



Role of Benzydamine mouthwash in radiation induced oral mucositis- Single blind randomized control study

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ABSTRACT

The aim of this paper is to determine the effect of Benzydamine in addition to normal saline mouthwash and compare it with normal saline mouthwash only, in reducing radiation/chemo-irradiation induced oral mucositis in patients with Head and Neck Malignancies. An open-label single-blind randomized controlled trial was conducted. Arm A - Radiotherapy/Chemo-irradiation who were randomized to receive Benzydamine mouth wash and normal saline mouth wash. Arm B - Radiotherapy/Chemo-irradiation who were randomized to receive normal saline mouthwash only. Forty patients were accrued in the trial, 20 in the control arm and 20 in study arm. All patients completed the treatment protocol except 4 patients in the control group who discontinued treatment after 4 to 5 weeks. A number of patients in control vs. study arm of Chemo irradiation group were 14 vs. 13 and in Radiotherapy group 6 vs. 7 patients. The occurrence of Grade 3 mucositis was less in the control arm 30% vs. 40% but 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 (16% vs. 28.5%) were more in study arm of Radiotherapy only group but the number of patients included was small (6 vs. 7). Nausea and vomiting were the predominant complaints in study arm probably induced by the study mouth wash. The occurrence of dryness of oral mucosa and throat was more in study arm of the chemo-irradiation group but less in radiotherapy only group. Overall the addition of Benzydamine mouth wash to normal saline mouthwash along with oral care protocol during treatment did not show significant benefit. But there seems to be some benefit with the use of study mouth wash in the chemo-irradiation group only. Since the sample size is small will need to do the study with larger numbers to document statistically significant benefit

Keywords— Benzydamine mouth wash, Normal saline, Oral mucositis, Radiotherapy, Chemo-irradiation

1. INTRODUCTION

Head and neck malignancies constitute about 5% of newly diagnosed cancers in the world and about 30-50% of all cancers diagnosed in India (1). About 90% of them are squamous cell carcinomas (3). These include malignancy of Oral cavity, Oropharynx, Hypopharynx, Nasopharynx and Larynx. The majority of head and neck malignancies are treated by external radiation therapy.

Radiation-induced oral mucositis is a common problem with patients undergoing radiation therapy or chemotherapy (30). Grade 3 to grade 4 oral mucositis occurs in 10% to 50% of patients on radiotherapy for head and neck malignancies.

Mucositis is not only painful but also can limit adequate nutritional intake and decrease the patient's willingness to continue treatment. Severe mucositis with extensive ulceration may necessitate hospitalization, parenteral nutrition, and use of narcotics. Mucositis diminishes the quality of life and may result in serious clinical complications. A healthy oral mucosa serves to clear microorganisms and provides a chemical barrier that limits the penetration of many compounds into the epithelium. A mucosal surface that is damaged increases the risk of secondary infection. Mucositis may result in the need to reduce the dosage of subsequent chemotherapy cycles or to delay radiotherapy, which ultimately may affect a patient's response to therapy.

Cancer chemotherapeutic drugs that produce direct stomatotoxicity include the alkylating agents, antimetabolites, natural products, and other synthetic agents. According to the meta-analysis by Sonis et al concurrent chemoradiation with cisplatin was found to produce grade 3 to 4 oral mucositis in 11% of patients and 5-Fluorouracil continuous infusion in 6% of patients with head and neck malignancies.

Mucositis is an inevitable side effect of irradiation. The severity of the mucositis depends on the type of ionizing radiation, the volume of irradiated tissue, the dose per day, and the cumulative dose. As the mucositis becomes more severe, pseudo membranes and ulcerations develop, a poor nutritional status further interferes with mucosal regeneration by decreasing cellular migration and renewal. The nonkeratinized mucosa is most affected. The most common sites include the labial, buccal, and soft palate mucosa, as well as the floor of the mouth and the ventral surface of the tongue. Normally, cells of the mouth undergo rapid renewal over a 7 to 14 days cycle. Direct stomatotoxicity usually is seen 5 to 7 days after the administration of radiotherapy or chemotherapy. In the nonmyelosuppressed patient, oral lesions heal within 2 to 3 weeks.

Clinically, mucositis presents with multiple complex symptoms. The condition begins with asymptomatic erythema and progresses through solitary, white, elevated desquamate patches that are slightly painful to contact pressure, to large, contiguous, pseudomembranous, acutely painful lesions with associated dysphagia and decreased oral intake. Histopathologically, edema of the rete pegs will be noted, along with vascular changes that demonstrate a thickening of the tunica intima and concomitant reduction in the size of the lumen and destruction of the elastic and muscle fibres of the vessel walls. The loss of basement membrane epithelial cells exposes the underlying connective tissue stroma with its associated innervations, which, as the mucosal lesions enlarge, contributes to increased pain levels.

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.

1.1 Treatment options

Many different treatments are used to prevent or treat oral mucositis. The various options can be broadly classified as follows.

- Mouth wash with mixed action like Benzylamine hydrochloride, Chamomile and corticosteroids.
- Immuno modulatory agents like GM-CSF and G-CSF.
- Topical anaesthetics like Dyclonine Hcl, viscous lignocaine with 1% Cocaine and a solution containing kaolin-pectin and diphenhydramine.
- Antiseptics like Chlorhexidine mouth wash, Povidone iodine gargle and hydrogen peroxide mouth rinses.
- Antibacterial, Antifungal and Antiviral agents like Nystatin, Clotrimazole alone or in combination with Polymyxin, Tobramycin, Acyclovir and lozenges containing Polymyxin E Tobramycin and Amphotericin B (PTA lozenges).
- Mucosal barrier and coating agents like Sucralfate, sodium alginate, kaolin-pectin, plastic wrap film, radiation guards and antacid.
- Cytoprotectants like Beta carotene, vitamin E, Oxpentifylline, Azelastine Hcl and Prostaglandins E1 and E2
- Mucosal cell stimulants like low energy laser treatment, Silver nitrate and Glutamine.
- Analgesics like Capsaicin candies.

It is very difficult for the clinician to choose from this bewildering array of treatment options. It appears many interventions have little evidence suggesting that they may be effective. Only the studies by Epstein et al using 0.15% Benzylamine oral rinse which showed a statistically significant delay in the use of analgesics and the study by Etiz et al using sucralfate mouthwash which showed an almost significant reduction in mouth pain and a significant reduction in grade 4 mucositis and topical anaesthetic use.

2. MATERIALS AND METHODS

An open-label single-blind randomized controlled trial was conducted which compared the effect of Benzylamine mouth wash and normal saline vs. normal saline only in reducing the severity of radiation /chemoradiation induced oral mucositis in patients with head and neck malignancies. The study was approved by the ethical committee as well.

The study group consisted of patients accrued from December 2018 to March 2019. Patients were randomized into group A and group B. They were simultaneously stratified and randomized such that both groups had an equal number of patients undergoing radiotherapy and chemoradiation.

Arm A consisted of patients on radiotherapy/chemoradiation for head and neck malignancy who were randomized to receive Benzylamine mouth wash and normal saline mouth wash.

Arm B consisted of patients on radiotherapy/chemoradiation who were randomized to receive normal saline mouthwash only.

2.1 Inclusion criteria

- Age greater than 18 years and less than or equal to 70 years.
- Histopathological proof of head and neck malignancy-Squamous cell or undifferentiated carcinoma.
- Malignancies of oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and secondary neck node with unknown primary.
- All stages except stage I larynx.
- Karnofsky performance status more than or equal to 60%.

- Haemoglobin more than or equal to 10grams% with or without transfusion.
- Patients who were for radical radiotherapy or chemoradiation and radiation field involved more than 50% of the oral mucosa.
- Parallel opposing lateral field for face and upper neck (field1and2) and direct anterior field for lower neck field (field3).
- 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.
- Chemotherapy using Cisplatin only as a single agent.
- Informed consent signed by the patient.

2.2 Exclusion criteria

- Postoperative patients.
- Patients who have already received some form of treatment for the same disease.
- Patients with double malignancies.
- 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 pretreatment evaluation, all patients were instructed about the oral care protocol. Patients receiving radiation therapy/chemoradiation for carcinomas of oral cavity, pharynx or larynx were included in the study.

2.3.1 Arm A: Patients were instructed to swish both Benzylamine mouthwash and normal saline mouthwash. 10ml of Benzylamine mouthwash and 10ml of normal saline mouthwash were used before each meal. 10ml of only normal saline mouthwash was used after each meal and before bedtime. Benzylamine mouthwash was swished for 3minutes, and normal saline mouthwash was swished for 5 minutes and spat out. Hence the Benzylamine mouthwash was used three times a day and normal saline mouthwash seven times a day. Mouthwashes were started from day 1 of RT and only normal saline mouthwash was continued after radiotherapy.

2.3.2 Arm B: Patients were instructed to swish normal saline mouthwash only. 10ml of normal saline mouthwash was used before and after each meal and before bedtime. Normal saline mouthwash was swished for 5minutes and spat out. It was used seven times a day. Mouthwash was started from day1 of radiotherapy and continued after radiotherapy. Benzylamine mouthwash BP 0.15% w/v 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 3weeks (nasopharynx).

2.6 Oral care protocol

- Twice a day brushing of teeth, gums and tongue done carefully with a soft toothbrush and fluoride toothpaste.
- Precautions regarding food to be taken during radiotherapy:
 - a) Allow hot food to cool before eating it.
 - b) Avoid spicy, acidic and peppery foods and irritants such as alcohol or tobacco.
 - c) Avoid acid containing fruit juices such as orange juice and lemonade.
 - d) Avoid coffee.
 - e) Take about 3 litres of water/fluid per day. Try straw for drinking fluids in case of difficulty in taking directly.
 - f) Eat bland food high in protein.
 - g) Eat soft, moist food such as cooked cereals, mashed potatoes and scrambled eggs.
- 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.

- **Mucositis:** Grade of mucositis was assessed using RTOG acute radiation morbidity criteria. Each subsite of the oral cavity was examined for mucosal reactions. If patients developed grade 3 mucositis then treatment was stopped till the mucositis heals.
- **Mouth pain:** Pain was graded as mild, moderate-severe or no pain.
- **Swallowing impact:** Swallowing difficulty was graded as nil, mild, moderate and severe. Severe dysphagia being a requirement for Ryle's tube for feeding.
- **Dryness:** Dryness of the throat and oral cavity was graded as nil, mild, moderate and severe.
- Oral candidiasis and the antifungal requirement were evaluated.

- The requirement of analgesics was noted.
- Break in treatment was noted.
- The occurrence of other symptoms and other drug consumption was also looked for.

2.8 Pre-treatment evaluation

- **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.
- **Hematological:** Total count, differential count, haemoglobin and platelet count were done.
- **Biochemical:** Serum creatinine and liver function test were done
- **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's' 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

Forty patients were accrued in the trial, 20 in the control arm and 20 in study arm. Thirty-six 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 Chemoirradiation and Radiotherapy groups. In control arm 14 had Chemoirradiation and 6 Radiotherapy only. In study arm 13 patients had Chemoirradiation and 7 Radiotherapy only. They were simultaneously stratified and randomized such that both groups had an equal number of patients undergoing Radiotherapy and Chemoirradiation.

4.2 Patient characteristics

- **Age:** The mean age of patients in Chemoirradiation 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.
- **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.
- **Habits:** The habit wise distribution was as follows, alcoholic 25% Vs 15%, smokers 65% Vs 60% and tobacco chewers 65% Vs 35%.
- **Performance status:** All patients in the study had a Karnofsky performance status of 90.
- **Dental caries:** Pretreatment dental caries was seen more in control arm patients as compared to study arm 25% Vs 5%.
- **Unhealthy gums:** Pretreatment checkup showed a number of patients in control arm with unhealthy gums as compared to study arm 25% Vs 15%.
- **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 %.
- **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.
- **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%). A 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, 14 patients had concurrent Chemoirradiation and 6 had Radiotherapy only. In the study group, 13 patients had Chemoirradiation and 7 patients had Radiotherapy only.

- **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%.
- **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 an 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

- **Oral Mucositis occurrence: (table 1)** Among the patients who underwent chemoradiation 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 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.
- **Oral mucositis occurrence - Week wise:** Among the patients receiving Chemoradiation grade 3 mucositis occurred earlier (week 2) in control arm 14% Vs 0% ($p=0.13$) and in radiotherapy only patients also the grade 3 mucositis occurred earlier in control arm (week 3) 16% Vs 0% ($p=0.164$). Among the chemoradiation patients by the end of week 6, grade 3 mucositis was more in control arm as compared to study arm 27% Vs 7.6% ($p=0.21$) whereas in Radiotherapy only patients by the end of week 6 there was a trend towards more patients in study group having grade 3 mucositis 0% Vs 28.5% ($p=0.093$). However, the differences noted were not significant statistically.
- **Oral mucositis occurrence – site wise:** Among the patients undergoing Chemoradiation site wise evaluation of grade 3 mucositis showed that soft palate was the commonest site of involvement 96% Vs 92% followed by tongue and buccal mucosa, in both the arms. Among the Radiotherapy only group also soft palate was the commonest site of occurrence of grade 3 mucositis followed by tongue and buccal mucosa in both the arms. Overall the soft palate was the commonest site for occurrence of mucositis in both the arms 90% vs 95%.
- **The occurrence of oral thrush and antifungal usage:** Incidence of oral thrush and antifungal usage was more in study arm of Chemoradiation group 42% Vs 53% ($p=0.536$) and in the study arm of radiotherapy alone group also 16% Vs 28.5% ($p=0.263$). All patients with oral candidiasis in both arms were treated with oral fluconazole 200 mg stat and 100mg once daily for 5 days. Overall the occurrence of oral thrush and antifungal usage was more in study arm as compared to control arm 35% Vs 45% ($p=0.687$). There was no statistically significant difference found between the chemoradiation, radiotherapy and combined groups.
- **Break in treatment due to mucositis:** Among the Chemoradiation 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 Chemoradiation group was not significant statistically. The difference seen in the Radiotherapy group was statistically significant. Overall the difference was not significant statistically.
- **Number of days of break in treatment:** In the Chemoradiation group 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 only group again the number of days were more in study arm 0 Vs 4.5 days ($p=0.12$). The difference between the two arms was not statistically significant.
- **Overall treatment time:** Among the Chemoradiation 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

- **Mouth pain:** Among the patients undergoing Chemoradiation 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.
- **Swallowing difficulty:** Swallowing difficulty was a presenting complaint in 28.5% patients in control arm and 23% patients in study arm of Chemoradiation 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 Chemoradiation 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, 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% ($p=0.248$).
- **Dryness of mouth and throat:** Among the patients in Chemoradiation 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.
- **Analgesic requirement:** Among the patients receiving Chemoradiation 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.
- **Type of oral analgesic:** In the control arm Chemoradiation group Rofecoxib was the commonest analgesic prescribed (49%) whereas in the study arm it was Tab Diclofenac 31%. But among patients receiving Radiotherapy alone Tab Diclofenac (33.3%) was more commonly prescribed in control arm and Tab Rofecoxib (42.8%) in study arm. Overall Tab Rofecoxib usage was more in control arm whereas Tab Diclofenac and Tab Rofecoxib were prescribed equally in study arm 35% Vs 30%.

- **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: Mucositis grade

Mucositis grade	Control			Study		
	I	II	III	I	II	III
CT +RT	3 (21.4%)	6 (42.8%)	5 (35.7%)	1 (7%)	7 (53%)	5 (35%)
RT	1 (16.6%)	4 (66.6%)	1 (16.6%)	0 (0%)	4 (57.2%)	3 (42.8%)
Total	4 (20%)	10 (50%)	6 (30%)	1 (5%)	11 (55%)	8 (40%)

Table 2: Oral care protocol

	Control	Study
CT+RT	10 (71%)	12 (92%)
RT	4 (66%)	4 (57%)
Total	14 (70%)	16 (80%)

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.

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 (309patients) 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 oral cavity and Oropharynx in the RT field. Normal Saline (NS) and Hydrogen Peroxide (HP) mouthwashes along with an 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.

In standard 200cGy daily fractioned radiotherapy programs, mucosal erythema occurs within the first week of treatment. Patchy or confluent pseudomembranous radiation-induced mucositis peaks during the fourth to the fifth week of therapy. Less severe mucositis is noted in programs with daily fractions lower than 200cGy.

Perch et al(7) showed that by using midline mucosa sparing blocks treatment breaks of more than 5 days was 16% in shield arm and 30% in no shield arm. To reduce mucosal injury, the panel of Rubenstein et al (9) recommends the use of midline radiation blocks and three-dimensional radiation treatment (level of evidence, II; grade of recommendation, B).

The movable no keratinized mucosa of the soft palate, cheeks and lips, the ventral surface of the tongue, and the floor of the mouth are most vulnerable to radiotherapy, whereas the gingiva, dorsal surface of tongue, or the hard palate are rarely affected – probably due to their slower rate of cellular turnover(13).

Leandro et al (11) compared the effect of morphine mouthwash and magic mouthwash. In the magic mouthwash arm, 34% of patients used step2 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.

Epstein et al's (13) study with oral rinse of 0.15% Benzylamine showed that 33% of patients in the benzylamine group didn't develop mucosal ulceration whereas only 18% in the placebo group. Benzylamine delayed the use of systemic analgesics compared to placebo (p<0.05). The panel of Rubenstein et al recommends Benzylamine for the prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate dose radiotherapy (level of evidence I; grade of recommendation).

Forty patients were accrued in the trial, 20 in the control arm and 20 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 14 in chemoradiation and 6 in the radiotherapy group. In study arm 13 patients in chemoradiation and 7 in the radiotherapy group.

Patients included in the study were in the age group of 23 to 70years (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 per cent 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%), and 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 to2 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.

Week-wise evaluation showed that by the end of week1 50% vs 40% ($p= 0.435$) of patients developed mucositis. By the end of week 3 grade 3 mucositis was seen in 14% vs 23% ($p= 0.257$) of patients in chemoradiation group and 16% vs 0% ($p= 0.164$) of patients in radiotherapy group. The peak incidence of grade 3 mucositis in chemoradiation group was seen in week 6 in control and week 3 in the study arm (27% and 23%). In the radiotherapy group peak incidence of grade 3 mucositis was seen in week3 in control and week 6 in study arm (16% and 28.5%). Hence the occurrence of grade 3 mucositis was earlier in chemoradiation group of study arm and radiotherapy group of the control arm. No statistical significance found. Site wise evaluation showed that soft palate was the most common site for mucositis in both arms (90% vs 95%). Lips and floor of mouth were found to be the least common site for mucositis in both 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($p= 0.193$).Tablet Diclofenac was the most commonly used analgesic. Viscous xylocaine alone or in combination with NSAIDS was used in 7 patients in control arm and 3 patients in study arm ($p=0.14$). The occurrence of oral thrush and antifungal usage was 35% vs 45% ($p= 0.687$). No statistically significant difference was found between the two arms.

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.

6. CONCLUSION

There was no additional benefit found by using the Benzylamine mouthwash in controlling radiation-induced oral mucositis in patients undergoing radiation or chemoradiation for head and neck malignancies.

- The incidence of grade 3 mucositis was marginally higher in the study arm.
- The mucositis also seems to occur earlier in the study arm.
- There was no major decrease in mouth pain, dysphagia and dryness of oral mucosa in study arm.
- The analgesic requirement appears to be less in chemoradiation group of study arm but no statistical significance was found.
- The incidence of oral thrush appears to be more in study arm with no statistical significance.
- A number of patients having a break in treatment appear to be more in study arm with no statistical significance.
- Nausea and vomiting were the predominant complaints in study arm probably induced by the study mouthwash.

It can be concluded by this small study that radiation and chemoradiation induced oral mucositis can be fairly prevented by using normal saline mouthwash in the required frequency and instructing the patient well about oral care protocol to be followed during treatment. In view of the small sample size study, mouthwash can't be called ineffective. It needs to be studied with larger sample size.

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