



Effect of adding clotrimazole lozenges in reducing the severity of radiation/chemo- irradiation induced oral mucositis in patients with head and neck malignancies

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ABSTRACT

This paper aims to determine the effect of clotrimazole lozenges in addition to soda bicarbonate mouthwash and compare it with soda bicarbonate mouthwash only, in reducing radiotherapy/chemo-irradiation induced oral mucositis in patients with Head and Neck Malignancies. A randomized controlled trial was conducted. Arm A - Radiotherapy/Chemo-irradiation who were randomized to receive clotrimazole lozenges and soda bicarbonate mouth wash. Arm B- Radiotherapy/Chemo-irradiation who were randomized to receive soda bicarbonate mouthwash only. Fifty-six patients were accrued in the trial, 28 in the control arm and 28 in study arm. Fifty-two patients completed the treatment protocol. 4 patients in control arm defaulted due to various reasons. A number of patients in the control vs. study arm of Chemo-irradiation group was 16 vs. 16 and in Radiotherapy group 12 vs. 12 patients. The occurrence of Grade 3 mucositis was more in the control arm 30% vs. 40% and the onset was later among patients in the study arm (week 3). In the Chemo-irradiation group requirement for analgesic (92.8% vs. 53.8%), topical anaesthetic (35.7% vs. 7.6% - significant), occurrence of mouth pain (28.5% vs. 15.3%) and Ryles tube feeding (28.5% vs. 15.3%) were less in the study arm and also tolerated more number of cycles of concurrent chemotherapy (76% vs. 14% p= 0.036). A number of patients having a break in treatment (0% vs. 42.8% -significant) and occurrence of oral thrush (32% vs. 9%) were less in study arm of chemo-irradiation and Radiotherapy. Nausea and vomiting were the predominant complaints in study arm probably induced by the chemotherapy. The occurrence of dryness of oral mucosa and throat was more in study arm of chemo-irradiation group but less in radiotherapy only group. Overall the addition of clotrimazole lozenges to soda bicarbonate mouthwash along with oral care protocol during treatment showed significant benefit in decreasing the incidence of oral thrush.

Keywords— Soda bicarbonate mouthwash, Clotrimazole lozenges, Oral mucositis, Radiotherapy and Chemo-irradiation

1. INTRODUCTION

Mucositis occurs in almost all radiotherapy treated head and neck cancer patients. Mucositis is painful, may affect all oral functions, and is a dose- and rate limiting toxicity of therapy for cancer. Radiation-associated mucositis (onset, intensity, and duration) has been shown in recent clinical trials to be modified by the use of antibacterial/antifungal lozenges. Radiation-induced mucositis is initiated by direct injury to basal epithelial cells and cells in the underlying tissue. DNA strand breaks can result in cell death or injury. Non-DNA injury is initiated through a variety of mechanisms, some of which are mediated by the generation of reactive oxygen species. Radiation and chemotherapy are effective activators of several injury-producing pathways in endothelia, fibroblasts, and epithelia. In these cells, the activation of transcription factors such as nuclear factor- κ B (NF- κ B) and NRF-2 leads to the up-regulation of genes that modulate the damage response. Immune cells (macrophages) produce pro-inflammatory cytokines, such as tumour-necrosis factor- α (TNF- α) and interleukin-6, which causes further tissue injury. These signalling molecules also participate in a positive-feedback loop that amplifies the original effects of radiation and chemotherapy. For example, TNF- α activates NF- κ B and sphingomyelinase activity in the mucosa, leading to more cell death. In addition, direct and indirect damages to epithelial stem cells result in a loss of renewal capacity. As a result, the epithelium begins to thin and patients start to experience the early symptoms of mucositis.

An oropharyngeal epithelial surface has a rapid rate of cell turnover and appears to be at high risk of injury from ionizing radiation. A healthy oral mucosa serves to clear microorganism and provides a chemical barrier that limits the penetration of many

compounds into the epithelium. A damaged mucosal surface increases the risk of a secondary infection. Acute mucositis results from the loss of squamous epithelial cells owing to the sterilization of mucosal stem cells and the inhibition of transit cell proliferation. This leads to a gradual linear decrease in epithelial cell numbers. Normally, cells of the mouth undergo rapid renewal over a 7-14 day cycle. Radiation therapy interferes with cellular mitosis and reduces the ability of the oral mucosa to regenerate.

As radiation therapy continues, a steady state between mucosal cell death and regeneration may occur because of an increased cell production rate from the surviving cells. Usually, however, cell regeneration cannot keep up with cell death, and therefore, partial or complete denudation develops. This presents as patchy or confluent mucositis. As the mucositis becomes more severe, pseudomembranes and ulceration develop. Poor nutritional status further interferes with mucosal regeneration by decreasing cellular migration and renewal. The loss of the epithelial barrier enhances insults from physical, chemical, and microbial agents.

Oral infections, which may be due to bacteria, viruses, or fungal organisms, can further exacerbate the mucositis and may lead to systemic infections. If the patient develops both severe mucositis and thrombocytopenia, oral bleeding may occur and may be very difficult to treat.

2. MATERIALS AND METHODS

- A randomized controlled trial was conducted. Arm A- Radiotherapy/Chemoirradiation who were randomized to receive clotrimazole lozenges and soda bicarbonate mouth wash. Arm B- Radiotherapy/Chemoirradiation who were randomized to receive soda bicarbonate mouthwash only.
- The study was approved by the ethical committee as well.
- The study group consisted of patients accrued from July 2018 to November 2018. Patients were randomized into Arm A and Arm B. They were simultaneously stratified and randomized such that both groups had an equal number of patients undergoing radiotherapy and chemoirradiation.
- Arm A consisted of patients on radiotherapy/chemo-irradiation for head and neck malignancy who were randomized to receive clotrimazole lozenges and soda bicarbonate mouth wash. Arm B consisted of patients on radiotherapy/chemo-irradiation who were randomized to receive soda bicarbonate mouth wash only.
- Both arms followed the oral care protocol.

2.1 Inclusion criteria

- (a) Age greater than 18 years and less than or equal to 70 years.
- (b) Histopathological proof of head and neck malignancy-Squamous cell or undifferentiated carcinoma.
- (c) Malignancies of oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and secondary neck node with unknown primary.
- (d) All stages except stage I larynx.
- (e) Karnofsky performance status more than or equal to 60%.
- (f) Haemoglobin more than or equal to 10 grams% with or without transfusion.
- (g) Patients who were for radical radiotherapy or chemoirradiation and radiation field involved more than 50% of the oral mucosa.
- (h) Parallel opposing lateral field for face and upper neck (field 1&2) and direct anterior field for lower neck field (field 3).
- (i) Radiotherapy dose of 66Gy equivalent in 180cGy or 200cGy fractions to face and upper neck and 50Gy in 25 fractions to lower neck, with 5 fractions per week.
- (j) Chemotherapy using Cisplatin only as a single agent.
- (k) Informed consent signed by the patient.

2.2 Exclusion criteria

- (a) Postoperative patients.
- (b) Patients who have already received some form of treatment for the same disease.
- (c) Patients with double malignancies.
- (d) Histopathology is other than squamous cell or undifferentiated carcinoma.

2.3 Treatment regimen

Patients eligible for the study were randomized into two groups. After the pre-treatment evaluation, all patients were instructed about the oral care protocol. Patients receiving radiation therapy/chemo-irradiation for carcinomas of oral cavity, pharynx or larynx were included in the study.

Arm A: Patients were instructed to swish soda bicarbonate mouthwash and chew clotrimazole lozenges. 20ml of soda bicarbonate mouthwash was used before and after each meal and before bed time. Mouthwash was swished for 5 minutes and spat out. It was used seven times a day. Clotrimazole lozenges were chewed three times a day after meals. Mouthwash and lozenges were started from day 1 of radiotherapy.

Arm B: Patients were instructed to swish soda bicarbonate mouthwash only. 20ml of soda bicarbonate mouthwash was used before and after each meal and before bed time. Mouthwash was swished for 5 minutes and spat out. It was used seven times a day. Mouthwash was started from day 1 of radiotherapy. Clotrimazole lozenge 10mg was used.

2.4 Radiation therapy details

All patients had treatment using parallel opposing lateral technique for face and upper neck region and direct anterior technique for lower neck region. The dose prescribed was 6600cGy in 33 fractions to face and upper neck and 5000cGy in 25 fractions to

lower neck. All patients were treated on Linear accelerator 6MV photons. All fields were treated every day with single fraction per day for five days a week.

2.5 Chemotherapy details

Cisplatin (40gm/m²) was used concurrently with radiotherapy. Cisplatin was administered either weekly or every 3 weeks (nasopharynx).

2.6 Oral care protocol

- (a) Twice a day brushing of teeth, gums and tongue done carefully with a soft tooth brush and fluoride toothpaste.
- (b) Precautions regarding food to be taken during radiotherapy:
 - Allow hot food to cool before eating it.
 - Avoid spicy, acidic and peppery foods and irritants such as alcohol or tobacco.
 - Avoid acid containing fruit juices such as orange juice and lemonade.
 - Avoid coffee.
 - Take about 3 litres of water/fluid per day. Try straw for drinking fluids in case of difficulty in taking directly.
 - Eat bland food high in protein.
 - Eat soft, moist food such as cooked cereals, mashed potatoes and scrambled eggs.
- (c) Do not use dentures during the whole duration of radiotherapy to avoid sores or irritation. They may be used only during mealtime if necessary. Following the completion of radiation, dentures can be used regularly once mucositis has settled completely.

2.7 Assessment

Patients were assessed at every 1000cGy equivalent dose of radiotherapy, by a blinded observer. The assessment was based on objective and subjective criteria.

- (a) Mucositis: Grade of mucositis was assessed using RTOG acute radiation morbidity criteria. Each sub site of the oral cavity was examined for mucosal reactions. If patients developed grade 3 mucositis then treatment was stopped till the mucositis heals.
- (b) Mouth pain: Pain was graded as mild, moderate-severe or no pain.
- (c) Swallowing impact: Swallowing difficulty was graded as nil, mild, moderate and severe. Severe dysphagia being a requirement for Ryle's tube for feeding.
- (d) Dryness: Dryness of the throat and oral cavity was graded as nil, mild, moderate and severe.
- (e) Oral candidiasis and the antifungal requirement were evaluated.
- (f) The requirement of analgesics was noted.
- (g) Break in treatment was noted.
- (h) The occurrence of other symptoms and other drug consumption was also looked for.

2.8 Pre-treatment evaluation

- (a) Clinical: Patients with malignancies of oral cavity, pharynx, larynx and secondary neck node with unknown primary were included in the study. The oral cavity was examined for dental caries, gingivitis, periodontitis and premalignant conditions. Dental surgeon clearance was sought before treatment.
- (b) Hematological: Total count, differential count, haemoglobin and platelet count were done.
- (c) Biochemical: Serum creatinine and liver function test were done
- (d) Radiological: Chest X-ray was done to rule out metastasis.

3. STATISTICAL ANALYSIS

To test the association between the experimental and control groups the chi-square test was used. For comparing averages between the groups the student's Independent 't' test was used. If the number of mean categories is more than two ANOVA (analysis of variance) was carried out to compare the averages. SPSS (statistical packages for social sciences) version 9 software was used to analyse the data.

4. RESULTS

Fifty-six patients were accrued in the trial, 28 in the control arm and 28 in study arm. Fifty-two patients completed treatment and were available for assessment until the end of 7 weeks. Four patients in the control arm discontinued treatment after 4 to 5 weeks, so partial data was available from them One patient developed herpes labialis, one patient developed hypotension, one patient developed severe odynophagia and put on ryles tube, and one patient discontinued for personal reasons.

4.1 Distribution of patients

In each arm, patients were also stratified into Chemoradiation and Radiotherapy groups. In control arm 16 had Chemoradiation and 12 Radiotherapy only. In study arm 16 patients had Chemoradiation and 12 Radiotherapy only. They were simultaneously stratified and randomized such that both groups had an equal number of patients undergoing Radiotherapy and Chemoradiation.

4.2 Patient characteristics

- (a) **Age:** The mean age of patients in Chemoradiation group of control arm and study arm was almost similar 50.5 years vs. 48.5 years and was also similar in the Radiotherapy only group, 59 years vs. 55.5 years. Overall the mean age was similar in control and study arm 53 vs. 51 years. The groups were comparable for age.

- (b) **Sex:** The sex wise distribution showed a number of males than females in both arms. The male to female ratio was more in study arm of chemoirradiation group 12:2 vs 12:1. The male to a female ratio more in the study arm of Radiotherapy only group as compared to the control arm. Overall the arms were comparable by a male to female ratio 17:3 vs. 19:1.
- (c) **Habits:** The habit wise distribution was as follows, alcoholic 25% Vs 15 %, smokers 65% vs. 60% and tobacco chewers 65% Vs 35%.
- (d) **Performance status:** All patients in the study had a Karnofsky performance status of 90.
- (e) **Dental caries:** Pre-treatment dental caries was seen more in control arm patients as compared to study arm 25% vs. 5%.
- (f) **Unhealthy gums:** Pre-treatment checkup showed a number of patients in control arm with unhealthy gums as compared to study arm 25% Vs 15%.
- (g) **Hemoglobin:** The mean hemoglobin distribution was similar in both the arms 12.2gms% vs. 13.1%, with all patients with hemoglobin equal to or above 10gms%.
- (h) **Absolute neutrophil count (at the beginning):** In the Chemoirradiation group the ANC was similar in both the arms, control vs. study was 4941.0 vs. 5409.5 and it was similar in Radiotherapy only group also 4411.0 vs. 3552.8. Overall the mean ANC was similar in the two arms 4676.0 vs. 4481.1.
- (i) **Primary disease:** The distribution of patients with regard to primary disease showed a number of patients with an oral cavity (25% vs. 10%) and larynx (30% vs. 25%) in control arm as compared with study arm. In the study arm, there were a number of patients with primary in the oropharynx (15% vs. 30%) and hypo pharynx (15% vs. 20%). The number of patients with Nasopharynx (10% vs. 10%) and unknown primary (5% vs. 5%), were equally distributed in both the arms. There was no statistically significant difference found between the two arms.

4.3 Treatment characteristics

In the control group, 16 patients had concurrent Chemoirradiation and 12 had Radiotherapy only. In the study group, 16 patients had Chemoirradiation and 12 patients had Radiotherapy only.

- (a) **Oral care protocol: (Table 2)** In the Chemoirradiation group the oral care protocol was better followed by patients in study arm 71% vs. 92% whereas in the Radiotherapy only group number of patients in control arm followed the oral care protocol strictly 66% vs. 57%. An overall number of patients in the study arm followed the oral care protocol better 70% Vs 80%.
- (b) **Chemotherapy schedule:** In the Chemoirradiation group, two schedules were followed depending on the primary disease. Three weekly concurrent chemotherapy was followed for nasopharyngeal malignancies and both arms had almost equal number of such patients 14% vs. 15%. Weekly concurrent chemotherapy was used for all other primary disease and both arms had an equal number of those 86% vs. 85%.

4.4 Outcome analysis

4.4.1 Objective Assessment

- (a) **Oral Mucositis occurrence:** Among the patients who underwent chemoirradiation grade 1 mucositis was more among patients in control arm 21.4% Vs. 7% ($p=0.09$), grade 2 mucositis occurred more in study arm 42.8% vs. 53% and grade 3 mucositis was almost similar in both arms 35.7% vs. 35%. Among the patients receiving Radiotherapy
- (b) only grade 1 mucositis was seen in more patients in control arm 16.6% vs. 0% ($p=0.082$), grade 2 mucositis occurred almost equally in both arms 66.6% Vs. 57.2% and grade 3 mucositis was more in study arm 16.6% vs. 42.8% ($p=0.17$). Overall grade 1 mucositis was seen more in control arm 20% vs. 5%, grade 2 was similar in both arms and grade 3 was marginally more in study arm 30% vs. 40%. Overall no statistically significant difference was found between the two arms.
- (c) **The occurrence of oral thrush and antifungal usage: (Table 1)** Incidence of oral thrush and antifungal usage was less in study arm of Chemoirradiation group 9% vs. 32% ($p=0.536$) and in the study arm of radiotherapy alone group also 6% vs. 28% ($p=0.523$). All patients with oral candidiasis in both arms were treated with oral fluconazole 200 mg stat and 100mg once daily for 5 days. There was a statistically significant difference found between the chemoirradiation, radiotherapy groups.
- (d) **Break in treatment due to mucositis:** Among the Chemoirradiation group the break in treatment was seen in more number of patients in study arm 35.7% vs. 53% ($p=0.352$) and in the Radiotherapy only patients also it was more in the study arm 0% vs. 42.8% ($p=0.042$) Overall number of patients in study arm had broken in treatment as compared to control arm 25% vs. 50% ($p=0.171$). The difference in the Chemoirradiation group was not significant statistically. The difference seen in the Radiotherapy group was statistically significant. Overall the difference was not significant statistically.
- (e) **A number of days of break in treatment:** In the Chemoirradiation group an average number of days of break in treatment were more in study arm as compared to control 9 days vs. 11 days ($p=0.637$) and in Radiotherapy the only group again the number of days were more in study arm 0 Vs. 4.5days ($p=0.12$). The difference between the two arms was not statistically significant.
- (f) **Overall treatment time:** Among the Chemoirradiation patients the average number of days of treatment was almost similar in both arms 56.5 days Vs. 57.08 days ($p=0.853$) whereas in the patients who had Radiotherapy alone the average number of days of treatment was more in the study arm as compared to control arm 46.2 days vs. 52.57 days ($p=0.463$). Overall the mean numbers of days were almost similar in both the arms 53.78 days vs. 55.42 days. The difference noted was not significant statistically.

4.4.2 Subjective assessment

- (a) **Mouth pain: (Table 2)** Among the patients undergoing Chemoirradiation the occurrence of moderate to severe mouth pain was found to be more in control arm 35.7% vs. 23% ($p=0.473$) whereas in patients receiving Radiotherapy only it was more among patients in the study arm as compared to control 0% vs. 28.5% ($p=0.173$). Overall the occurrence of moderate to severe mouth pain was similar in both the arms 25% vs. 25% ($p=0.114$). No statistically significant difference was noted.
- (b) **Swallowing difficulty:** Swallowing difficulty was a presenting complaint in 28.5% patients in control arm and 23% patients in study arm of Chemoirradiation group, and 16.6% of control and 42% of study arm of Radiotherapy group. No patients in

both the arms were on Ryle's tube feed while starting treatment. Hence the only progression in swallowing difficulty necessitating Ryle's tube feeding (grade 4) was looked for. In Chemoirradiation group progression of dysphagia to grade 4 was in more number of patients in control arm 28.5% vs. 15.3% (p= 0.352) and similarly, among the Radiotherapy only patients, a number of patients in control arm had grade 4 dysphagia 16.6% vs. 0% (p= 0.131). An overall number of patients in the control arm progressed to grade 4 dysphagia as compared to study arm 25% vs. 10% (p= 0.248).

- (c) **Dryness of mouth and throat:** Among the patients in Chemoirradiation group number of patients in the study arm had moderate to severe dryness of mouth and throat 50% vs. 69.2% (p=0.537). whereas in the Radiotherapy only group more patients in control arm had moderate to severe dryness as compared to patients in study arm 83.3% vs. 28.5% (p= 0.072) Overall more number of patients in control arm had moderate to severe dryness of mouth and throat 60% Vs 55% (p= 0.276). Overall there was no statistically significant difference found.
- (d) **Analgesic requirement:** Among the patients receiving Chemoirradiation more number of patients in control arm required analgesics for mucositis induced pain 92.8% vs. 53.8%(p= 0.093) whereas among the Radiotherapy only patients more number of patients in study arm required analgesics as compared to the other arm 66.6% vs. 85.7%(p= 0.472. Overall, the use of analgesics for mucositis induced pain was more in control arm as compared to study arm 85% vs. 65% (p=0.687). The differences noted were not significant statistically.
- (e) **Topical anaesthetic usage:** Viscous xylocaine was used alone or in combination with NSAID. Among the Chemoirradiation patients more patients in control arm required xylocaine 35.7% vs. 7.6% (p= 0.03) whereas in Radiotherapy only patients the requirement was almost equal in both arms 33.3% vs. 28% (p= 0.42). Overall the requirement of viscous xylocaine was found to be more in control arm 35% vs. 15% (p= 0.13). This decrease in requirement in study arm may be because xylocaine was an ingredient of study mouth wash which was used by the patient every day.

Table 1: Oral thrush and antifungal therapy

	Control	Study
CT+RT	5 (32%)	1 (9%)
RT	3 (28%)	1 (6%)
Total	8 (28%)	2 (7%)

Table 2: Moderate to severe mouth pain

	Control	Study
CT+RT	5 (35.7%)	3 (23%)
RT	0	2 (28.5%)
Total	5 (25%)	5 (25%)

5. DISCUSSION

Oral mucositis represents a major complication of radiotherapy and chemotherapy associated with significant morbidity, pain, odynophagia, dysgeusia, and subsequent dehydration and malnutrition reduce the quality of life of affected patients. The term oral mucositis emerged in the late 1980s to describe the radiotherapy and chemotherapy-induced inflammation of the oral mucosa, which represents a separate entity distinct from oral lesions with other pathogenic background summarized as stomatitis. The degree and duration of mucositis in patients treated with radiotherapy is related to the radiation source, cumulative dose, dose intensity, the volume of irradiated mucosa, smoking and alcohol consumption habits, and other predisposing factors such as xerostomia or infection.

El-Sayed S et al (1) conducted a pilot study evaluating the safety and microbiologic efficacy of and economically viable antimicrobial lozenge in patients with head and neck cancer receiving radiation therapy. This study demonstrated that the Bacitracin Clotrimazole Gentamycin lozenge is tolerable and microbiologically efficacious, achieving the elimination of Candida in all patients and reduction in gram-negative flora in most patients. A phase III study is underway to evaluate the clinical efficacy of this lozenge.

Sonis et al. did a meta-analyses of 58 trials of head and neck cancer (2206 patients). The risk of grade 3-4 oral mucositis was found to be 42% (40-44 95%CI). He also analysed 6 studies (309 patients) of chemo-irradiation with platinum. The risk of grade 3-4 oral mucositis was found to be 11% (8-14 95%CI)

Rubenstein et al. (10) (panel of 36 members who reviewed literature published between January 1966 and May 2002) suggested the use of oral care protocols that include patient education in an attempt to reduce the severity of mucositis from chemotherapy or radiotherapy (level of evidence, III; grade of recommendation, B).

Feber et al. (30) conducted a study on patients undergoing radical radiotherapy and 50% of the oral cavity and Oropharynx in the RT field. Normal saline (NS) and hydrogen peroxide (HP) mouthwashes along with oral care protocol were used. It was concluded that mouthwashes alone do not constitute effective management and should be part of an oral care protocol.

Leandro et al. (11) compared the effect of morphine mouthwash and magic mouthwash. In the magic mouthwash arm, 34% of patients used step 2 analgesics (NSAID + weak opioids), 25% of patients used step3 analgesics (NSAID + strong opioids). The occurrence of oral candidiasis was in 50% of patients in the magic mouthwash arm.

Fifty-six patients were accrued in the trial, 28 in the control arm and 28 in study arm. All patients completed the treatment protocol except 4 patients in the control group who discontinued treatment after 4 to 5 weeks. One patient developed herpes

labialis, one patient developed hypotension and tiredness, one patient developed severe odynophagia and put on ryles tube, and one patient discontinued for personal reasons. In each arm, patients were stratified into chemoradiation and radiotherapy groups. In control arm 16 in chemoradiation and 12 in the radiotherapy group. In study arm 16 patients in chemoradiation and 12 in the radiotherapy group.

Patients included in the study were in the age group of 23 to 70 years (mean 53.3). Thirty-six males and 4 females were in the study. More patients had stage 4 disease and the majority being squamous cell carcinoma. Twenty-seven percent of patients had a primary malignancy in the larynx.

The distribution of habits among control vs. study group was, alcoholics (25% vs. 15%), smokers (60% vs. 60%), tobacco chewers (65% vs. 35%). The pain was a presenting complaint in 60% of patients in the control arm and 65% of patients in study arm. Dysphagia was a presenting complaint in 25% of controls and 30% of study arm patients.

Mean hemoglobin level was 12.2gms% in control vs. 13.1gms% in study arm. Mean absolute neutrophil count was 4676 in control arm and 4481.15 in study arm. Oral cavity examination showed poor oral hygiene in 25% of controls and 15% of the study arm.

On evaluation grade 1 to 2 mucositis was seen in 64% vs. 61.5% (control vs. study) ($p=0.324$) of patients in chemoradiation group and 83% vs. 57.2% ($p=0.425$) of patients in radiotherapy group. Grade 3 mucositis was seen in 36% vs. 38.5% ($p=0.332$) of patients in chemoradiation group and 17% vs. 42.8% of patients in radiotherapy group ($p=0.135$). No patients developed grade 4 mucositis as treatment was stopped at grade 3 mucositis. No statistically significant difference was found between the two arms.

Subjective evaluation showed that moderate to severe mouth pain developed in 35.7% vs. 23% ($p=0.332$) in chemoradiation group and 0% vs. 28.5% ($p=0.142$) in radiotherapy group. Severe swallowing difficulty occurred in 25% vs. 10% ($p=0.248$) of patients. Moderate to severe dryness of mouth and throat was found in 60% vs. 55% ($p=0.276$) of patients. No statistically significant difference was found between the two arms.

Analgesic requirement was 92.8% vs. 53.8% in chemoradiation group and 66.6% vs. 85.7% in radiotherapy group ($p=0.193$). Viscous xylocaine alone or in combination with NSAIDs was used in 7 patients in control arm and 3 patients in study arm ($p=0.14$). Among the other symptoms while on treatment cough was found in 55% vs. 35% of patients. Nausea and vomiting was a predominant symptom in study arm 5% vs. 30% ($p=0.04$), probably chemo-induced. Antitussives were used in 20% vs. 15% of patients. Antiemetics were used in 10% vs. 20% of patients.

Break in treatment was seen in 35.7% vs. 53% of patients in chemoradiation group and 0% vs. 42.8% in the radiotherapy group. Overall the p -value was 0.171. The average number of breaks was one in both arms and the number of days of break ranged from 7 to 11 days in the control arm and 2 to 17 days in study arm. The overall treatment time was 53.78 vs. 55.42 days. No statistically significant difference was found between the two arms.

Incidence of oral thrush and antifungal usage was less in study arm of Chemoradiation group 9% vs. 32% ($p=0.536$) and in the study arm of radiotherapy alone group also 6% vs. 28% ($p=0.523$). All patients with oral candidiasis in both arms were treated with oral fluconazole 200 mg stat and 100mg once daily for 5 days. There was a statistically significant difference found between the chemoradiation, radiotherapy groups.

6. CONCLUSION

There was an additional benefit of adding clotrimazole lozenges to soda bicarbonate mouthwash in controlling radiation-induced oral mucositis in patients undergoing radiation or chemoradiation for head and neck malignancies. Oral care protocol should be followed for all patients.

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