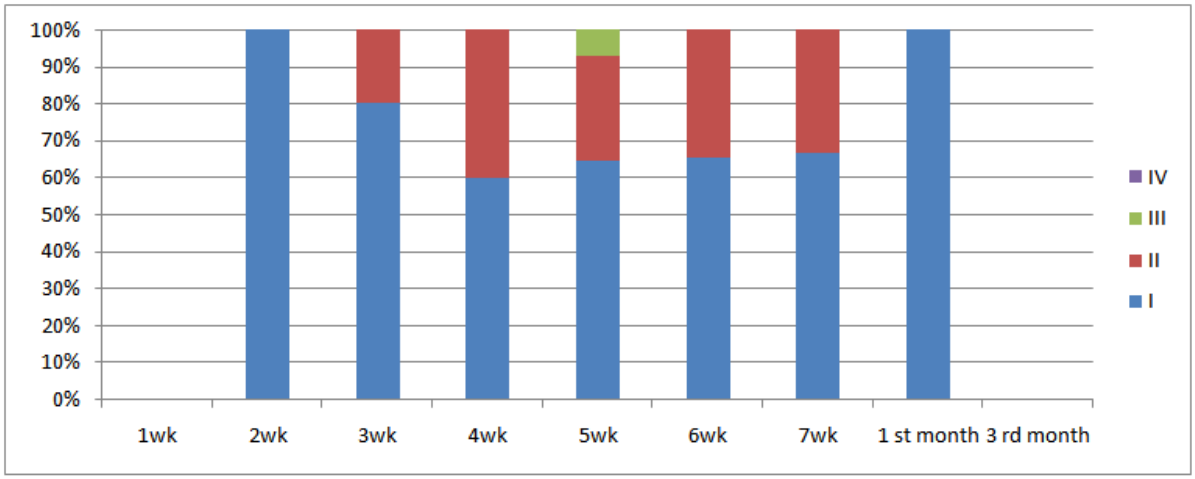
Incidence of Mucositis in Both Groups-Graph 1



Weekly Assessment of Mucositis in Group A-Graph 2



Weekly Assessment of Mucositis in Group B-Graph 3



V. Discussion

Mucositis is a common acute complication of radiation usually manifested by painful lesions with dysphagia that adversely affects patient's quality of life and may lead to discontinuation of treatment. The development of oral mucositis may result from both direct and indirect effects of radiotherapy and chemotherapy on cells[17]. The direct effect is determined by interference of drugs in cell production, maturation and replacement, whereas the indirect effect is related to myelosuppressive action of drugs, which deregulates the immune system and repair process, increasing the risk of infection associated with oral mucositis[18]. According to Beumer et al[19]inhibition of cell growth and maturation by radiotherapy damages the primary mucosal barrier of the oral cavity and oropharynx and thereby creates a pathway for establishment of infection by the resident oral microflora.This disruption leads to several complications like oral mucositis and gingivitis, oral candidiasis, xerostomia, trismus, dental caries, osteoradionecrosis, cellulitis and viral mucosal eruptions.These oral complications may challenge radiation oncologists from many perspectives, such as radiation dose limitations, changes in dose fractionation protocol, and dramatic negative effects on patients' quality of life [20]. The major clinical consequences of Radiation Induced Oral Mucositis(RIOM) include hospital admission or extended hospitalization for total parenteral nutrition, intravenous (IV) analgesia, and IV antibiotics. Sixty-two percent of patients require hospitalization, and 70% of patients with grade 3–4 oral mucositis (OM) require feeding tube insertion. Reduction or cessation of cancer treatment occurs in 35% of patients due to the developed dose-limiting toxicity [21]

Intraoral lesions are commonly localized in oral mucosa, such as lip, buccalmucosa, tongue, floor of the mouth, and soft palate. The hard palate and gums seem to be less susceptible to the effects of chemotherapy andradiotherapy[22]

Chlorhexidine has recognized fungicidal and bactericidal properties, and it has been shown that preventive treatment with this drug and oral hygiene care can reduce the occurrence of oral complications related to hematological cancer treatment [23].

In our study ,early mucositis was not reported in any of the patients in both arms group A and group B which differ from the study of Vees et al and that of De Arruda et al who detected grade I - II of mucositis in 54% and 38% respectively [24,25].In our study the incidence of mucositis was gradually increased to 60% (grade I) and 40%(grade II) in group A at the end of 5th week of treatment but this trend was significantly reduced to 26.6%(grade I) at the end of 1st month after treatment completion. There was a gradual increase in the incidence of mucositis to 60%(grade I) ,26% (grade II) and 6.66%(grade III) in group B at the end of 5th week of treatment but this trend was significantly reduced to 13.3% (grade I) at the end of 1st month after treatment completion. Grade III mucosal toxicity was considerably less (6.66%) compared with other studies [26-30]. In our study, the maximum incidence of mucositis was observed in 5th and 6th week of treatment that was consistent with Medina et al observation [31] and Majdaeen et al study[32].

The reason for low incidence of mucositis could be attributed to good nutritional counselling, generous use of Non-steroidalanti-inflammatory drugs (preferential COX-2 inhibitor), G-CSF and supportive care and special emphasis on oral hygiene and use of Chlorhexidine solution for mouth wash. Stokman and co-workers[8], in a meta-analysis of 45 studies and 8 interventions, concluded that "to date, no single intervention completely prevents oral mucositis". However, they identified treatments with significant preventive effect, such as PTA (combination of the antimicrobials polymyxin E, tobramycin and amphotericin B), GM-CSF (granulocyte-macrophage colony stimulating factor), oral cooling by means of ice chips, and amifostine. More recently, two systematic reviews on preventive (including 89 studies and 29 interventions) and on therapeutic approaches [33] (with 26 studies)concluded that some benefit could be obtained with certain strategies, such as: amifostine, natural remedies from Chinese medicine and hydrolytic enzymes, especially in the prevention and the reduction of its severity. It has been suggested, therefore, that the best approach may be the use of a combined preventive therapy strategy.

Data from several randomized clinical trials reveal that chlorhexidine mouthwash usage does not have a significant impact on the prevention of mucositis in patients undergoing chemoradiotherapy[34,35]. Chlorhexidine rinses is a treatment that is applied across the surface of the oral cavity without acting specifically on lesions, so the use of chlorhexidine gel would seem to have a more advantageous indication for the treatment of injuries caused by mucositis because of the localized application [36].

Chlorhexidine has also been compared with benzydamine hydrochloride oral rinses for the prevention and treatment of irradiation mucositis in patients with head and neck cancer. Significant differences were not detected between groups on outcome measures; a trend has emerged toward a lessening of oropharyngeal mucositis for patients who received benzydamine compared to patients who received chlorhexidine. However, these results contrast with those published by Cheng, who stated that from the patients' perspective, chlorhexidine is more helpful than benzydamine in reducing mucositis and palliating oral discomfort [37].

Our study is not in agreement with the evidence indicating that chlorhexidine rinse is not useful for the prevention and treatment of the mucositis induced by chemoradiotherapy of headand neck cancer [38, 39].Further, other clinical trials done with chlorhexidine also concluded that it cannot be recommended for the prophylaxis or the treatment of RIOM [40-43].

Thus,it can be suggested from our study and the data presented here that chlorhexidine may play a part in reducingOral damage during radio-chemotherapy, possibly through plaque control and a reduction in the oral microflora as supported by other studies [44].However, it cannot be used to cause a reduction in the pain produced by mucositis. These results are in accordance with those published with chlorhexidine mouthwash studies in past[45].

VI. Conclusion

In our study, chlorhexidine mouthwash 0.2% along with other supportive measures have provided better clinical results on oral mucositis caused by chemoradiotherapy in the treatment of head and neck cancer.Thus we recommend that chlorhexidine rinses along with adequate supportive measures like antibiotic coverage and use of G-CSF and COX-2inhibitors can enhance the quality of life of patients experiencing radiation induced oral mucositis.

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