



Role of oral glutamine in reducing the severity of radiation induced oral mucositis - A prospective randomized study

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ABSTRACT

Aim and Objective: To determine the effect of oral Glutamine powder supplement in reducing radiation/chemoirradiation induced oral mucositis in patients with Head and Neck malignancies

Design and Methodology: An open-label single-blind randomized controlled trial was conducted. Arm A - Radiotherapy/Chemoirradiation who were randomized to receive oral Glutamine powder supplement in addition to the regular oral care protocol. Arm B - Radiotherapy/Chemoirradiation who were randomized to receive regular oral care protocol only without Glutamine supplement.

Results: Forty-eight patients were accrued in the trial, 24 in the control arm and 24 in study arm. All patients completed the treatment protocol except 4 patients in the control group who discontinued treatment after 4 to 5 weeks. The number of patients in the control Vs study arm of Chemoirradiation group were 16 Vs 15 and in Radiotherapy group 8 Vs 9 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 (week3). In the Chemoirradiation 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%vs15.3%) were less in the study arm and also tolerated more number of cycles of concurrent chemotherapy (76% Vs 14% p= 0.036). The number of patients having a break in treatment (0% Vs 42.8% -significant) and occurrence of oral thrush (16% Vs 28.5%) was 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 chemoirradiation group but less in radiotherapy only group.

Inference: Overall the addition of oral Glutamine powder supplement 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 chemoirradiation group only. Since the sample size is small will need to do the study with larger numbers to document statistically significant benefit

Keywords— Glutamine powder, Oral care protocol, Oral mucositis, Radiotherapy, and Chemoirradiation

1. INTRODUCTION

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 chemoirradiation with cisplatin was found to produce grade 3 to 4 oral mucositis in 11% of patients and 5Fluorouracil 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, pseudomembranes 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 desquamative 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 fibers 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.

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

Glutamine is the most abundant free amino acid in the body.[8] In several animal species, glutamine was shown to be the major respiratory fuel for the intestinal tract.[9,10] Moreover, reduction of plasma glutamine levels by administration of glutaminase caused edema and ulceration of the intestinal mucosa as well as patchy areas of necrosis.[11] Glutamine may help decrease mucous membrane injury induced by radiation by altering the inflammatory response. Glutathione, a byproduct of glutamine metabolism protects against oxidant injury.[12,13] Glutathione is an antagonist to prostaglandin E2 (PGE2) production, which is a strong inflammatory mediator. Klimberg et al. used a rat breast cancer model to show that glutamine-supplemented rats with mammary tumors had greater glutamine and glutathione concentrations, and decreased PGE2 production than rats that received no glutamine.[14] In another study, PGE2 levels from the tissues obtained by serial mucosal biopsies from dogs experiencing acute radiation effects increased with increased inflammation.[15]

In patients with cancer, marked glutamine depletion develops over time; cancer cachexia is marked by massive depletion of skeletal muscle glutamine. This can have a negative impact on the function of host tissues that are dependent upon adequate stores of glutamine for optimal functioning.[16,17] Furthermore, the extent of normal tissue damage from radiation or chemotherapy may be influenced by the presence of adequate tissue glutamine stores. Both of these facts suggest a possible therapeutic role for glutamine in the prevention of host normal tissue toxicity during cancer treatment.[18]

A recent pilot trial by Huang et al.[19] demonstrated that oral glutamine suspension may significantly reduce the duration and severity of objective oral mucositis during radiotherapy. It may also shorten the duration of \geq grade 3 mucositis. Similar observations were made by Dr. Silvermann in his review article on oral mucositis.[20] However, an adequately powered randomized clinical study required to establish these findings has not been carried out so far, to the best of our knowledge.

Oral administration of glutamine is a convenient way of providing nutrients to patients with the preserved oral intake. Therefore, we proceeded to perform this study where the utility of glutamine was tested in head neck cancer patients undergoing radiotherapy at our clinic.

2. MATERIALS AND METHODS

An open-label single-blind randomized controlled trial was conducted which compared the effect of oral Glutamine powder supplement in reducing radiation/chemo-irradiation 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 January 2015 to April 2015. 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 chemo-irradiation.

Arm A consisted of patients on radiotherapy/chemo-irradiation for head and neck malignancy who were randomized to receive either oral glutamine suspension daily 2h before radiation in the study arm (10 g in 1000 ml of water) along with oral care as per institute protocol. Arm B consisted of patients on radiotherapy/chemo-irradiation who were randomized to receive oral care only without glutamine supplement.

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) Hemoglobin more than or equal to 10grams% with or without transfusion.
- (g) Patients who were for radical radiotherapy or chemo-irradiation 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 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/chemo-irradiation for carcinomas of oral cavity, pharynx or larynx were included in the study.

Arm A: After obtaining informed consent, patients with head and neck cancer receiving definitive or adjuvant radiation therapy were randomized (1:1) to receive either oral glutamine suspension daily 2 hours before radiation; study arm (10 g in 1000 ml of water). Glutamine crystalline powder in sachets, each containing 10 g, 1 sachet dissolved in 1 litre of water was consumed daily within 2 hours before radiation. Patients were instructed to swish their mouths first with the glutamine solution and then swallow within 2 hours before radiation treatment 5 days/week on treatment days only. Patients who took up to 800 ml of glutamine solution on an average were also accepted. 10ml of normal saline mouthwash was used before and after each meal and before bedtime. Normal saline mouthwash was swished for 5 minutes and spat out. It was used seven times a day. Mouthwash was started from day 1 of radiotherapy and continued after radiotherapy along with oral care protocol.

Arm B: Patients were instructed to swish normal saline mouthwash and follow oral care protocol only. No glutamine was administered to these patients. 10ml of normal saline mouthwash was used before and after each meal and before bedtime. Normal saline mouthwash was swished for 5 minutes and spat out. It was used seven times a day. Mouthwash was started from day 1 of radiotherapy and continued after radiotherapy.

I. 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.

II. Chemotherapy details:

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

Oral care protocol:

1. Twice a day brushing of teeth, gums and tongue done carefully with a soft toothbrush and fluoride toothpaste.
2. 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.
3. 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.

III. 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 was 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.

IV. 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

Forty patients were accrued in the trial, 24 in the control arm and 24 in study arm. Forty-four 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.

Distribution of patients: In each arm patients were also stratified into Chemoirradiation and Radiotherapy groups. In control arm 16 had Chemoirradiation and 8 Radiotherapy only. In study arm 15 patients had Chemoirradiation and 9 Radiotherapy only. They were simultaneously stratified and randomized such that both groups had an equal number of patients undergoing Radiotherapy and Chemoirradiation.

4.1 PATIENT CHARACTERISTICS

- (a) **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.
- (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 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 number of patients with 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 hypopharynx (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.

4.2 TREATMENT CHARACTERISTICS

In the control group, 16 patients had concurrent Chemoirradiation and 8 had Radiotherapy only. In the study group, 15 patients had Chemoirradiation and 9 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 75% Vs 93% whereas in the Radiotherapy study group followed it better 50% vs 55%. An overall number of patients in the study arm followed the oral care protocol better 66% Vs 79%.

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%.

4.3 OUTCOME ANALYSIS

- (a) **Objective Assessment:** Oral Mucositis occurrence: (Table 1) Among the patients who underwent chemoirradiation grade 1 mucositis was more among patients in control arm 25% Vs 13% ($p= 0.09$), grade 2 mucositis occurred more in study arm 43.7% Vs 53% and grade 3 mucositis was slightly more in study arm 31% Vs 33%. Among the patients receiving Radiotherapy only grade 1 mucositis was seen in more patients in control arm 25% Vs 14% ($p= 0.082$), grade 2 mucositis occurred almost equally in both arms 62.5% Vs 71.4% and grade 3 mucositis was more in study arm 12% Vs 33.3% ($p= 0.17$). Overall grade 1 mucositis was seen more in control arm 25% Vs 12.5%, grade 2 was more in study arm 50% vs 54% and grade 3 was marginally more in study arm 25% Vs 33%. Overall no statistically significant difference was found between the two arms.
- (b) **Oral mucositis occurrence - Week wise:** Among the patients receiving Chemoirradiation 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 chemoirradiation 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.
- (c) **Oral mucositis occurrence – site-wise:** Among the patients undergoing Chemoirradiation 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%.
- (d) **The occurrence of oral thrush and antifungal usage:** Incidence of oral thrush and antifungal usage was more in study arm of Chemoirradiation 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 chemoirradiation, radiotherapy and combined groups.
- (e) **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 break 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.
- (f) **Number of days of break in treatment:** In the Chemoirradiation 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.
- (g) **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 SUBJECTIVE ASSESSMENT

- (a) **Mouth pain:** 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:** The 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 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.
- (d) **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.
- (e) **Type of oral analgesic:** In the control arm Chemoradiation group Tramadol 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 Tramadol (42.8%) in study arm. Overall Tab Tramadol usage was more in control arm whereas Tab Diclofenac and Tab Tramadol were prescribed equally in study arm 35% Vs 30%.
- (f) **Topical anaesthetic usage:** Viscous xylocaine was used alone or in combination with NSAID. Among the Chemoradiation 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: Subjective assessment

MUCOSITIS GRADE	CONTROL			STUDY		
	I	II	III	I	II	III
CT +RT	4 (25%)	7 (43.7%)	5 (31%)	2 (13%)	8 (53%)	5 (33.3%)
RT	2 (25%)	5 (62.5%)	1 (1.2%)	1 (14%)	5 (71.4%)	3 (33.3%)
TOTAL	6 (25%)	12 (50%)	6 (25%)	3 (12.5%)	13 (54%)	8 (33.3%)

Table 2: Subjective assessment

	CONTROL	STUDY
CT+RT	12 (75%)	14 (93%)
RT	4 (50%)	5 (55%)
TOTAL	16 (66%)	19 (79%)

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-analysis 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.

Glutamine has already proved to be efficacious against radiation and chemotherapy-induced intestinal injury[12,23] and stomatitis.[24] A recent trial of oral glutamine was conducted in patients of metastatic breast cancer treated with paclitaxel and melphalan as a conditioning regime for autologous stem cell transplantation. The decrease in duration and incidence of oral mucositis (grade \geq 2) was statistically significant ($P = 0.048$ and $P = 0.026$ respectively) with glutamine (Saforis) compared to the placebo arm.[24] A recent pilot trial by Huang et al.[19] and a study carried out by Silvermann[20] demonstrated that oral glutamine suspension may significantly reduce the duration and severity of oral mucositis during radiotherapy.

Forty-eight patients were accrued in the trial, 24 in the control arm and 24 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 chemoirradiation and radiotherapy groups. In control arm 16 in chemoirradiation and 8 in the radiotherapy group. In study arm 15 patients in chemoirradiation and 9 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 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 68.7% vs 66.6% (control vs study) ($p= 0.324$) of patients in chemoirradiation group and 87.5% vs 66.6% ($p= 0.425$) of patients in radiotherapy group. Grade 3 mucositis was seen in 31.2% vs 33.3% ($p= 0.332$) of patients in chemoirradiation group and 12.5% vs 33.3% 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 chemoirradiation group and 16% vs 0% ($p= 0.164$) of patients in radiotherapy group. The peak incidence of grade 3 mucositis in chemoirradiation 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 chemoirradiation 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 chemoirradiation 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 chemoirradiation 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 chemoirradiation 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 Oral Glutamine supplement in controlling radiation-induced oral mucositis in patients undergoing radiation or chemoirradiation for head and neck malignancies.

- (a) The incidence of grade 3 mucositis was marginally higher in the study arm.
- (b) The mucositis also seems to occur earlier in the study arm.
- (c) There was no major decrease in mouth pain, dysphagia and dryness of oral mucosa in study arm.

- (d) The analgesic requirement appears to be less in the chemoirradiation group of study arm but no statistical significance was found.
- (e) The incidence of oral thrush appears to be more in study arm with no statistical significance.
- (f) The number of patients having a break in treatment appears to be more in study arm with no statistical significance.
- (g) 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 chemoirradiation 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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