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Assessing Role of Oral Glutamine Supplementation in Radiation Induced Oral Mucositis in Head and Neck Cancers.

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ABSTRACT

Background: Radiotherapy with or without concurrent chemotherapy forms the mainstay of treatment of head and neck cancers. Oral mucositis is one of the most common complications of Chemo Radio-Therapy(CRT) which outweighs the systemic complaints both in terms of severity and difficulty in management. The aim of our study was to assess the role of oral glutamine supplementation in prevention of oral mucositis in patients receiving CRT to the head and neck. **Methods**: This was a Prospective Randomized study performed between April 2017 to November 2017.Total 60 patients (30 in each arm) were enrolled. Patients in ARM A were advised to take Glutamine crystalline powder dissolved in water to be consumed daily within 1 hour before radiation and were again asked to repeat the same dose 7 to 8 hours post radiation. Glutamine Treatment was 5 days/week on Radio-therapy days only. Patients in ARM B were given Placebo twice a day in same fashion as ARM A.Weekly Cisplatin was given in both arms. **Results**: Average no of days for onset of mucositis in glutamine arm was 17 days vs 32 days in control arm. 26.67% of patients in the glutamine arm developed mucositis in the 5th to 6th week, whereas 60% patients in the control arm developed mucositis as early as the 3rd week. 13% of the patients in the glutamine arm developed G3 mucositis whereas 23.3% of patients in the control arm developed G3 mucositis. 46.6% percent of patients in the glutamine arm received complete six cycles of chemotherapy, whereas only 13.33% of the patients in the control arm could complete six cycles of chemotherapy($p<0.001$) 93.3% of patients in the glutamine arm completed treatment within the stipulated period of 7 weeks, whereas only 33.3% patients in the control arm completed treatment within 7 weeks.($p<0.05$). **Conclusion**: Glutamine significantly decreases the onset as well as the severity of mucositis in patients receiving CRT to the head and neck thus translating into lesser treatment gaps and improvement in patient quality of life.

Keywords: Chemo Radio-Therapy, Head and Neck Cancer, Mucositis, Glutamine.

INTRODUCTION

Head and neck cancers are the third most common cancers worldwide, accounting for more than 550,000 cases annually.[1] Squamous cell carcinoma of the head and neck is one of the most frequent cancer seen in India, constituting up to 25% of the overall cancer burden. Radiotherapy with or without concurrent chemotherapy forms the mainstay of treatment of head and neck cancers. Those patients who receive Chemo radiotherapy (CRT) have improved local control and survival,[2] however the drawbacks are the local toxicities such as mucositis, loss of taste, xerostomia, oral thrush, dysphagia, and osteoradionecrosis which clearly outweigh the systemic complaints both in terms of severity and difficulty in management.[3]

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Oral mucositis is the most frequently occurring, painful and dose-limiting side-effect of radiotherapy in the head and neck.[4] Conventional fractionation schedules caused grade 3 and grade 4 mucositis in approximately 25% of the Radiation Therapy Oncology Group (RTOG) studies,[5,6] whereas, accelerated regimes like concomitant boost or hyperfractionation increased the same to 50%.[6] Addition of concomitant chemotherapy during the radiotherapy further aggravates these lesions.[3]

Oral mucositis manifests as progressive thinning of the oral mucosa to form erythematous patches and finally leads to ulceration with severe pain and difficulty in swallowing.[7] which can lead to treatment delays and adversely affect treatment outcomes,[8,9] To date, several efforts have been made for the prevention and treatment of severe mucositis, such as oral care, topical anesthetic use, antimicrobial agent use and oral rinsing; however, no consensus on standard therapy has been established,[10-12] Glutamine is a conditionally

essential amino acid, this means that is usually not essential, except in times of illness and stress.

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,[13,14] Glutathione is an antagonist to prostaglandin E2 (PGE2) production, which is a strong inflammatory mediator.

In patients with cancer, marked glutamine depletion develops over time and the extent of normal tissue damage from radiation or chemotherapy may be influenced by the presence of adequate tissue glutamine stores.[15,16] Both of these facts suggest a possible therapeutic role for glutamine in the prevention of host normal tissue toxicity during cancer treatment (shorten or remove)

Oral supplementation of glutamine is a convenient way of providing nutrients to patients with preserved oral intake. The present study assesses the role of oral glutamine supplementation in prevention of oral mucositis in patients of head and neck cancer undergoing chemoradiotherapy.

MATERIAL AND METHODS

This Prospective study was performed at the Department of Radiation Oncology, GMCH, Nagpur, India between April 2017 to November 2017. We compared the influence of oral glutamine on radiation induced mucositis in head and neck cancer patients. Total 60 patients (30 in each arm) who had histopathologically proven squamous cell carcinoma of the head and neck, receiving either definitive or adjuvant radiation therapy were enrolled for the study. Institutional ethics committee approval was taken, and informed consent was obtained from all the patients.

Consecutive patients were randomly assigned one after the other into either treatment arm A or arm B using a block randomization protocol.

Patients in ARM A were advised to take Glutamine crystalline powder in sachets, each containing 10 g, 1 sachet dissolved in 2 glasses of water to be consumed daily within 1 hour before radiation and were again asked to repeat the same dose 7 to 8 hours post radiation. Patients were instructed to swish their mouths first with the glutamine solution and then swallow it. Glutamine Treatment was 5 days/week on Radio-therapy days only. Patients in ARM B were given Placebo twice a day in same fashion as ARM A.

All patients had complete dental and oral examination before treatment. A dose 1.8 to 2 Gray per fraction daily, 5 fractions a week, to a total dose of upto 66 to 70 Gy was given. All patients were evaluated every week on Mondays for the onset of mucositis; severity of mucositis; appearance of adverse events like dysphagia, nausea, edema, cough, and pain; use of analgesics to alleviate pain; and insertion of a nasogastric tube to maintain nutrition if they had severe swallowing difficulty. Adverse events was graded as per CTCAE Version 4.0 All patients in Glutamine arm completed chemoradiation. There was one drop out in control arm. Treatment delays did occur in patients who developed mucositis since Radiation was stopped when the patients developed grade 3 or grade 4 mucositis. When patients were unable to consume glutamine or placebo orally due to severe mucositis, we dissolved the agent in water and administered it via a feeding tube.

Concurrent Cisplatin, if indicated, was given in patients with normal kidney function, at the dose of 40mg/m2 iv weekly on every Monday upto a maximal dose of 300mg/m^2.

Inclusion criteria

- Histopathologically proven squamous cell carcinoma of the oral cavity
- No distant metastases
- Age 20 to 70 years
- Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0,1 or 2
- Normal hematologic and biochemical parameters
- Willingness to fulfill the study requirements and give consent

Exclusion criteria were the following

- Previous chemotherapy or radiotherapy in head and neck region
- Uncontrolled systemic or widely disseminated disease
- Uncontrolled comorbid conditions like diabetes,hypertension,chronic kidney disease.
- Presence of a synchronous double primary malignancy

RESULTS

A total of 60 patients with squamous cell carcinoma of the head and neck were treated with radical chemoradiation and evaluated for the study. Their baseline profile including demographic and clinicopathologic parameters and ECOG (Eastern Cooperative Oncology Group) Performance Status are shown in Table 1.

Table 2 shows the number of chemotherapy cycles received and the duration of Radio-Therapy treatment in each arm. 46.6% percent of patients in the glutamine arm could complete six cycles of injection cisplatin, whereas only 13.33% of the patients in the control arm could complete six cycles of cisplatin.

93.3% of patients in the glutamine arm completed treatment within the stipulated period of 7 weeks, whereas only 33.3% patients in the control arm completed treatment within 7 weeks. 20% of patients in the control arm continued treatment upto 9 weeks.

The onset and development of mucositis after various weeks of radiation is shown in Table 3. Average no of days for onset of mucositis in glutamine arm was 17 days vs 32 days in control arm.

	Glutamine Arm (n=30)	Control Arm (n=30)
Male/Female	19/11	16/14
Average Age (Years)	47 ± 8.5	52 ± 10.5
Primary tumor location		
CA Buccal Mucosa	14 (46.67 %)	14 (46.67 %)
CA Gingivobuccal Sulcus	5 (16.67 %)	4 (13.33 %)
CA Tongue	11 (36.67 %)	12 (40.00 %)
Stage		
Stage 2	3 (10 %)	2 (7 %)
Stage 3	9 (30 %)	12 (40 %)
Stage 4A	9 (30 %)	9 (30 %)
Stage 4B	9 (30 %)	7 (23 %)
ECOG Performance Status		
0	13 (43.3)	11 (36.67)
1	15 (50.0)	11 (36.67)
2	2 (6.7)	8 (26.67)

	No. (%)			
	Glutamine Arm	Control Arm		
Total Cycles of chemotherapy /Duration of RT	(n=30)	(n=30)	p-value	
No of Chemo cycles				
3	0	1 (3.33)	< 0.001	P < 0.001
4	4 (13.33)	14 (46.67)		
5	12 (40)	11 (36.67)		
6	14 (46.67)	4 (13.33)		
Duration of Radiotherapy (in weeks)				
7	28 (93.33)	10 (33.33)	< 0.05	P = 0.0000028
8	1 (3.33)	14 (46.67)		
9	1 (3.33)	6 (20.00)		

	No. (%)	
	Glutamine Arm	Control Arm
Mucositis	(n=30)	(n=30)
Onset week		
0-1	0	2 (6.67)
1-2	0	6 (20.0)
2-3	2 (6.67)	18 (60.0)
3-4	4 (13.33)	4 (13.33)
4-5	16 (53.33)	0
5-6	8 (26.67)	0
>6	-	-
Average no of days for onset of Mucositis	32.86 ± 4.61	17.06 ± 3.47

53.33% of patients in the glutamine arm developed mucositis between 4th to 5th week, whereas 60% of patients in the control arm developed mucositis in the second to third week. 26.67% of patients in the glutaminearm developed mucositis in the 5th to 6th week, whereas 60% patients in the control arm developed mucositis as early as the 3rd week.

13% of the patients in the glutamine arm developed G3 mucositis whereas 23.3% of patients in the control arm developed G3 mucositis.

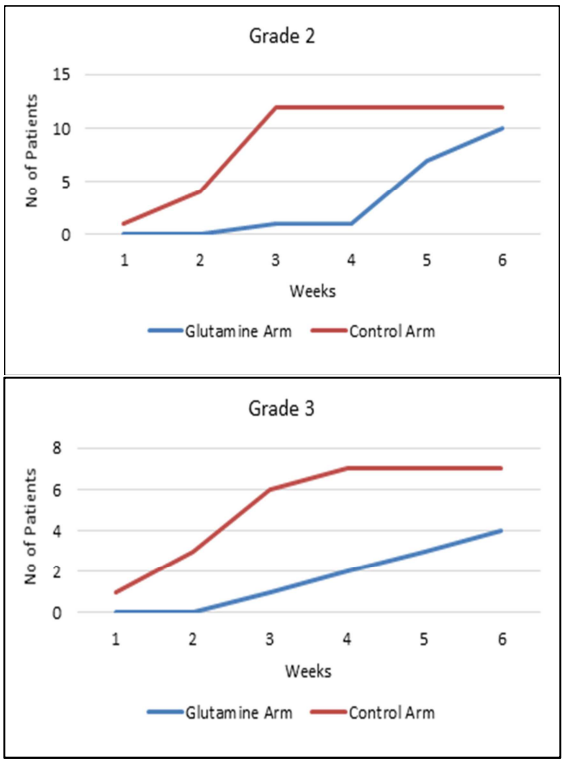

Figure 1: demonstrates the cumulative incidence rate of G2 and G3 mucositis in both the arms.

43.3 %of patients in the glutamine arm vs 66.67% of patients in the control arm required WHO step 2 and higher pain medications. However, this difference was not statistically significant.

	No. (%)		p-value
	Glutamine Arm (n=30)	Control Arm (n=30)	
WHO Step-Ladder pain score			
0	11 (36.67)	6 (20.0)	0.078
1	9 (30.0)	4 (13.3)	
2	6 (20.0)	11 (36.67)	
3	4 (13.3)	9 (30.0)	

30% patients in the control arm Vs 20% patients in the control arm required Ryles tube feeding during RT, this difference was non significant.

	No. (%)		p-value
	Glutamine Arm (n=30)	Control Arm (n=30)	
RT feeding			
Yes	6 (20)	9 (30)	0.371
No	24 (80)	21 (70)	

DISCUSSION

Radiotherapy plays an important role in the treatment of Head and Neck Cancers (HNC), and concurrent chemotherapy is indicated for locally advanced, surgical margins positive and cases with extra capsular extension on post operative histopathology. Oral common toxicity of chemoradiation in head and neck cancers.

Several guidelines including those of the National Comprehensive Cancer Network recommend basic oral care as a standard practice to prevent infections and alleviate mucositis. Although basic oral care maintains mucosal health, little evidence suggests that it can reduce the onset and severity of mucositis.[19]

The present study demonstrated that glutamine significantly decreased the severity of CRT-induced mucositis in patients with HNC. Glutamine has important and unique metabolic properties. Free and abundant glutamine in the circulation as well as in intracellular pools is essential for DNA synthesis, cell division and cell growth, all of which are necessary for wound healing and tissue repair It also enhances the immune system and is an important fuel for both macrophages and lymphocytes.[20] Furthermore, glutamine has antioxidant properties as a glutathione precursor. Leitao et al showed that glutamine or alanyl glutamine accelerated mucosal remodeling from 5-fluorouracil-induced OM by increasing glutathione stores in hamster mucosa.[21] Nose et al demonstrated that bolus enteral glutamine prevented cisplatin-induced intestinal mucosal injury in rats, possibly resulting in increased intracellular glutathione.[22] Several clinical studies have shown the protective effects of glutamine on the mucosal epithelium. Topkan et al reported that oral glutamine decreased the incidence and duration of acute radiation-induced esophagitis in non-small cell lung cancer patients treated with radiotherapy.[23]

In another study conducted by Savarese et al,[24] glutamine was combined with an advanced drug delivery system involving a swish-and-swallow technique. The drug protected the mucosa from damage caused by chemotherapy or radiotherapy.

CONCLUSION

In conclusion, the present study demonstrated that glutamine significantly decreases the time to onset and severity of CRT-induced mucositis in HNC cancer patients. Glutamine supplementation during radiotherapy treatment leads to decreased incidence of oral mucositis, which translates, into lesser treatment gaps and improvement in patient quality of life.

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