Effectiveness of prophylactic agents in prevention of oral mucositis in patients with head and neck cancer receiving radiotherapy

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ABSTRACT

Background: Oral mucositis is regarded as one of the major complications of radiation therapy especially in patients with head and neck cancer. The aim of this study was to evaluate the efficacy of glutamine in preventing or minimizing the development of mucositis of the oral cavity.

Subjects and methods: Forty-six participants were randomly selected amongst those who were planned to receive radiation therapy for head and neck region cancers. They were randomly divided into two groups of 23 subjects, one group received glutamine and the second group received a placebo.

Results: Glutamine had a statistically significant effect in reducing the occurrence and/or severity of oral mucositis in the treated patients compared to patients in the control group. Gender and age had no effect in the development or severity of oral mucositis in the studied patients.

Conclusions: It can be concluded that glutamine can be used effectively to prevent or minimize oral mucositis amongst cancer patients who receive radiation therapy.

Key wards: Oral mucositis, head and neck cancer, radiation therapy, glutamine. (J Bagh Coll Dentistry 2013; 25(4):56-59).

INTRODUCTION

Oral mucositis refers to lesions that characterize by sore erythematous and ulcerative changes of the mouth which are regarded as common complications in patients undergoing cancer therapy. They are painful and negatively influence the nutrition and quality of life, and sometimes can contribute to local and systemic infections.[1] Radiation-induced oral mucositis have been observed and studied since a long time.[2] It is often the dose limiting factor that interferes greatly with the intensification of anticancer therapy.[3,4]

Patients with head and neck cancer usually receive approximately 200 cGy daily dose of radiation, five days per week, for five to seven continuous weeks.[5-8] Almost all such patients will develop some degree of oral mucositis within the first three weeks of radiotherapy; it peaks at week five and can persist for weeks following the end of the radiation therapy.[9,10] The development of oral mucositis depends on a number of factors such as the type and dose of ionizing radiation, angulation of the radiation beam, location of the tumor, volume of irradiated tissue, dose per fraction, cumulative dose and, also importantly, the degree of oral hygiene.[11]

Pathologically, radiation therapy is an effective activator of several injury-producing pathways such as nuclear factor-κB (NF-κB) and NRF-2 that lead to the upregulation of genes that modulate the damage response.

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Macrophages produce pro-inflammatory cytokines that causes further tissue injury.[12] In addition, direct and indirect damages to epithelial stem cells result in a loss of renewal capacity. As a result, the epithelium begins to thin and patients start to experience the symptoms of radiation-induced mucositis.[13]

Clinically, mucositis is characterized by painful mouth sores, sloughing of the epithelium, crusting of the lips and ulcerations at various parts of the oral mucosa.[14] It often causes severe pain and increases the risk for the development of systemic infection due to bacterial, fungal, or viral infections in the mouth.[15]

Glutamine is a neutral amino acid that acts as a substrate for nucleotide synthesis in most dividing cells.[16] It is a major energy source for mucosal epithelial cells and stimulates mucosal growth and repair. A number of studies have shown its effectiveness in the prevention and treatment of oral mucositis due to radiation therapy.[17-20]

The aim of this study was to evaluate the efficacy of glutamine preventing the development or minimizing the severity of oral mucositis in patients with head and neck cancer receiving radiation therapy. Additionally to evaluate whether factors such as gender and age have any impact on the protective effect of glutamine.

PATIENTS AND METHODS

The study aimed at comparing the efficacy of glutamine on preventing or minimizing radiation-induced oral mucositis. It was conducted over a period of six months, from April through to

September 2012. During this period, 60patients were enrolled in the study amongst the patients who were attending the Department of Radiation Therapy at Rizgary Teaching Hospital in Erbil City for the purpose of receiving therapeutic radiation for head and neck region cancers. The ages of the patients ranged from 20 to 70 years, who classified to young (aged 45 or younger) and older (aged more than 45 years).

The participants were randomly divided into two groups as follows: the first group was the control group who received a placebo (distilled water 50 cc), and the second group was regarded as intervention group who received glutamine (10 grams of glutamine powder, dissolved in water (50 cc), taken three times per day). From the 60 patients, who were enrolled initially in the study, only 46 patients (23 in the control and 23 in the treatment arm) were continued until the end of the study.

The treatment protocol was started on the first day of radiation therapyand continued regularly through to the end of the course, during which the subjects were evaluated at intervals of every week starting from the beginning of the radiation therapy course thought to the end of the course. The patients received conventionally fractionated radiotherapy as an average of 2.0 Gy/day, 5 days per week to the total dose of 50 Gy by 5 weeks (end of the radiation therapy course).

The oral examination was performed blindly by two specialist dentists, and the mean of their readings were taken for the final analysis. Severity of oral mucositis was assessed using WHO grading criteria as illustrated in table (1).

Table 1. Criteria for the severity of oral mucositis according to the WHO grading (Mucositis of grades 2-4 was regarded as "moderate to severe")

Source	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO	No Changes	Soreness with erythema	Erythema, ulcers, can eat solids	Ulcers, liquid diet only	Alimentation not possible

The data entry and statistical analysis was done using SPSS version 18. The mean difference, standard errors of mean difference and significance was calculated using Independent-Samples T-Test. A p value of less than 0.05 was regarded as significant.

RESULTS

Forty-six patients with various types of head-and-neck cancers, who were on some sort of radiation therapy, were continued until the end of the study upon which the final data analysis was performed. Table (2) showed that glutamine, which was used as intervention, had a statistically significant effect in reducing the occurrence and/or severity of oral mucositis in the treated patients by week 4 and 5 compared to patients in the control group (who received a placebo). The mean degree of mucositis in the control arm was 1.65, meanwhile, this mean of mucositis decreased significantly in the patients in the intervention are, who received glutamine, to 0.87 with a p value of 0.001. As it is illustrated in Figure (1), the protective effect of glutamine started to appear in the very first weeks of commencing the radiation therapy, and became more evident after the 3rd week of treatment by glutamine.

Table 2. Distribution of mean levels of oral mucositis in control group andintervention (glutamine) group, and mean difference between the groups (wk5)

Treatment		No.	Mean	S.E.	Mean Difference	S.E.	95% Confidence Interval of Difference	p value
Mucositis	**Control**	23	1.65	0.18	0.78	0.23	0.33 – 1.24	0.001
	Glutamine	23	0.87	0.13				

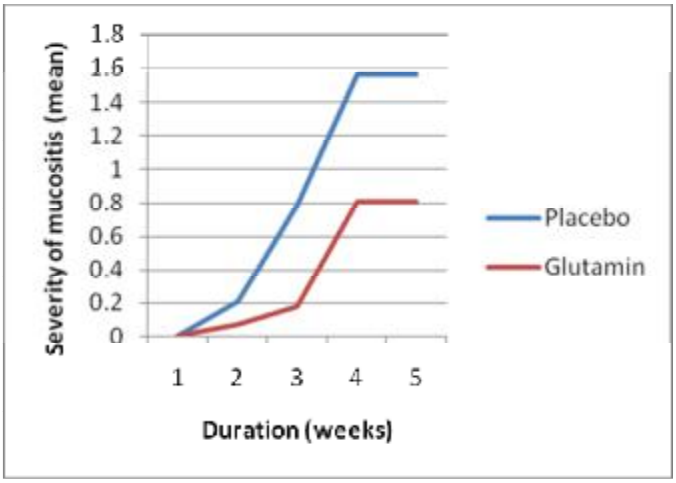

Figure 1: Mean severity of mucositis amongst patients on glutamine vs. placebo from the start through to the end of radiation therapy course.

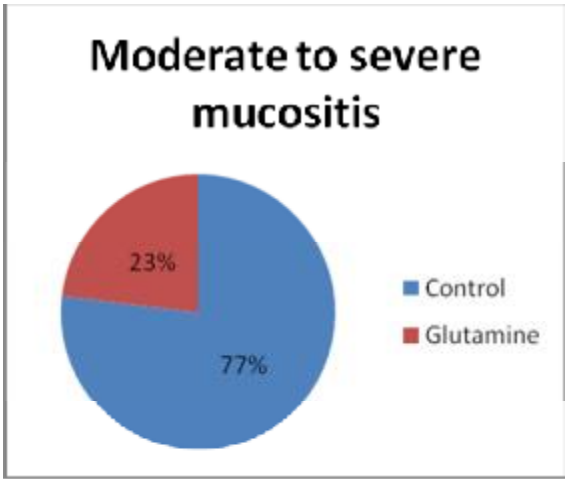

Figure 2: Percentage of patients who developed "moderate to severe mucositis amongst the control group vs. the intervention group

Additionally, as it is shown in figure (2), amongst the twenty-three patients in the control group (without intervention), ten (77%) of them developed some degree of moderate to severe mucositis (Grades 2-4), while less than a quarter of patients the intervention groups (who received glutamine) developed moderate to severe mucositis.

The study also showed that gender had no effect in the development or severity of oral mucositis in the studied patients. As the mean difference of severity of mucositis between males and females in both the control and intervention arms, was very small; although slightly favoring the male gender, but the difference was not statistically significant, as it is illustrated in table (3).

Table 3. Distribution of mean levels of oral mucositis between the male and female patients in both the control and intervention arms

Treatment		No.	Mean of mucositis	S.E.	Mean Difference	S.E.	95% Confidence Interval of Difference	p value
Mucositis	Male	26	1.12	0.15	0.34	0.26	-0.86 – 0.19	0.21
	Female	20	1.45	0.21				

Additionally, the study showed that age had no effect in the development or severity of oral mucositis in the studied patients. As the mean difference of severity of mucositis, between those who aged equal or less than 45 years compared to those older than 45 years of age in both of the control and intervention arms was small. Although the younger patient developed slightly less severe mucositis comparing their older counterparts, but the difference was not statistically significant, as it is illustrated in table (4).

Table 4. Distribution of mean levels of oral mucositis according to age groups

Treatment		Number	Mean	S.E.	Mean Difference	S.E.	95% Confidence Interval of Difference	p value
Mucositis	Young	19	1.05	0.21	0.36	0.26	-0.88 – .017	0.18
	Older	27	1.41	0.15				

DISCUSSION

Glutamine is a neutral amino acid that acts as a substrate for nucleotide synthesis in most dividing cells. It is a major energy source for mucosal epithelial cells and stimulates mucosal growth and repair.[20,21] Animal studies have suggested that dietary supplementation with glutamine may protect the gut mucosa from both radiotherapy and chemotherapy side effects,[21,22] and some other studies have showed, with limited evidence, that glutamine may decrease the duration of mucositis.[18-20]

Many studies have been done in order to define the best clinical protocol for prophylaxis and treatment of radiation-induced mucositis.[1,3,4,9,14] In this study we used glutamine powder for preventing and treating oral mucositis in patients with head and neck cancer receiving radiation therapy. Concordantly with other studies that have been done before on glutamine, our study results revealed that glutamine was significantly reduced both the occurrence and severity of mucositis amongst the studied twenty-three patients with head and neck cancer who received radiation therapy.

This protective effect is may be due to the fact that malignancy produces a state of physiologic stress that is characterized by a relative deficiency of glutamine, a condition that is further exacerbated by the effects of cancer treatment (radiation therapy). Glutamine deficiency may impact on normal tissue tolerance and repair following antitumor treatment. Therefore, providing glutamine during cancer treatment has the potential to abrogate treatment-related toxicity; and its supplementation may enhance the therapeutic index by protecting normal tissues, and sensitizing tumor cells to chemotherapy and radiation-related injury.[16-21] Additionally, glutamine helps the function immune system which is part of protection against development of cancer and treatment-related complications.[23]

As a conclusion, glutamine, which is an amino acid that acts as a substrate for nucleotide synthesis in most dividing cells and is a major energy source for mucosal epithelial cells that stimulate mucosal growth and repair, can be used effectively in clinical practice to prevent or to reduce the development of oral mucositis as a side effect of radiation therapy amongst patients with head and neck cancer.

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