A prospective randomized controlled study to evaluate the role of oral glutamine in chemo-radiation induced oral mucositis among carcinoma of oropharynx and larynx patients

Authors

Dr Seema Mutha¹, Dr Arpit Jain^{2*}, Dr Taruni Bhattacharya³, Dr Anuj Gupta⁴

¹MD Resident, Radiation Oncology, Bhagwan Mahaveer Cancer Hospital & Research Center, Jaipur

²MS, DNB Surgical Oncology, Bhagwan Mahaveer Cancer Hospital & Research Center, Jaipur

³DNB Radiation Oncology Bhagwan Mahaveer Cancer Hospital & Research Center, Jaipur

⁴MD, DNB, Medical Oncology, Bhagwan Mahaveer Cancer Hospital & Research Center, Jaipur

*Corresponding Author

Dr Arpit jain, MS, DNB Surgical Oncology

Bhagwan Mahaveer Cancer Hospital, Jaipur-302017, India

Abstract

Background & Objective: Head and neck carcinoma forms 30% load of India's cancer burden. More than 90% of head and neck cancers are squamous cell carcinomas that arise from the mucosal surfaces of the oral cavity, oropharynx, and larynx. The Aim is to evaluate the role of oral glutamine for alleviation of chemo-radiation induced oral mucositis in patients of locally advanced carcinoma oropharynx and supraglottic larynx.

Methods: Randomised controlled and Prospective study

Results: Total 60 patients of locally advanced carcinoma oropharynx and supraglottis larynx were enrolled in the study. All patients were randomized and equally distributed in two groups study group (Glutamine group) and Control group. Mean age of the patients was 57 years (range 40-71 years). 54 patients (90%) were male and 6 patients were female (10%). 37 patients (61.67%) had carcinoma oropharynx while 23 patients (38.33%) had carcinoma supraglottis larynx. 56 patients (93.33%) completed the full course of chemo-radiotherapy treatment. After 1st week of chemo-radiotherapy, total 7 patients developed grade I oral mucositis. After 2nd week of chemo-radiotherapy total 6 patients developed grade II oral mucositis. At 4th week of the treatment, 6 patients (20.69%) in control arm developed grade III oral mucositis. At 5th week of the treatment 20 patients (71.43%) in control arm developed grade III oral mucositis. At 6th week 26 patients (93%) in control arm compared to 12 patients (42.83%) in glutamine arm developed grade III oral mucositis. At 7th week of chemo-radiotherapy treatment, 27 patients (96.43%) in control arm developed grade III oral mucositis compared to only 12 patients (42.83%) in Glutamine arm.

Conclusion: The present study showed that Oral Glutamine reduced oral mucositis among carcinoma of oropharynx and larynx patients

Keywords: Glutamine, oral mucositis, Oropharynx. Cancer.

Introduction

It is one of the most common cancers in developing countries like India¹. In India, it is the

most common cancer in males while in females it is 5th most common cancer. Head and neck carcinoma forms 30% load of India's cancer

burden. More than 90% of head and neck cancers are squamous cell carcinomas that arise from the mucosal surfaces of the oral cavity, oropharynx, and larynx^(3,4).

Cigarette-smoking and alcohol consumption are the main reasons for head neck cancer in the Western population, whereas the use of smokeless tobacco and areca nut is the most common cause in Southeast Asia. The various forms in which smokeless tobacco is used in developing countries include khaini, mava, paan (betel quid), zarda, snuff³.

Radiation therapy along with chemotherapy forms the main cornerstone and important part of the standard treatment for head and neck cancer. Common acute toxicities include mucositis, skin desquamation, depression and anxiety, cachexia, fatigue, nausea and vomiting⁴. When these toxicities are not properly managed they can lead to treatment delays, chemotherapy dose deviations, hospitalizations and poor quality of life. Increased severity of side effects including mucositis, dermatitis and hematological toxicities can have a negative impact on survival rates and quality of life, as well as decrease treatment efficacy secondary to delays in treatment⁴. Conventional radiotherapy fractionation schedules for head neck cancers caused severe grade III & IV mucositis in approximately 25% of Radiation Therapy Oncology Group (RTOG) studies (12,13), whereas accelerated regimens like concomitant boost or hyperfractionation increase the same to 50%⁵.

According to various available literature, incidence of oral mucositis ranges between 80 and 97% while grade 3 and 4 mucositis being 40–55% depending upon type of radiotherapy and concomitant use of chemotherapy⁶. Radiation and/or chemotherapy induce cellular damage causing death of the basal epithelial cells generating free radicals⁷. This up-regulates pro-inflammatory cytokines specially TNF- α causing inflammation and ulceration. Finally healing occurs by epithelial proliferation, as well as, cellular and tissue differentiation, restoring the

integrity of the epithelium. However, cell regeneration often cannot keep up with the rate of cell death, resulting in some or complete denudation of the mucosa⁸.

Few small studies have evaluated the role and efficacy of glutamine for the management of chemotherapy and radiotherapy induced toxicity. The present study assessed whether glutamine decreases the severity of chemo-radiotherapy induced mucositis in patients with carcinoma oropharynx and larynx. In this study we aim to evaluate the role and efficacy of oral glutamine for alleviation of chemo-radiation induced mucositis.

Aim

To evaluate the role of oral glutamine for alleviation of chemo-radiation induced oral mucositis in patients of locally advanced carcinoma oropharynx and supraglottic larynx.

Material and Methods

Study Site: Department of Radiation Oncology, Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, Rajasthan

Study Population: Total 60 patients of carcinoma oropharynx and supraglottic larynx with squamous cell carcinoma histology, suitable for Intensity Modulated Radiotherapy with concurrent cisplatin chemotherapy were included.

Study Type: Randomised controlled study

Study Design: Prospective study

Sample Size: Sample size was calculated at 80% study power and alpha error of 0.05 assuming 62.5% incidence of oral mucositis in treatment group and 98.7% in control group as per result obtained in study of Lucy Pattanayak et al (Journal of Global Oncology 2016.page no.1-6)(48).

23 Patients in each group was required as sample size, which was further enhanced and rounded off to 30 patients in each group (total 60 patients) as final sample size for present study expecting 20% drop out/lost to follow up/attrition.

Time Frame: August 2016 to April 2018

Inclusion Criteria

- Patients with carcinoma oropharynx (stage III-IV)
- Patients with carcinoma supraglottis (stage III-IV)
- Patients with age >18 years to <70 years suitable for IMRT with concurrent chemotherapy

Exclusion Criteria

- Patients with primary site carcinoma oral cavity and carcinoma nasopharynx
- Patients with history of previous radiotherapy to head and neck region
- Patients with abnormal LFT/RFT

Results

From August 2016 to April 2018, total 60 patients of locally advanced carcinoma oropharynx and supraglottis larynx were enrolled in the study. All patients were randomized and equally distributed

in two groups study group (Glutamine group) and Control group.

Mean age of the patients was 57 years (range 40-71 years). 54 patients (90%) were male and 6 patients were female (10%). 37 patients (61.67%) had carcinoma oropharynx while 23 patients (38.33%) had carcinoma supraglottis larynx. 56 patients (93.33%) completed the full course of chemo-radiotherapy treatment. 2 patients (1 patient from each group) died due to Ischemic Heart Disease (Myocardial Infarction) before completion of the chemo-radiotherapy treatment. 2 patients (1 patient from each group) did not complete the full radiotherapy treatment. These 2 patients defaulted after 20-25 fractions of radiotherapy treatment. Baseline patient characteristics (sex, age, primary tumor site) were similar between the both groups (Table 1, 2) (Figure 1).

Table 1 Age characteristics of patients between both groups

Age (Years)	Control Group		Study Group		Total	
	No.	%	No.	%	No.	%
40-50	9	30.00	8	26.67	17	28.33
51-60	14	46.67	15	50.00	29	48.33
>60	7	23.33	7	23.33	14	23.33
Total	30	100.00	30	100.00	60	100.00

Chi-square = 0.093 with 2 degrees of freedom; P = 0.954

Table 2 Gender characteristics between both groups

Gender	Control Group		Study Group		Total	
	No.	%	No.	%	No.	%
Male	27	90.00	27	90.00	54	90.00
Female	3	10.00	3	10.00	6	10.00
Total	30	100.00	30	100.00	60	100.00

Fisher Exact Test P = 1.000

Figure 1 Primary tumor site characteristics between both groups

Oral Mucositis

There was significant difference in the time to onset and severity of oral mucositis in control arm versus glutamine arm. All grades of oral mucositis appeared early in control arm compared to glutamine arm (Table 4-10).

After 1st week of chemo-radiotherapy, total 7 patients developed grade I oral mucositis. All of these seven patients were from control arm. After 2nd week of chemo-radiotherapy total 6 patients developed grade II oral mucositis. All of these 6 patients (20%) were from control arm. At 4th week of the treatment, 6 patients (20.69%) in control

arm developed grade III oral mucositis compared to only 1 patient (3.33%) in glutamine arm. At 5th week of the treatment 20 patients (71.43%) in control arm developed grade III oral mucositis compared to only 5 patient (17.24%) in glutamine arm. At 6th week 26 patients (93%) in control arm compared to 12 patients (42.83%) in glutamine arm developed grade III oral mucositis. At 7th week of chemo-radiotherapy treatment, 27 patients (96.43%) in control arm developed grade III oral mucositis compared to only 12 patients (42.83%) in Glutamine arm.

Table 3. Severity of oral mucositis at Week 1

Oral Mucositis at Week 1	Control Group		Study Group		Total	
	No.	%	No.	%	No.	%
Grade 0	23	76.67	30	100.00	53	88.33
Grade 1	7	23.33	0	0.00	7	11.67
Total	30	100.00	30	100.00	60	100.00

Table 4. Severity of oral mucositis at Week 2

Oral Mucositis at Week 2	Control Group		Study Group		Total	
	No.	%	No.	%	No.	%
Grade 0	1	3.33	23	76.67	24	40.00
Grade 1	23	76.67	7	23.33	30	50.00
Grade 2	6	20.00	0	0.00	6	10.00
Total	30	100.00	30	100.00	60	100.00

Table 5. Severity of oral mucositis at Week 3

Oral Mucositis at Week 3	Control Group		Study Group		Total	
	No.	%	No.	%	No.	%
Grade 0	1	3.33	6	20.00	7	11.67
Grade 1	3	10.00	21	70.00	24	40.00
Grade 2	24	80.00	3	10.00	27	45.00
Grade 3	2	6.67	0	0.00	2	3.33
Total	30	100.00	30	100.00	60	100.00

Table 6. Severity of oral mucositis at Week 4

Oral Mucositis at Week 4	Control Group		Study Group		Total	
	No.	%	No.	%	No.	%
Grade 1	0	0.00	22	73.33	22	37.29
Grade 2	23	79.31	7	23.33	30	50.85
Grade 3	6	20.69	1	3.33	7	11.86
Total	29	100.00	30	100.00	59	100.00

Table 7 Severity of oral mucositis at Week 5

Oral Mucositis at Week 5	Control Group		Study Group		Total	
	No.	%	No.	%	No.	%
Grade 1	0	0.00	7	24.14	7	12.28
Grade 2	8	28.57	17	58.62	25	43.86
Grade 3	20	71.43	5	17.24	25	43.86
Total	28	100.00	29	100.00	57	100.00

Table 8. Severity of oral mucositis at Week 6

Oral Mucositis at Week 6	Control Group		Study Group		Total	
	No.	%	No.	%	No.	%
Grade 2	2	7.14	16	57.14	18	32.14
Grade 3	26	92.86	12	42.86	38	67.86
Total	28	100.00	28	100.00	56	100.00

Table 9 Severity of oral mucositis at Week 7

Oral Mucositis at Week 7	Control Group		Study Group		Total	
	No.	%	No.	%	No.	%
Grade 2	1	3.57	16	57.14	17	30.36
Grade 3	27	96.43	12	42.86	39	69.64
Total	28	100.00	28	100.00	56	100.00

Discussion

The present study calculated mean age of the patients was 57 years (range 40-71 years). 54 patients (90%) were male and 6 patients were female (10%). 37 patients (61.67%) had carcinoma oropharynx while 23 patients (38.33%) had carcinoma supraglottis larynx. 56 patients (93.33%) completed the full course of chemo-radiotherapy treatment. 2 patients (1 patient from each group) died due to Ischemic Heart Disease

(Myocardial Infarction) before completion of the chemo-radiotherapy treatment.

Oral mucositis is a major concern during chemoradiotherapy of head neck cancer. Mucositis causes pain, dysphagia, poor nutrition, poor treatment compliance and decreased quality of life. Incidence rates of mucositis as high as 80 to 97% have been reported (18-21). In this study also, grade III oral mucositis was reported in 62% and 63% patients respectively. Mucositis, also known as mucosal barrier injury, is a biologically

complex process involving several phases⁹. Initially, mucosal injury is induced by oxidative stress and reactive oxygen species (ROS) generated by radiation and chemotherapy. The aim of this randomized trial was to determine whether oral glutamine decreased the severity of chemo-radiotherapy induced acute toxicities in carcinoma oropharynx and supraglottis patients. Cerchiatti et al¹⁰, in a double blinded, placebo controlled trial, compared 14 patients who received intravenous L-alanyl-L-glutamine during chemo-radiotherapy of head and neck cancer versus 15 patients in placebo group. The number of patients with severe objective mucositis (OMS >1.49) was higher in the placebo group compared with the L-alanyl-L-glutamine group (67% vs. 14%, $p = 0.007$). (110)

Lucy Pattanayak et al¹¹ in a randomized controlled trial of 162 patients with locally advanced head and neck cancer, treated with concomitant chemoradiation, found significant difference in the incidence, severity and onset time of mucositis in favor of glutamine arm compared to control arm.

Conclusion

The present study showed that Oral Glutamine reduced oral mucositis among carcinoma of oropharynx and larynx patients

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