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Comparative Study of the Effect of Licorice Root Extract Mouthwash and Combined Mouthwash on the Incidence and Severity of Chemotherapy-Induced Mucositis Symptoms in Colon Cancer Patients Admitted to Intensive Care Units

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Abstract

Background: Colon cancer is the third leading cause of death globally, and mucositis is one of the complications of cancer treatment following drug therapy.
Objectives: This study investigated the effect of licorice root extract mouthwash with combined mouthwash on the incidence and severity of chemotherapy-induced mucositis symptoms in colon cancer patients admitted to intensive care units (ICUs).
Methods: In this clinical trial, 72 colon cancer patients were treated with chemotherapy. A purposive random sample of patients was divided into two groups of intervention (n = 36) and control (n = 36). Patients in the control group received routinely used combined mouthwash. However, the intervention group received licorice root extract 5% from the beginning of the treatment according to the researcher's plan. Then, the degree of mucositis and ulcer area were recorded on the first, third, and seventh days of treatment based on the WHO standard tool for measuring mucositis severity.
Results: The intervention and control groups had no significant difference on the first, third, and seventh days of treatment in the incidence of mucositis (P = 0.554, P = 0.308, and P = 0.601, respectively) and the severity of mucositis (P = 0.357, P = 0.857, P = 0.607, respectively).
Conclusions: There was no difference in the efficacy of combined mouthwash and licorice root extract mouthwash in the incidence and severity of mucositis. Due to the interest of many patients in the use of herbal compounds, licorice root extract mouthwash can be used as an alternative to combined mouthwash.

Keywords: Mouthwash, Licorice Root Extract, Oral Mucositis, Chemotherapy, Colon Cancer

1. Background

Cancer is a major health problem worldwide (1). Cancer deaths are expected to rise to 13 million worldwide by 2030. Cancer is the leading cause of death in developed countries and the second leading cause of death in developing countries (2). In Iran, cancer is the third most common cause of death after cardiovascular diseases and vehicle accidents (3). Colon cancer is one of the most common types of cancer and is the second most common cause of cancer death that affects both men and women in developed countries (4). The incidence of colon cancer is high in many Asian countries and more profoundly in developed and western countries (5). In 2010, it accounted for 10% of all cancer deaths in the United States, causing 50 to 60% of patients to experience metastases and more than 30% of patients with metastatic symptoms to refer to the hospital (6).

One of the most important therapeutic options for cancer is chemotherapy that uses anti-cancer agents to kill tumor cells. Chemotherapy is the cornerstone of cancer treatment and, as a systematic treatment, kills cancer cells

in the furthest parts of the body (7). Several chemotherapy regimens are used to treat colon cancer, and the basis of all is 5-FU (5-fluorouracil), which is used as an effective drug in the first-line treatment for colon cancer. The main side effect of this drug in different regimens is bone marrow suppression, mucositis, and diarrhea (8). Mouth flora in a healthy person remains constant over time; however, special conditions can cause mouth flora to collapse. For example, within 48 hours of the patient's hospitalization, this flora changes in favor of gram-negative organisms with higher pathogenicity (9). These changes can lead to the accumulation of bacteria and the proliferation of opportunistic pathogens in the oral cavity, causing general and local complications (10), such as inflammation, mouth ulcers, increased prevalence of viral, fungal, and bacterial infections, and bleeding. These complications lead to significant pain and malnutrition (11).

In patients needing intensive care, a defensive substance called fibronectin, commonly found on the surface of the teeth and mouth, deteriorates (12), and develops mucositis as a significant complication (13). The incidence of severe mucositis has been reported in more than 60% of patients receiving radiation therapy in the body as a whole and 30 to 50% of patients not receiving general radiotherapy (14). The severity of mucositis varies in the mouth from small scars with redness to severe ulcers and ruptured mucous and epithelium. Severe mucositis can cause damage to the lining of the mouth, which impairs its function and can lead to morbidity and poor quality of life of patients (15). Clinically, it can cause major problems, including many disabling symptoms, such as dysphagia, weight loss, and malnutrition during treatment (16). The prevalence of mucositis is 80 to 100% in high-dose chemotherapy, 40% in standard-dose chemotherapy, and 10 to 15% in low-dose chemotherapy (17). The only way to treat and prevent chemotherapy-induced mucositis is by observing oral hygiene and using mouthwash (18). Due to complications such as burning, allergies, bitter and intolerable taste and exacerbation of mouth ulcers, non-chemical mouthwash is recommended to use, especially herbal mouthwash (19).

Over the past few years, the use of complementary and alternative medicine has become popular (20). One of the treatments in complementary medicine is the use of herbal medicine, which has received general public acceptance due to lower side effects (21). One of these medicinal herbs is licorice, which is considered by pharmaceutical and food industries due to a large number of flavonoids (22). The natural form of this substance is useful in the treatment of mouth and digestive tract ulcers (23). A study conducted by Das et al. in 2011 found that licorice was effective in preventing and treating oral mucositis caused by radiotherapy in patients with cancer in the head and neck without any interruption in treatment (24). According to these studies and the use of complementary medicine in mucositis by patients undergoing chemotherapy, licorice can be applied to reduce the complications of chemotherapy due to its prominent anti-inflammatory symptoms.

2. Objectives

This study aimed to compare the effect of a mouthwash prepared from licorice root extract and combination mouthwash on the incidence and severity of chemotherapy-induced mucositis symptoms in colon cancer patients admitted to ICUs.

3. Methods

This double-blind randomized clinical trial was conducted on 72 patients (males and females) undergoing chemotherapy in the intensive care unit of Baghaee Hospital, Ahvaz, Iran. The patients had been diagnosed by oncology specialist. The inclusion criteria for patients include an age of 18 years or older, a diagnosis of colon cancer treated with FOLFOX, and at least one episode of mucositis in previous chemotherapy. Patients who had undergone radiotherapy in addition to chemotherapy or died during the study were excluded. After obtaining permission from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences and receiving written consent from patients for the purpose of participating in the study, the patients were randomized using the blocks of six into two groups of intervention (36 patients) receiving licorice root extract 5% and control (n = 36) receiving combined mouthwash.

The data gathering tools included a two-part questionnaire and a checklist. The questionnaire contained a part for gathering demographic information (age, sex, and education) and another part with questions on the history of smoking, history of oral and dental complications (decayed and missing teeth), the duration of chemotherapy, and the number of white blood cells. The checklist was used to determine the severity of oral mucosal inflammation based on the World Health Organization 2005 criteria that categorizes oral mucositis into five distinct grades (4 - 0). The instrument was used to determine the status of the oral mucosa, incidence, and severity of oral mucositis before and after the intervention. Content validity and reliability were obtained by evaluation of the inter-rater, with the correlation coefficient of 0.93.

The intervention group used mouthwash prepared from licorice root extract 5% prepared at the Pharmaceutical Faculty of Ahvaz Jundishapur University of Medical

Sciences while the control group used a combined mouthwash (aluminum MG, diphenhydramine, nystatin powder, and lidocaine 2%). Both mouthwash solutions were administered every eight hours daily at a dose of 10 cc from the first day of chemotherapy for one week. Then, the oral mucosa of the patients was studied in this period. In this double-blind study, the researcher and the patients were unaware of the nature of the solutions.

Data obtained from the two groups were statistically analyzed. To test the relationship between qualitative variables, the chi-square test was used and the Mann-Whitney test was used to compare the quantitative variables between the two groups by the independent t-test or nonparametric equivalence. The significance level was set at P = 0.05.

4. Results

The mean age of the patients was 12.44 ± 55.02 in the intervention group and 12.56 ± 56.47 in the control group. There was no significant difference between the two groups in terms of age (P = 0.581). There was also no significant difference between the groups in terms of gender, occupation, tumor location, Family history of cancer, education level, smoking, white blood cells, duration of chemotherapy, type of teeth, and decayed teeth (Tables 1 and 2).

Table 1. Mean ± SD of Variables in the Experimental and Control Groups[a]

Variable	Experimental Group	Control Group	P Value
Age	55.02 ± 12.40	56.47 ± 12.40	0.581
Chemotherapy duration	8.2 ± 1	7.9 ± 1.1	0.309
Chemotherapy period	6.2 ± 3.5	6.4 ± 4.1	0.874
White blood cells	5444.4 ± 2230.8	5261.1 ± 2273.4	0.770

[a] Values are presented as mean ± SD.

Most of the patients in both intervention and control groups did not develop mouth ulcers on the first day. According to the chi-square test, there was no significant difference in the incidence of mucositis between the two groups on the first day of the study (P = 0.544).

On the third day of the study, most of the patients in the intervention and control groups did not develop mouth ulcers. However, the number of patients in the intervention group who had ulcers between 1 and 5 cm in size was more than that in the control group and none of the patients in both groups had ulcers of more than 5 cm. According to the chi-square test, there was no significant difference between the two groups in this regard (P = 0.308).

Table 2. Comparison of Demographic Data Between the Groups[a]

Variable	Experimental Group	Control Group	P Value
Gender			0.149
Male	25 (69.4)	18 (50.0)	
Female	11 (30.6)	18 (50.0)	
Occupation			0.87
Unemployed	14 (38.8)	15 (41.7)	
Employee	11 (30.6)	12 (33.3)	
Retired	11 (30.6)	9 (25.0)	
Location of the tumor			0.475
Right	18 (50.0)	13 (36.1)	
Left	11 (30.6)	15 (41.7)	
Rectum	7 (19.4)	8 (22.2)	
History of disease			0.811
Yes	14 (38.9)	16 (44.4)	
No	22 (61.1)	20 (55.6)	
Level of education			0.055
Illiterate	2 (5.6)	12 (33.3)	
Elementary	5 (13.9)	5 (13.9)	
Secondary	10 (27.8)	6 (16.7)	
High school	12 (33.3)	8 (22.2)	
Academic	7 (19.4)	5 (13.9)	
Smoking			0.149
Yes	25 (69.4)	18 (50.0)	
No	11 (30.6)	18 (50.0)	
Type of teeth			0.096
Natural	24 (66.7)	16 (44.4)	
Artificial	12 (33.3)	20 (55.6)	
Decayed teeth			> 0.99
Yes	30 (83.3)	61 (84.7)	
No	6 (16.7)	5 (13.9)	

[a] Values are presented as No. (%).

On the seventh day of the study, most of the patients in the intervention and control groups had no mouth ulcers. In the control group, no ulcers of 1 cm or more were reported. The chi-square test showed no significant difference between the two groups in the incidence of mucositis on the seventh day of the study (P = 0.601; Table 3).

The results showed that on the first day of the study, most of the patients in both groups were without mucositis. There was no significant difference in the severity of mucositis between the two intervention and control

Table 3. Comparison of the Incidence of Mucositis on the First, Third, and Seventh Days in the Intervention and Control Groups[a]

Occurrence of Mucositis	First Day	Third Day	Seventh Day
Intervention group (n = 36)			
No mouth ulcer	32 (88.9)	14 (38.9)	25 (69.4)
Less than 1 cm ulcers	3 (8.3)	13 (36.1)	10 (27.8)
Between 1 and 5 cm ulcers	1 (2.8)	9 (25)	1 (2.8)
Control group (n = 36)			
No mouth ulcer	31 (86.1)	17 (47.2)	26 (72.2)
Less than 1 cm ulcers	2 (5.6)	15 (41.7)	10 (27.8)
Between 1 and 5 cm ulcers	3 (8.3)	4 (11.1)	0 (0)
P value	0.544	0.308	0.601

[a] Values are presented as No. (%).

groups on the first day of the study based on the chi-square test (P = 0.357).

On the third day of the study, most of the patients in the intervention group had erythema, redness, ulcers, and little ability to eat solid food. In the control group, most people had non-ulcer redness. However, based on the chi-square test, there was no statistically significant difference in the severity of mucositis between the intervention and control groups on the third day of the study (P = 0.857).

On the seventh day of the study, most of the patients in both intervention and control groups had erythema without ulcers. In the intervention group, the number of subjects without mucositis was more than that in the control group. According to the chi-square test, there was no significant difference in the severity of mucositis between the two groups (P = 0.607; Table 4).

5. Discussion

Mucositis is the most common side effect of chemotherapy, and a complex biological process that involves direct destruction of the oral mucosa along with the reduction of epithelium due to the immune system response, inflammatory process, or secondary infection by oral bacteria.

In the study of Akhavan Karbasi et al. with the aim of evaluating the effect of Propolis mouthwash on the treatment of chemotherapy-induced mucositis in two intervention and control groups on the third and seventh days, there was a significant difference in the degree of ulcers between the two intervention and control groups (17). Thus, there is a discrepancy between the result of the mentioned study and those of the present study. This can be due to differences in the type of treatment regimen used to treat patients with different cancers in the mentioned study, while in the present study, colon cancer patients were treated with FOLFOX regimen. In a study conducted by Aghamohammadi et al. in 2017 to determine the effect of *Zataria multiflora* extract on the prevention and reduction of oral mucositis in patients with head and neck cancer treated with local radiotherapy, they showed that the incidence of mucositis in the intervention group was significantly lower than that in the control group (25). The result of this study is inconsistent with the findings of the present study in terms of the mucositis incidence in the intervention and control groups. The reason for this difference is that in the mentioned study, the control group received a placebo, but in the present study, the control group received standard routine mouthwash used in the hospital ward. The study conducted by Ghoreishi et al. aimed to investigate the effect of vitamin E on the incidence and severity of mucositis and the improvement of chemotherapy-induced neutropenia in patients with leukemia undergoing allogeneic bone marrow transplantation and showed no significant difference between the two intervention and control groups in the incidence of mucositis (26). The results of the mentioned study are consistent with those of the present study in terms of the incidence of mucositis. The reason for this consistency can be the similarity of the drug regimen for the intervention and control groups in both studies. In a study conducted by Kong et al. to determine the effectiveness and efficacy of clove mouthwash in reducing the incidence of mucositis in patients with head and neck cancer, there was no significant difference between the two intervention and control groups regarding the incidence of mucositis (27). The result of the mentioned study is consistent with those of the present study in terms of mucositis, which is due to the similarity in the methodology of both studies.

In the study conducted by Stokman et al. to deter-

Table 4. Comparison of Mucositis Severity on the First, Third, and Seventh Days in the Intervention and Control Groups[a]

Occurrence of Mucositis	First Day	Third Day	Seventh Day
Intervention group (n = 36)			
Without mucositis	23 (63.9)	6 (16.7)	14 (38.9)
Erythema, without ulcers, redness, pain, allergy	9 (25)	13 (36.1)	16 (44.4)
Erythema, redness, ulcers, and a little ability to eat solid food	4 (11.1)	15 (41.7)	6 (16.7)
Ulcer, need for liquids	2 (11.1)	2 (5.5)	0 (0)
Control group (n = 36)			
Without mucositis	20 (55.6)	5 (13.9)	12 (33.3)
Erythema, without ulcers, redness, pain, allergy	14 (38.9)	16 (44.4)	20 (55.6)
Erythema, redness, ulcers, and a little ability to eat solid food	2 (5.5)	14 (38.9)	4 (11.1)
Ulcer, need for liquids	0 (0)	1 (2.8)	0 (0)
P value	0.375	0.857	0.607

[a] Values are presented as No. (%).

mine the effect of calcium phosphate mouthwash on the duration and severity of oral mucositis in patients with head and neck cancer undergoing radiotherapy showed no significant difference between the intervention and control groups in terms of the severity of mucositis (28). The result of the mentioned study is consistent with those of the present study in terms of the severity of mucositis. The similarity of the results of the studies can be attributed to the similarity of the methods and the use of standard routine mouthwash for the control group. In the study conducted by Wong et al. to determine the effect of Caphosol mouthwash on reducing the incidence and severity of radiotherapy-induced mucositis in patients with head and neck cancer undergoing radical radiotherapy and chemotherapy, there was no significant difference between the two groups of study in terms of the severity of mucositis (29). The result of the mentioned study is consistent with those of the present study. The reason for this consistency may be due to the use of standard mouthwash routinely used in the hospital setting and their efficacy in patients of control groups in the two studies. In the study of Najafi et al. to determine the preventive effect of licorice root extract on the severity of oral mucositis in patients undergoing head and neck radiotherapy, there was a significant difference between the two groups in terms of the severity of mucositis (30). These studies show an inconsistency in the results of mucositis severity. The reason for this contradiction is that in the mentioned study, licorice root extract 50% was used. However, in the present study, licorice root extract was used at a concentration of 5%. Therefore, the concentration of licorice was higher in the mentioned study than in the present study and it had a greater effect on the outcome of the study. In the control group of the mentioned study, water containing approved brown food colors was used as the mouthwash solution, but routine mouthwash was used in the present study. In the study conducted by Bahramnezhad et al. to determine the effect of honey mouthwash in preventing head and neck radiotherapy-induced mucositis showed that in the intervention group, the patients had mild mucositis on the first day while they did not have mucositis on the seventh and 14th days. The severity of mucositis in the control group was mild in most patients on the first day and moderate on the seventh and 14th days. The severity of mucositis on the first, seventh, and 14th days was significantly different between the two intervention and control groups (19). The result of this study is inconsistent with those of the present study, which can be due to that the patients in the mentioned study were those with head and neck cancer undergoing radiotherapy while in the present study, patients were those with colon cancer undergoing chemotherapy. It means that both cancer and treatment are different in the two studies. In the mentioned study, patients in the control group used water as the mouthwash solution, but in the present study, the control group used standard routine mouthwash.

The mental, physical, and psychological state of patients during the intervention process and completing the questionnaires could have affected the patients' response to treatment, which is one of the limitations of the present study.

5.1. Conclusions

According to the results of this study, comparing a combined mouthwash solution containing various drugs and a dilute solution of licorice root extract as a plant com-

pound, no differences were observed in the effectiveness of the two mouthwash solutions in terms of the incidence and severity of mucositis in cancer patients undergoing chemotherapy.

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Footnotes

Ethical Considerations: The study received ethical approval (IR.AJUMS.REC.1396.942).

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