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Original Article

Effect of glutamine on oral mucositis in patients undergoing chemotherapy-radiotherapy: A Randomized Clinical Trial

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Abstract

Background: In most malignant diseases, chemotherapy drugs are used as a main complementary method of treatment and have different side effects, which should not be overlooked if we are to provide complete treatment for the patient. These complications include inflammation and oral wounds, referred to as mucositis. This study aimed to investigate the effect of glutamine on oral mucositis in patients undergoing chemotherapy-radiotherapy.

Methods: The present conducted on 40 patients with head and neck tumors undergoing chemotherapy or radiotherapy. Each patient was placed in a group that received either the drug (glutamine) or placebo (maltodextrin) based on a random even or odd number that the patient drew from a box. Before the beginning of chemotherapy, the mouth was examined by a trained last-year student, and all patients received oral health education on subjects including brushing and flossing. All patients (medication and placebo) took 10 g of powder. Oral examination of patients was performed in the beginning (day zero) and on the first, fourth, sixth, and tenth days. Mucositis was evaluated according to the Radiation Therapy Oncology Group (RTOG) criteria (zero = no erythema, 1 = light red or pink erythema, 2 = non-dark red, and 3 = dark red). Also, the level of pain and burning in the mouth and throat were measured on all days of the study using the visual analogue scale (VAS). All obtained data were coded and analyzed by SPSS 24.

Results: The present study was conducted on 39 patients who were undergoing chemotherapy (female = 17 and male = 22). On days three, seven, and ten of the study, only two subjects in the glutamine group were RTOG grade 1, and the rest of the group were grade 0. In the placebo group, only 2 subjects were grade 1 and the rest were grades 2 and 3. The mean duration of wound healing in the drug treatment group was 4.5 ± 0.5 days, and its range was 3–9 days.

Conclusion: Results showed that glutamine reduced pain and burning and the number of wounds. It also affected patients' outcomes according to the RTOG criteria and improved patients' symptoms.

Keywords: Glutamine, Oral mucositis, Chemotherapy, Radiotherapy

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Introduction

Millions of people are affected by cancer around the world every year. Not considering the age of death, this disease causes more death than heart disease. The number of deaths caused by cancer has been estimated to increase by 50% over the next 20 years, even in developed countries.[1] Anticancer therapies consist of surgery, radiotherapy, chemotherapy, and immunotherapy.[2] Treatment of cancer patients aims to cure the disease definitively. In most malignant diseases, chemotherapy drugs are used as a main component or as a complementary method of treatment, but with have different side effects, which should not be overlooked if we are to provide a complete treatment for the patient. These complications include inflammation and oral wounds, referred to as mucositis.[3] The potential characteristics of mucositis can be appeared as severe pains including dysfunction in the mouth and throat, mouth bleeding, and increased risk of local and systemic infections potentially affecting the quality of life. Mucositis also increases the duration of the patient feeling ill and prolongs their hospital stay so they may receive supportive complementary treatments because mucositis causes pain and limits nutrition in the patient; in severe cases, the patient has to use intravenous feeding and analgesics.[4]

It is estimated that 400 000 patients suffer from acute or chronic oral mucosal complications of chemotherapy each year in the United States. This difference has been attributed to genetic differences in people and other unknown factors. A trend similar to that of the United

States is seen around the world.[4]

The first sign of mucositis may be a white view caused by increased mucin keratinization or a red view caused by hyperemia and thinning of the epithelium. Pseudomembrane formation with wounds and fibrin-containing secretions are also observed. At present, no drug can definitively treat or prevent mucositis, and treatment of mucositis focuses on reducing its severity and duration and preventing infection at the affected site until it heals. Patients often need to use narcotic analgesics to control their pain. Combined mouthwashes can also be used to alleviate this problem. One of these mouthwashes contains equal amounts of lidocaine and Zovirax, which should be gargled every two to four hours. Antacids and vitamin E can also be used to reduce burning. Antiseptic or chlorhexidine mouthwashes can be used to prevent infection.[5-12]

The first research was published by Skubitz and Anderson.[13] on the effect of glutamine in the treatment of oral mucositis in the treatment of cancer. Several studies have indicated that supplementation with this amino acid might reduce the level and severity of mucositis, reduce cell damage, and improve cell recovery during treatment.[14-16] However, others have not achieved significant results and have stated that more studies are required to gather more comprehensive and consistent evidence and higher methodological validity.[17,18] The goal of the present research is the effect of glutamine on reducing the incidence and severity of oral mucositis in patients undergoing chemotherapy-radiotherapy in Kerman hospitals in 2020.

Materials and Methods

This present investigation is a randomized double-blind placebo-controlled clinical trial conducted on 39 patients, based on other studies,[19-23] with head and neck tumors undergoing chemotherapy or radiotherapy.

These patients are selected from the three centers of Shafa, Bahonar, and Afzalipour hospitals.

Inclusion criteria of study[14]:

- Having cancer based on the diagnosis of a physician and the approval of a pathologist
- Not receiving radiotherapy before chemotherapy
- Age over 18 years
- Willingness to participate in the research and filling out the consent form
- Not taking chemical drugs such as interleukin, chlorhexidine, topical and systemic steroids, sucralfate, hydrogen peroxide, pilocarpine, or herbal medicines to treat mucositis.

Exclusion criteria of study[13,14]:

- Radiotherapy of head and neck
- Start of chemotherapy
- White blood cell count less than 1500 mm^3, platelets below 50 000 mm3, or hemoglobin below 10mg/ dl
- Having diseases, such as lichen planus or vesiculobulosis, that cause mouth wounds.
- Bleeding disorders
- The use of blood-diluting drugs such as aspirin or warfarin
- Seafood sensitivity
- Very high and uncontrolled blood pressure
- Uncontrolled diabetes
- Liver cancer or liver disorders

Before the examination of each person, the goal of this project and the process of examination were explained to the patients. The patients were examined after they announced their willingness and completed the consent form, and they then received either the drug or the placebo. First, each patient was placed in a group that received the drug (glutamine) or the placebo (maltodextrin) based on an even or odd number they randomly selected. In this randomization method, the numbers from 1 to 40 were placed in a box, and the patient was placed in the drug or placebo group based on the number they drew from the box. The drug and the placebo were packaged in identical packages that had a special code so that the patient or the examiner was unaware of the placement of patients in the two groups until the end of the study and only the person giving the drug was aware of it.

Before chemotherapy started, the mouth was examined by a trained last-year student, and all patients received oral health education on subjects including brushing and flossing. Patients' mouths were examined with disposable mirrors, gloves, dental gauze, and a flashlight. Then, patients were provided enough information about how the research was conducted and how they were allocated to one of the two groups of drugs or placebo, and patients signed the consent form if they were willing to participate in the study. All patients received acyclovir tablets (made by Izad Daru Company) at a dose of 200 mg daily to prevent herpes infection, gargled nystatin emulsion (made by Zahravi Pharmacy) four times a day, 20 drops each time to prevent candida infection, and gargled benzydamine 0.15% mouthwash (made by Behvazan Pharmacy) for 10 minutes three times a day before meals as standard treatment. All patients (medication and placebo) took 10 g of powder (dissolved in a glass of water) with their three daily meals. It was advised to the patients that they use only the provided drug and to avoid taking any chemical or herbal drug during this period (except drugs prescribed by the oncologist). They were also advised to avoid eating sour or spicy food. Oral examination of patients was performed at the beginning (day zero) and on the first, fourth, sixth, and tenth days, and the associated forms were completed on the same days. If patients had oral symptoms after 10 days, the examination was performed until the symptoms disappeared completely.

Mucositis evaluation criteria

Mucositis was evaluated according to the RTOG criteria

(zero = no erythema, 1 = light red or pink erythema, 2 = non-dark red, and 3 = dark red).[14]

Also, the level of pain and burning in the mouth and throat on the four assessed days (zero, 3,7, and 10) of the study was measured by the visual analogue scale (VAS) (14). If the patient had moderate or severe pain (VAS ≥ 4) according to the WHO three-step analgesic ladder protocol, appropriate analgesics were prescribed for the patient. Also, 45 patients were initially included in the study and finally, 39 patients were studied (Figure 1).

All obtained data were coded and analyzed by SPSS 21 software and by using t-test, chi-square, analysis of variance (ANOVA) and variance tests.

Results

The present study was conducted on 39 patients who were undergoing chemotherapy, 17 of which (9 in the drug group and 8 in the placebo group) were female and 22 (11 in the drug group and 11 in the placebo group) were male. The age range of the subjects was between 20 and 82 years in the drug group with a mean of 32.1 ± 2.5 years and between 26 and 64 years in the placebo group with a mean of 31.4 ± 3.7 years. There was no significant difference between the two groups in mean age, sex, and tumor site (Table 1). However, on days three, seven, and ten of the study, only two subjects in the glutamine group were RTOG grade 1, and the rest of the group were grade 0. However, in the placebo group, only 2 subjects were grade 1 and the rest were grades 2 and 3 (Table 2). In fact, after ten days, there was no effect of mucositis in those

Table 1. Demographic characteristics of the subjects

Demographic characteristics		Drug		Placebo	
		No.	%	No.	%
Gender	Male	11	50	11	50
	Female	9	52.3	8	47.7
Mean age		32.1 ± 2.5		31.4 ± 3.7	
Employment status	Housewives	3	7	5	12.5
	Self-employed	10	25	7	18
	Employed	7	18	7	18
Education level	Illiterate	2	5	2	5
	Under diploma	5	12.5	4	10
	Diploma	6	14	5	12.5
	Bachelor & higher	7		7	18
Tumor type	Blood	4	10	3	7
	Other cases	16	40	14	36
Disease	Yes	7	18	6	14
	No	13	33.3	11	28.2

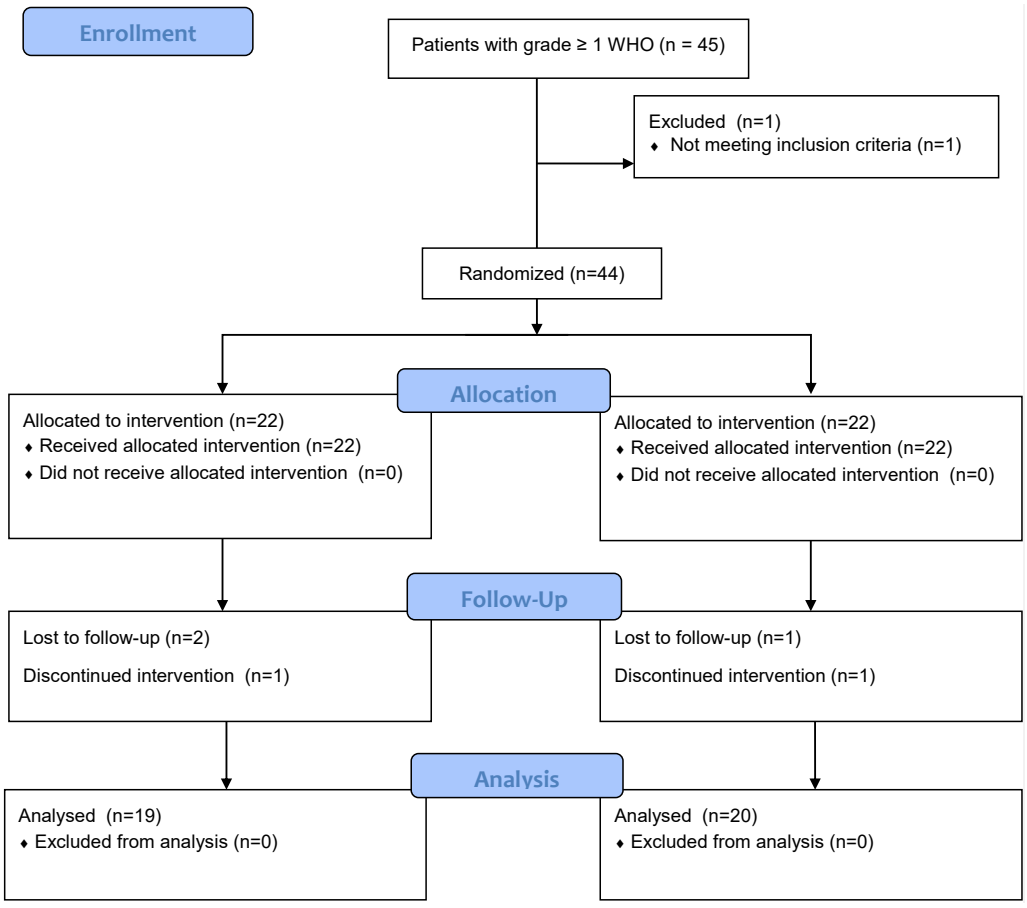

Figure 1. Flowchart related to the entry of patients into the study

Table 2. The severity of mucositis in the two study groups based on RTOG criteria

Criterion Name		Day 0		Day 3		Day 7		Day 10	
		Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
RTOG	Grade 0	3	2	5	3	12	1	18	0
	Grade 1	6	4	6	4	4	4	2	0
	Grade 2	7	8	6	7	2	7	0	10
	Grade 3	4	5	3	5	2	7	0	7

taking glutamine, and patients were satisfied with using the drug. The results showed that there was a significant relationship between the severity of mucositis in the two groups at the beginning and end of the study (Table 3).

The results of this study showed that only 2 people had one wound in the glutamine group at the end of the study, while in the placebo group, 5 patients had more than 3 wounds, and 6 patients had 2 to 3 wounds (Figure 2).

The mean duration of wound healing in the drug treatment group was 4.5±0.5 days, and its range was 3–9 days. In the placebo group, the minimum time required for the wounds to heal was 6.3±0.7 days, and it was even longer than 12 days in 3 patients. The highest pain severity was 7 in the drug group and the lowest was zero. In the placebo group, the highest pain severity was 9 and the lowest was 2. In this study, there was a significant difference between the two groups of drug and placebo in terms of pain intensity and mouth and throat burning on days 3, 7, and 10 based on the VAS (Table 4, Figures 2 and 3)

From the present study, it was found from that that glutamine reduced pain and burning and the number of wounds. It also affected patients' outcomes according to the RTOG criteria and improved patients' symptoms (Table 5 and Figure 4).

Almost all patients reported that glutamine reduced their wounds and no toxicity or allergy reactions or other side effects were reported as a result of using the drug or the placebo.

Table 3. Severity and prevalence of mucositis at the beginning and end of the study in the two groups of drug and placebo

	Beginning of study		End of study		*P* value[a]
	Drug	Placebo	Drug	Placebo	
Prevalence of mucositis	17	17	2	19	0.001*
Degree of mucositis					
0	3	2	18	0	0.001*
1	6	4	2	2	0.001*
2	7	8	0	10	0.001*
3	4	5	0	7	0.001*

[a] Chi-square, *$P<0.05$ is significant

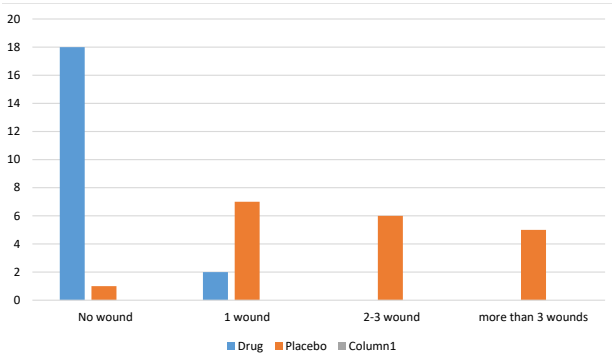

Figure 2. General evaluation of the mouth based on the number of wounds in the two groups of drug and placebo at the end of the study

Discussion

In this paper, the role of glutamine on mucositis in 39 patients who were undergoing chemotherapy (20 patients in the glutamine group and 19 patients in the placebo group) was examined. However, on day 10 of the study, only two subjects in the glutamine group were RTOG grade 1 and the rest of the group were grade 0, and glutamine significantly reduced mucositis. In the placebo group, only 2 subjects were grade 1 and the rest were grades 2 and 3. In fact, after ten days, mucositis did not affect people taking glutamine, and the patients were satisfied with taking the drug.

A study conducted by Leung and Chan[18] showed that glutamine significantly reduced mucositis severity compared to placebo or non-treatment. Studies conducted by Jebb et al,[19] Anderson et al,[20] Okuno et al,[21] and Ward et al[22] found glutamine to be effective in the treatment of mucositis while four studies conducted by Choi et al,[23] Rubio et al,[24] Cockerham et al. [25], and Peterson et al[26] did not report any result on the effectiveness of glutamine.

Animal studies have shown that gastrointestinal mucosal damage caused by ultraviolet radiation and chemotherapy can be improved by injecting glutamine.[27,28] Klimberg et al showed that rats that received a glutamine-deficient diet were affected by gastrointestinal wounds and edema. Adding glutamine to the diet also improved immune function and increased the movement of beneficial bacteria to the mesenteric nodes.[28-30]

Ziegler et al[29,30] showed that patients receiving glutamine supplementation showed a significant reduction of infection, positive culture, hospital stay, and increased recovery. Schloerb and Amare[31] showed that the length of hospital stay decreased significantly in

Table 4. Mean, standard deviation, and maximum and minimum severity of pain and burning in the mouth and throat in the two study groups based on the VAS

	Mouth and throat burning								Severity of pain in the mouth and throat							
	Day 0		Day 3		Day 7		Day 10		Day 0		Day 3		Day 7		Day 10	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Mean	4.5	5.6	5.3	5.4	5.1	3.3	0	1.1	3.5	5.5	7.3	2.4	1.1	1.3	0	2.2
SD	4.1	3.2	2.1	5.2	9.0	1.2	0	0	8.1	8.2	1	9.1	7.0	1.2	0	4.0
Max	7	10	6	7	4	6	0	3	7	9	5	6	3	6	0	3
Min	3	3	0	3	0	3	0	1	2	4	0	3	0	3	0	1
P value	0.05		0.001*		0.001*		0.001*		0.03*		0.001*		0.02*		0.001*	

A: Drug group B: Placebo group, * $P<0.05$ is significant, ANOVA.

Table 5. The effect of glutamine on patients' outcomes

	Drug	Placebo	*P* value
Pain (VAS=0–10)	1.8	3.4	0.01
Burning (VAS=0–10)	2.2	4.5	0.02
Number of wounds	2.1	5.2	0.001
Mucositis period	3.1	4.8	0.02
Average mucositis based on questionnaire, RTOG	1.1	2.7	0.04

*$P<0.05$ is significant.

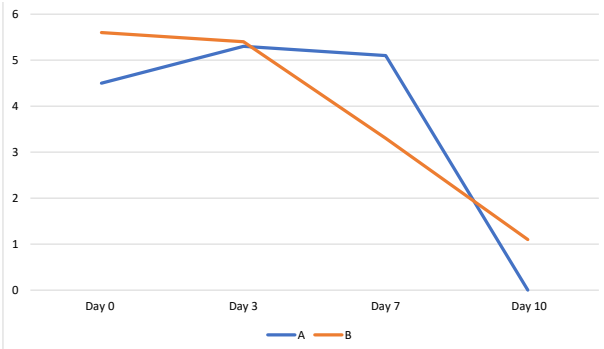

Figure 3. Mean mouth and throat burning in the two study groups based on the VAS

patients transplanted with glutamine-derived stem cells although it did not reduce mortality and infection.[32-35]

Several clinical studies have indicated the protective effects of glutamine on the mucosal epithelium.[16,32,33,36-40]

Souba et al[33] showed that oral glutamine reduces the incidence and duration of acute disease in lung cancer patients undergoing radiotherapy, which is in line with the results of other studies.[34,38] In the present study, a significant difference was found between the two groups of drug and placebo in terms of pain severity and burning and pain in the mouth and throat on days 4, 6, and 10 based on the VAS. The study conducted by Lopez-Vaquero et al[27] revealed no significant difference between the two groups of drug and placebo in terms of pain, mucositis onset, and quality of life. The study conducted by Aquino et al[36] showed that glutamine reduced pain in patients and led to lower morphine intake, which is in line with the results of previous studies.[41,42]

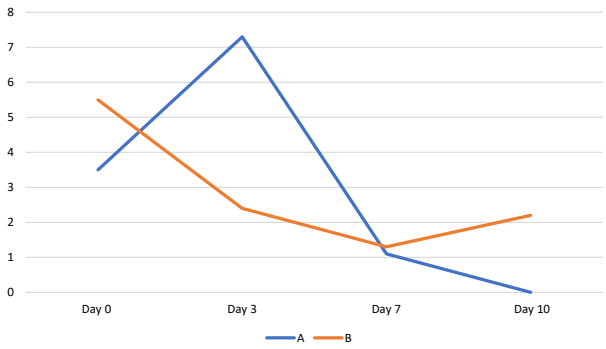

Figure 4. The mean severity of pain in the mouth and throat in the two study groups based on the VAS

Among the reasons for the difference between the results of some of these studies and those of the present study, we can mention the difference in the sample size, the number of patients, and the research methods.

Limitations

The limitations of the present study included the non-cooperation of some patients and the incorrect use of medicine in a number of patients.

Conclusion

The obtained findings revealed that glutamine reduced pain and burning and the number of wounds. It also affected patients' outcomes according to RTOG criteria and improved patients' symptoms.

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Authors' Contribution

Conceptualization: Maryam Alsadat Hashemipour.
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Writing–original draft: Maryam Alsadat Hashemipour.
Writing–review & editing: Maryam Alsadat Hashemipour.
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Competing Interests

None.

Ethical Approval

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