JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2023; 7: 589-600
https://doi.org/10.30621/jbachs.1072283
RESEARCH ARTICLE

THE EFFECT OF HONEY THERAPY ON THE MANAGEMENT OF ORAL MUCOSITES IN HEAD AND NECK CANCER PATIENTS WITH CHEMORADIOTHERAPY: A RANDOMIZED CONTROLLED STUDY

Özlem Uğur[1], Ezgi Karadağ[1], Oğuz Çetinayak[2], Volkan Semiz[2], Fadime Akman[2]

[1] Dokuz Eylül University Faculty of Nursing, Department of Oncology Nursing, İzmir, Turkey
[2] Dokuz Eylül University Faculty of Medicine, Department of Medical Sciences Radiation Oncology, İzmir, Turkey

ORCID: Ö.U. 0000-0002-1020-9962; E.K. 0000-0002-0629-3700; O.Ç. 0000-0002-8823-8341; V.S. 0000-0003-0283-1599; F.A. 0000-0001-6260-0165

Corresponding author: Özlem Uğur, **E-mail:** ozlem.ugur@deu.edu.tr
Received: 13.05.2022; **Accepted:** 29.03.2023; **Available Online Date:** 31.05.2023

Cite this article as: Uğur Ö, Karadağ E, Çetinayak O, Semiz V, Akman F. The Effect of Honey Therapy on the Management of Oral Mucosites in Head and Neck Cancer Patients with Chemoradiotherapy: A Randomized Controlled Study. J Basic Clin Health Sci 2023; 7: 589-600.

ABSTRACT

Purpose: The aim of our study is to examine the effect of honey treatment on oral mucositis management in patients with head and neck cancer receiving radiotherapy.
Material and Methods: The study was planned as a randomized controlled, single-blind, parallel group study. The study was conducted on 32 patients with 16 patients in each parallel group. Five data collection tools were used to collect the research data. Patient Identification Form , Researcher Mucositis Index, VAS- Pain, Honey Management Monitoring Chart (given to the patients in the treatment group). Oral Care Management Follow-up Form (given to the patients in the control group).
Results: The number of days with mucositis was similar in both parallel groups (Honey Group/Mean±SD: 14.88 ± 7.36, Bicarbonate Group / Mean ± SD: 14.38 ± 6.33). The average score of mucositis and score of pain between the groups is not statistically significant.
Conclusion: Honey application has not been found to be superior to bicarbonate mouthwash on the development and staging of oral mucositis.

Keywords: head and neck cancer , treatment – ınduced mucositis, pain and change in taste, honey

INTRODUCTION

Although head and neck cancers are not among the most important cancers in terms of epidemiological data, they are one of the complicated types of cancer that cause limitations in the daily lives of the patients depending on the disease process and the methods used in its treatment and negatively affect the quality of life (1). Head and Neck cancers were the seventh most common cancer worldwide, with approximately 930,000 new cases and 467,000 deaths annually, according to 2020 data from the GLOBOCAN study. Head and neck cancers are detected approximately three times more frequently in men than in women. The age-standardized incidence rates of head and neck cancers are 15.9 per 100,000 in men globally; it is 4.8 per hundred thousand in women (2). In our

Table 1. Baseline Characteristics at pretest between intervention and control groups

	Experiment: Honey (n=16)	**Control: Bicarbonate (n=16)**	**χ^2**	**P**
Age groups			3.529	0.060
45 years and under	5 (31.3)	1 (6.3)		
45 years and older	11 (68.8)	15 (93.8)		
Gender			1.689	0.194
Women	5 (31.3)	2 (12.5)		
Male	11 (68.8)	14 (87.5)		
Education level			0.613	0.736
Primary school	4 (25)	6 (37.5)		
Secondary School	8 (50)	7 (43.8)		
School / Faculty	4 (25)	3 (18.8)		
Body Mass Index (BMI)			2.032	0.154
18,5-24,9	9 (56.3)	5 (31.3)		
25 ve older	7 (43.8)	11 (68.8)		
Tumor area			3.639	0.162
Oral cavity	5 (31.3)	3 (18.8)		
Naso-oro-hypopharynx	10 (62.5)	8 (50)		
Larenx	1 (6.3)	5 (31.3)		
TNM phase			11.265	0.187
PT3N1	1 (6.3)	2 (12.5)		
T3N3AMx	3 (18.8)	3 (18.8)		
PT2N1	4 (25)	2 (12.5)		
T1N3M0	1 (6.3)	4 (25)		
Recurrence	0 (0)	1 (6.3)		
T2N2M0	3 (18.8)	0 (0)		
T1N0M0	1 (6.3)	0 (0)		
T1N2M0	0 (0)	1 (6.3)		
T4N1M0	3 (18.8)	3 (18.8)		
Systemic disease			1.412	0.235
Yes	3 (18.8)	6 (37.5)		
No	13 (81.3)	10 (62.5)		
Systemic disease classification			0.000	1.000
Hypertension	2 (12.5)	2 (12.5)		
COPD	2 (12.5)	2 (12.5)		
Diabetes Mellitus			7.863	**0.001***
Yes	0 (0)	5 (31.3)		
No	16 (100)	11 (68.8)		
The presence of a prosthesis			0.000	1.000
Yes	1 (6.3)	1 (6.3)		
No	15 (93.8)	15 (93.8)		
Smoking			0.000	1.000
Uses	3 (18.8)	3 (18.8)		
Not using	13 (81.3)	13 (81.3)		
Alcohol use			0.834	0.361
Uses	4 (25)	2 (12.5)		
Not using	12 (75)	14 (87.5)		
Dry mouth			0.000	1.000
Uses	6 (37.5)	6 (37.5)		
Not using	10 (62.5)	10 (62.5)		
Decreased taste			6.578	**0.010***
Uses	1 (6.3)	7 (43.8)		
Not using	15 (93.8)	9 (56.3)		

Table 1. Continue

Nutritional support			0.000	1.000
Uses	3 (18.8)	3 (18.8)		
Not using	13 (81.3)	13 (81.3)		
Fluid consumption			0.238	0.625
1000 -2000ml	2 (12.5)	3 (18.8)		
More than 2000 ml	14 (87.5)	13 (81.3)		
	Mean±SS	**Mean±SS**	**Z**	**P**
Age	55.38 ± 15.75	59.06 ± 9.57	-1.095	0.287
BMI	24.31 ± 4.22	27.5 ± 4.47	-1.929	0.056
Daily radiation dose	2.04 ± 0.05	2.06 ± 0.05	-1.046	0.381
Total radiation Dose	67.38 ± 3.77	65.06 ± 4.3	-1.529	0.149
Peformance point	87.5 ± 4.47	89.38 ± 4.43	-1.153	0.423

age-standardized incidence rates of head and neck cancers are 14.7 per hundred thousand in men; in women, it was found to be 3.1 per hundred thousand (3).

Patients receive radiation therapy involving the head and neck region for six weeks, thus the mucous membranes in mouth are affected. As oral, pharyngeal and laryngeal mucosa are exposed to ionizing radiation, in the second or third week, ulceration occurs in the epithelial tissue, oral mucosa swells, mouth-throat area aches and dries. Its incidence among patients receiving chemotherapy and radiotherapy reaches 80%.5 50% of the patients who receive radiotherapy treatment to the head and neck area experience 3rd stage mucositis (4-5).

Ulcers caused by damage to the oral mucosa pose a serious risk for bacterial contamination and systemic infection (6). It is very painful, makes speech difficult, affects chewing, swallowing, and oral intake of medicines. Additionally, oral mucositis increases the patient's hospital stay, treatment costs, use of narcotics to control pain, and parenteral nutrition as well, while worsening the quality of life of the patient. The correct management of oral mucositis means to take preventive approaches in a timely manner and to minimize the patient's distress by providing pain assessment and management (7). In addition to the granulocyte monocyte colony stimulating factor, topical corticosteroids used in mucositis management, honey is reported to be an effective approach to prevent oral mucositis (6, 8-12). Honey has been used since the Egyptian civilization, it is used in modern medicine for burn wounds, oral infections and surgical wound healing. It has antibacterial properties and accelerates the wound healing by increasing epithelization (5). The reason for using honey to manage radiation mucositis is its rapid epithelization effect in tissue injuries (5-6,13). The use of honey to manage radiation mucositis is its rapid epithelializing effect in tissue injuries. Bergman et al. he observed accelerated wound healing when unboiled honey was applied topically and theorized that this effect might be due to its energy generating properties, hygroscopic effect on the wound and bacteriostatic effect. There are studies in the literature stating that honey does not prevent mucositis, but reduces the severity of mucositis (8, 14-15). In a meta-analysis study, it is stated that it reduces the development of mucositis by 80% (8). Therefore, the aim of this study is to investigate the effect of honey therapy on oral mucositis management in patients with head and neck cancer receiving radiotherapy.

Study hypotheses

This trial was designed to test the following hypotheses:

1. Regular oral care with a standard oral care protocol (oral care solution with sodium bicarbonate) influences the healing of oral mucositis in patients with head and neck cancer receiving radiotherapy treatment.
2. Honey administration influences healing of oral mucositis in patients with head and neck cancer receiving radiotherapy treatment.

MATERIAL AND METHODS

Study Design

The study was conducted as a randomized single-blind parallel group study in patients with head and neck cancer.

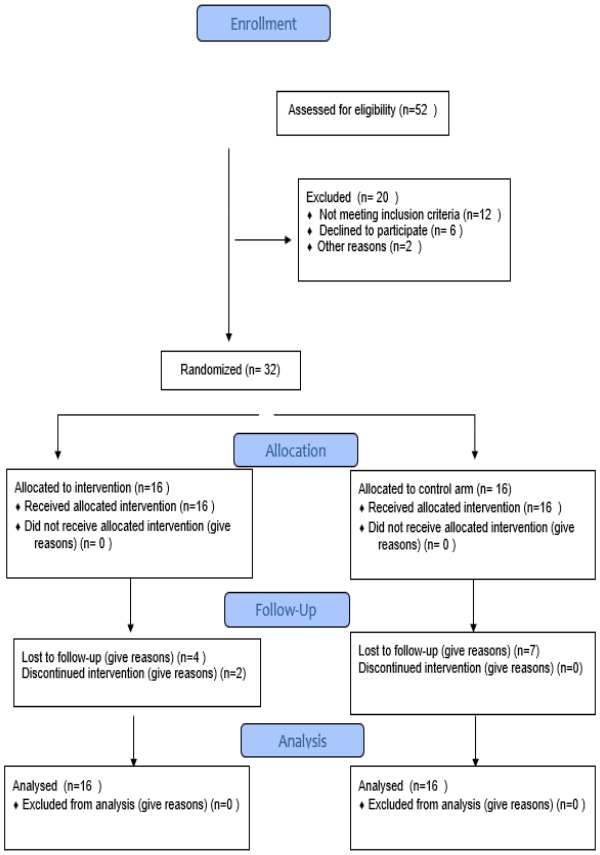

Figure 1. The flow Consort 2010 diagram of the study

Setting

The research was conducted a University Radiation Oncology Outpatient Clinic between February 2018 and March 2020. Head and neck cancer patients received radiation therapy at the clinic throughout the week except for Saturdays and Sundays, and their controls continued since the beginning of the treatment and throughout the process.

Recruiting, Randomisation and Masking

Patients were recruited by the consultants in radiation oncology based on predetermined inclusion and exclusion criteria. The patients included in the study were randomized by considering gender, age, smoking, primary tumor area, general health and radiotherapy dose, number of chemotherapy cycles (16-18). Consultants also obtained the informed consent by the eligible patients. The patients were randomised from the beginning of the treatment to either the intervention or the control arm by implementing simple randomisation using the envelope method. Based on this method, a pack of sealed envelopes including a card with either the word 'intervention arm' or 'control arm' written inside, was given to each patient after the agreement to participate to the study. Depending on which card was selected by the patients, they were allocated to the respective arm. He cares providers and those assessing outcomes were unaware of which arm the patient belonged to. In the study, it was planned to include 70 patients, 35 patients in each group, who met the selection criteria to reach 80% sampling power at a significance level of 5%.

Sample Size

Sample size calculation was performed by using G Power package version 3.1. A sample size of 32 (16 participants in each arm) was sufficient to identify an effect size of Cohen d= 1 with a statistical power 80% and 5% level of statistical significance (7-8). Data were collected over a 24-month period (February 2018 and March 2020).

Participants (Inclusion and Exclusion Criteria)

Selection criteria: Voluntary patients with head and neck cancer who had radical and/or adjuvant chemoradiotherapy indication, who were aged over 18, who were communicable, who had malignancy on oral cavity, pharynx (nasopharynx, oropharynx, hypopharynx) and larynx, who had TNM staging T 1-2 other than glottic laryngeal cancer, who had no hypersensitivity to bicarbonate oral care solution and honey, who had a Karnofsky performance scale of 70 and above, 22 who had a directly visible oral/oropharyngeal area in the area where the radiation is received (soft palate, tongue and mouth floor), who had normal liver and kidney functions, who had normal haematological values (hemoglobin>10 g/dl, thrombocyte>100.000mm3, leukocyte>3000 mm3), and who were mentally competent were selected to participate in the study (6).

Exclusion criteria: Patients with conditions such as unhealed wound in the oral cavity and oropharynx, sensitivity and poor oral hygiene, early stage glottic laryngeal cancer (T1-2), previously receiving chemotherapy or radiotherapy for upper respiratory tract, fasting blood glucose>150mg/dl, comorbidity such as diabetes or connective tissue diseases, were excluded from the sample (6, 18).

Intervention and Procedures

In the study, patients in the treatment group used honey; patients in the control group used sodium bicarbonate. All patients included in the study were

Table 2. Seven (7) weeks compared between groups of received measurements mucositis

	Experiment: Honey (n=16)	**Control: Bicarbonate (n=16)**	**χ^2**	**P**
Week - 1			1.588	0.452
No mucositis	13 (81.3)	13 (81.3)		
Painless ulcers, mild pain	2 (12.5)	3 (18.7)		
Edema, ulcers, can eat	1 (6.2)	0 (0)		
Week - 2			0.431	0.806
No mucositis	9 (56.3)	9 (56.3)		
Painless ulcers, mild pain	6 (37.5)	5 (31.3)		
Edema, ulcers, can eat	1 (6.2)	2 (12.4)		
Week - 3			9.874	**0.020***
No mucositis	1 (6.3)	8 (50)		
Painless ulcers, mild pain	10 (62.5)	4 (25)		
Edema, ulcers, can eat	4 (25)	2 (12.5)		
Erythema, edema, ulcers cannot eat	1 (6.2)	2 (12.5)		
Week - 4			0.840	0.840
No mucositis	3 (18.8)	5 (31.3)		
Painless ulcers, mild pain	7 (43.8)	5 (31.3)		
Edema, ulcers, can eat	4 (25)	4 (25)		
Erythema, edema, ulcers cannot eat	2 (12.4)	2 (12.4)		
Week - 5			3.430	0.330
No mucositis	2 (12.5)	5 (31.3)		
Painless ulcers, mild pain	4 (25)	6 (37.5)		
Edema, ulcers, can eat	8 (50)	4 (25)		
Erythema, edema, ulcers cannot eat	2 (12.5)	1 (6.2)		
Week - 6			2.076	0.557
No mucositis	4 (25)	6 (37.5)		
Painless ulcers, mild pain	3 (18.8)	5 (31.3)		
Edema, ulcers, can eat	7 (43.8)	4 (25)		
Erythema, edema, ulcers cannot eat	2 (12.4)	1 (6.2)		
Week - 7			1.322	0.516
No mucositis	4 (25)	7 (43.8)		
Painless ulcers, mild pain	6 (37.5)	5 (31.2)		
Edema, ulcers, can eat	6 (37.5)	4 (25.0)		
	Mean±SS	**Mean±SS**	**Z**	**P**
Number of days with mucositis	14.88 ± 7.36	14.38 ± 6.63	-0.133	0.894

* Significant at the 0.05 level; Likelihood ratio test.

instructed to rinse with mouthwash solutions recommended by the clinic for 1 minute, 4 times a day, every 6 hours (4x1), after each meal. In both groups, detailed information was given on adequate fluid intake, high protein dietary intake, avoidance of alcohol, spicy and acidic foods, and the importance of oral care. In parallel groups in the study, patients were admitted at the same time, the patient selection was planned appropriately and randomly assigned to the groups. Since the study is a single blind study, the nurse who evaluated the mucositis did not have information about which group the patient was in. Patients in the control group were instructed to perform oral care with 20 ml of bicarbonate oral care solution given in addition to the mouthwash solutions recommended by the clinic before and after the treatment and before going to bed. The patients in the treatment group receiving honey therapy received 20 ml honey for using it 15 minutes before and after radiotherapy treatment and 6 hours (before going to bed at night) to sweep the entire oropharyngel mucosa for an average of 2 minutes and swallow slowly (Biswal et al., protocol).

This practice was continued as long as radiotherapy continued (6-7 weeks) (5-6, 18, 20). At other times, it was reminded to continue oral care with the oral care solution recommended by the clinic. It was explained in detail to the person that the oral care with honey

Table 3. Comparison of pain, taste and weight change mucositis measurements within and between groups

	Experiment: Honey (n=16)		Control: Bicarbonate (n=16)		Comparison between groups	
	Mean±SS	**Median (%25-%75)**	**Mean±SS**	**Median (%25-%75)**	**Z**	**P**
Pain						
Week - 1	1.44 ± 2.22	1 (0 -1.5)	0.5 ± 1.1	0 (0 -0,5)	-1,728	0,128
Week - 2	2.06 ± 1.95	2 (0 -3)	0.38 ± 0.72	0 (0 -0,5)	-2,880	**0,007***
Week - 3	2 ± 1.63	2 (1 -3)	1.25 ± 1.34	1 (0 -2)	-1,318	0,210
Week - 4	2.25 ± 1.88	3 (0 -4)	1.63 ± 2.03	0,5 (0 -3)	-1,060	0,323
Week - 5	2.63 ± 2.03	3.5 (0 -4)	1.5 ± 2.13	0 (0 -3)	-1,685	0,110
Week - 6	2.69 ± 2.6	3 (0 -4.5)	1.44 ± 1.79	1 (0 -2,5)	-1,381	0,184
Week - 7	2.69 ± 2.36	2 (1 -4)	1.31 ± 1.78	0,5 (0 -2)	-1,938	0,061
Intragroup comparison	χ^2=10.587. P=0.102		χ^2=12.923. P=**0.044***			
Taste						
Week - 1	1.63 ± 1.45	1 (1 -1)	1.25 ± 0.58	1 (1 -1)	-0,221	0,897
Week - 2	1.88 ± 1.36	1 (1 -2)	2.06 ± 1.06	2 (1 -3)	-0,908	0,402
Week - 3	3 ± 1.46	3 (1.5 -4)	2.69 ± 1.54	2,5 (1 -4)	-0,599	0,564
Week - 4	3.31 ± 1.35	3.5 (3 -4)	3.06 ± 1.44	3 (2 -4)	-0,484	0,642
Week - 5	3.69 ± 1.35	4 (3 -5)	3.19 ± 1.52	3,5 (2 -4,5)	-0,913	0,381
Week - 6	3.44 ± 1.31	3.5 (3 -4.5)	3 ± 1.63	3 (1 -4,5)	-0,697	0,515
Week - 7	3.13 ± 1.15	3 (3 -4)	2.5 ± 1.46	2,5 (1 -3,5)	-1,332	0,210
Intragroup comparison	χ^2=36.389. P=0.001		χ^2=35.685. P=0.001			
Weight change						
Before treatment	70.94 ± 13.39		80.19 ± 14.94		-1.644	
After treatment	66.56 ± 12.88		75.56 ± 13.97		-1.622	
Intragroup comparison	Z: -3.550. p: 0.001*		Z: -3.530. p: 0.001*			

* Significant at the 0.05 level; Comparison between groups Mann Whitney u test. Intragroup comparison Wilcoxon test, SS: Standard deviation.

should be applied only on the days of radiotherapy and continued for 6-7 weeks during the treatment.

Questionnaire description

The data in the study were collected by five data total tools, including Patient Identification Form, Researcher Mucositis Index, VAS- Pain, Honey Management Monitoring Chart (given to the patients in the treatment group), Oral Care Management Follow-up Form (given to the patients in the control group).

Patient Identification Form; prepared based on literature includes the sociodemographic data of the patient and the data related to the patient's health diagnosis (The patient's diagnosis, systemic diseases, oral prosthesis, decayed teeth, periodontal diseases, regular tooth brushing habits, regular oral examination habits, dry mouth and taste. condition, oral hygiene status, daily fluid consumption) (5-6).

Karnofsky Performance Scale; is used to evaluate the general well-being of cancer patients. The condition of the individual is evaluated between 0-100 points. A score of 100 indicates very good health and a score of 0 indicates death. In 1949, Dr. Joseph H. Burchenal and Dr. David A. Karnofsky designed a scale according to which individuals with score 70 or higher are considered to have sufficient functional capacity (21). Patients with Karnofsky performance score of 70 and above were included in our study. Questionnaire Form for Assessing Mucositis, Pain and Nutrition Status of the Patient; In the study, the World Health Organization's Common Toxicity Criteria (CTC) mucositis grading system was used in the evaluation of mucositis.

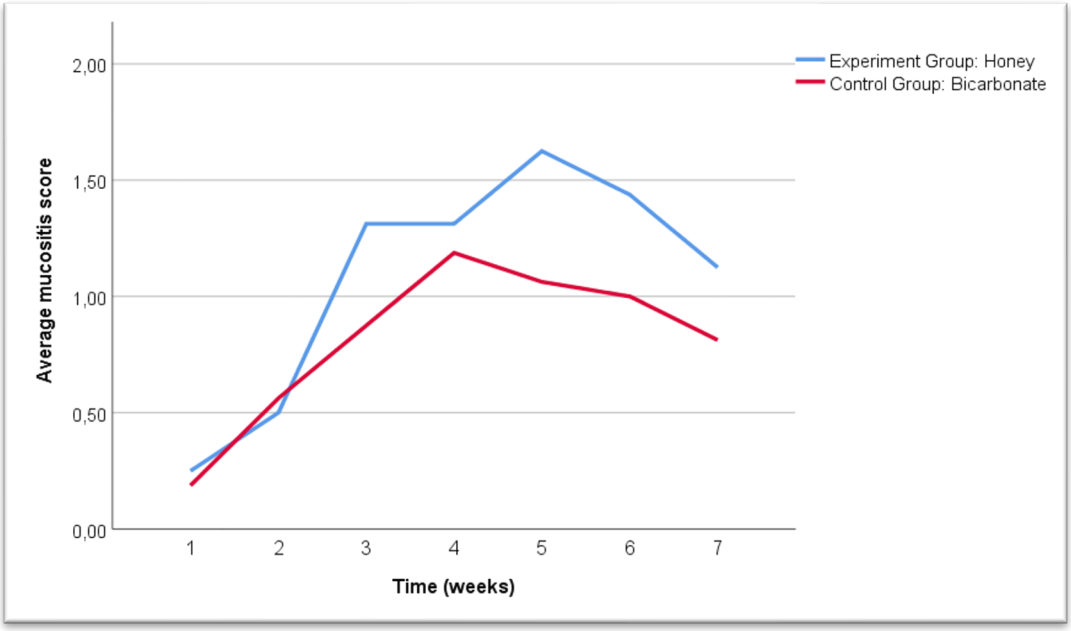

Figure 2. Line graph for variation of mean Mucositis score over time and groups

The scale, measurements wereas follows: 0 indicated no mucositis, 1 slight degree of mucositis, 2 moderate degree of mucositis, 3–4 indicated severe mucositis. WHO MAIis widely used at clinics for cancer patients to assess the degree of mucositis. Evaluation of the oral mucosa was performed by the investigator once a week, usually on Thursdays, when the patient came to the radiotherapy session. Since the total treatment period of patients was 6-7 weeks, a total of 7 measurement values were obtained for one patient. In case of intolerable mucositis, the number of days in which treatment could not be received was calculated. In addition, the pain in the mouth due to the formation of mucositis was evaluated with a visual analogue scale between 0 and 10, and the taste status was evaluated between 0 and 5. Pain was evaluated as 0: No pain, 1-3: Mild pain, 4-6: Moderate pain, 7-10: Severe pain; the taste perception was evaluated as 1: Good, 2-3: Moderate, 4-5: Bad (21). The nutritional status of the patients was evaluated according to the solid / liquid food intake and the use of nutritional support in the last 24 hours.

Honey Management Monitoring form was prepared to control the honey intake during the days / weeks of radiotherapy in order for the patient to perform his own monitoring. It was used only in patients in the treatment group.

Oral Care Management Follow-up Form was prepared to control the oral care application during the days / weeks of radiotherapy in order for the patient to monitor himself. It was administered to patients in both the control and treatment groups.

Quality Control of Honey

The chemical composition, pH, density and viscosity analysis of the honey to be used in the treatment of the patients were examined and assistance was received from Ege University Drug Development and Pharmacokinetics Research Application Center Research Clinic for chemical analysis. Before the study, it was planned to conduct aerobic cultures and candida colonization tests from the areas where infection was detected to examine the anti-microbial effect of honey on the oral mucosa of the patients, but no infected oral mucosa was encountered during the research process.

Application of Data Collection Tools

The data were collected face to face by the researchers. The researchers evaluated the patient's mouth in terms of oral mucosal tissue, color and moistness, formation of mucositis signals, pain in the oral mucosa, sense of taste and nutritional status.

Data Analysis

Compliance of numerical data with normal distribution was evaluated using the Shaphiro Wilk test. Mann Whitney U test was used to evaluate non-normally

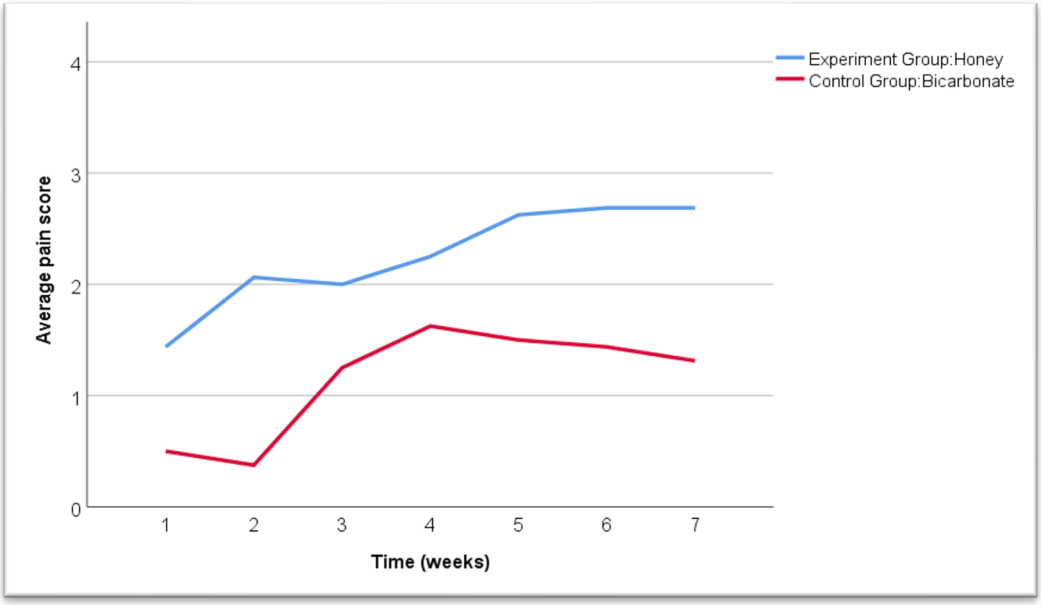

Figure 3. Line graph for the variation of the average Pain score over time and groups

distributed variables, and Freidman and Dunn multiple comparison tests were used to evaluate changes at 7 different times. Mean±standard deviation values were given for numerical variables, numbers and percentages were given for categorical variables. SPSS windows version 24 was used in the analyzes and a p value less than 0.05 was considered significant.

Ethical Considerations

During the planning of the study, necessary permissions were obtained from a Dokuz Eylul University Research and Application Hospital, and Department of Radiation Oncology where the study was carried out. The study was approved by Dokuz Eylul University, Clinical Research Ethics Committee (Date: 28.12.2017, Decision No: 2017/22-03). Written and verbal consent of the individuals included in the study was taken.

RESULTS

The sample was consisted of 26 men and 7 women with an age range from 32 to 87 years. Patients were diagnosed with various types of cancer in head and neck region including laryngeal, nasopharyngeal, hypopharyngeal, oral cavity. No statistically significant difference in relation to the cancer type of individuals in both arms was found. The 32 patients were randomized equally in the two arms (Fig. 1). Diabetes Mellitus was found in 27 patients in the study. Of the patients who meet the selection criteria, 26 interventions and 11 are used in the control group. Table 1 showed the good randomization between the two arms regarding clinical and demografic charecteristics of the partipicipants. A significant difference was observed between the experimental and control groups in terms of the presence of diabetes and decreased taste. In the control group, both the frequency of patients with diabetes and the frequency of patients with decreased sense of taste were found to be significantly higher. The groups show a balanced distribution in terms of other variables. When compared numerically, no significant difference was found between groups in terms of age and BMI. The daily, total radiation dose and performance scores were similar in the groups.

Except for the mucositis measurement taken at the 3rd week, there was no significant difference between the groups. No significant difference was observed between the groups in terms of the number of days with mucositis (Table 2).

While the pain measurements obtained in the second week were significantly higher in the experimental group (P = 0.007), there was no significant difference in the measurements in the other weeks and in the weekly measurements within the group. It was found that taste measurements increased as time progressed, but there was no significant difference between the groups in terms of measurements. Significant reduction in weight was observed in both

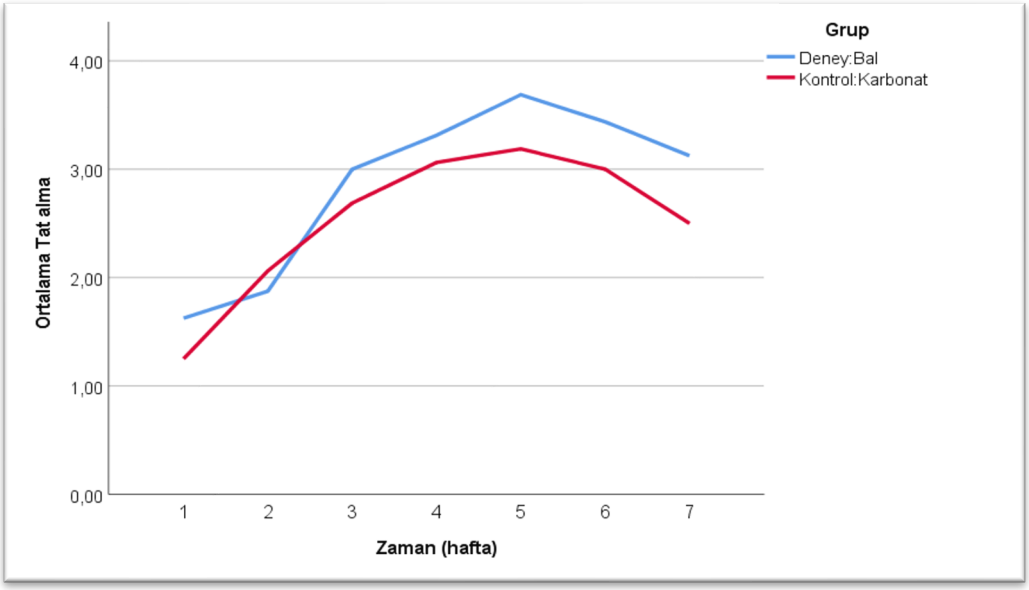

Figure 3. Line graph for the variation of the average Taste Score over time and groups

experimental and control groups after treatment. However, there was no significant difference between the groups before and after the treatment. This shows that the weight change is similar between the 2 groups (Table 3).

Below average mucositis, line charts for the change in pain score and take time to enjoy and groups are given.

- The average score of mucositis between the groups is not statistically significant (p> 0.05, Figure 2).
- The average pain score between the groups is not statistically significant (p> 0.05, Figure 3)
- The average taste score between the groups is not statistically significant (p> 0.05, Figure 4)

DISCUSSION

In our study we planned to evaluate the effect of honey on the healing process of oral mucositis due to radiation; the use of honey in oral care for oral mucositis management was not found superior to bicarbonate. In this context, the H1 hypothesis, which is one of our research hypotheses, "Regular oral care with a standard oral care protocol (oral care solution with sodium bicarbonate) has an effect on the healing of oral mucositis in patients with head and neck cancer receiving radiotherapy treatment." is accepted. There are studies in the literature with similar results (22-25). In MASCC / ISOO guidelines, patients are recommended to use a soft toothbrush as well as mouthwash with sodium bicarbonate and saline in oral care (25). In clinical practice, 0.9% saline solution, sodium bicarbonate and saline + sodium bicarbonate mixture (1 teaspoon of salt and 1 teaspoon of sodium bicarbonate in a glass of boiled cooled water) are cheap and easy-to-reach agents, so their use is recommended in oral care protocols (26). Maintaining good and regular oral hygiene is one of the main factors in reducing the reaction and severity of radiation on the mucosa (27). However, our result is not compatible with other studies that found the use of honey effective in the management of mucositis in patients with head and neck cancer, similar to our study (6-10, 14-15). This may be due to the small number of patients included in the study sample. Concordantly, one of our research hypotheses, H2 hypothesis, “Honey administration has an effect on healing of oral mucositis in patients with head and neck cancer receiving radiotherapy treatment.” is reject. In addition, the number of days with mucositis was similar in both groups, and the use of honey had no effect on the number of days with mucositis. However, in the study of Bulut & Tüfekçi (2016), it is stated that the use of oral care and honey together shortens the healing time of mucositis and reduces pain. In this context, the result of the study is incompatible with the literature (11).

The formation of oral mucositis may be affected by some variables. Age of the patient, poor oral hygiene, gender differences, genetic factors, alcohol & tobacco

use, renal and hepatic dysfunctions, oral care habits, body mass index, location of the tumor, hematological status, treatment plan and type, high dose chemotherapy and total body irradiation, dose and duration of treatment are among the factors affect the development of oral mucositis (9-10, 14). Factors that pose a risk and increase the susceptibility to bacterial colonization such as the patient's current oral conditions, dental caries, periodantal changes, pulpitis and xerostomia should be eliminated from the patient as much as possible during the treatment process (27). In our study, it was found that both groups showed a balanced distribution with regards to the above-mentioned variables. When compared numerically, there was no significant difference between the groups regarding age and BMI and the total daily radiation dose and performance scores were similar in the groups. In addition, it was observed that there was no significant difference in weight between the groups before and after the treatment, but a significant weight loss was experienced in both groups after the treatment. This shows that individuals receiving radiation therapy to the head and neck region should focus on the individuality and integrity of care. In the literature, malnutrition prevalence is observed in 44-88% of patients with head and neck cancer; It is stated that the eating problems that occur negatively affect the physical, psychological, social and existential structure of the person, and the importance of starting additional nutritional supplements and informing the patient and family on this issue is emphasized (28-29). It is included in the variables in which the difference was observed between the experimental and control groups in our study. In the control group, the frequency of patients with both diabetes and decreased sense of taste was found to be significantly higher. This may be due to the fact that patients with diabetes were included in the control group. At the same time, one of the long-term complications of diabetes is neuropathy. Besides, one of the long-term complications of diabetes is the development of neuropathies. Neuropathies in the nerves that transmit the sense of taste can cause taste disturbance in diabetic patients. In addition to diabetes, additional radiation therapy can cause salivary gland dysfunction and xerostomia, resulting in taste disturbance (30). In this context, it is important to carefully diagnose diabetic individuals who will receive radiation therapy to the head and neck region in terms of taste changes, loss of appetite (or anorexia) and weight loss, and management of this. In the current study, it was found that the analgesic use of the individuals in the treatment group and the pain measurements obtained in the second time measurement were significantly higher than the control group. However, since the groups are distributed in a balanced way in terms of variables, the exact reason for this is not known, and thought that it may be due to individual differences. According to literature, reasons such as decreased salivary secretion, decreased but concentrated salivary secretion, dry mouth and mucositis, decreased pharyngeal flexibility and peristalsis in patients with head and neck cancer who receive chemoradiotherapy trigger pain when swallowing and bring along increased use of analgesics (31). In this case, patients should be followed up in terms of late complications while the treatment process continues and in the following period. In our study, when the pain levels in all time intervals were checked, the differences occurred in the treatment and control groups at the same place at the 2nd and the 5th time. A borderline significance was also detected in the control group. Changes in these time intervals may occur due to the reason mentioned above. Oral mucositis usually begins in the second week of treatment in patients receiving radiotherapy. Chemotherapy combined with radiotherapy increases the release of nuclear factor -kB (NF-kB) known as pro-inflammatory responsible for mucosal toxicity. This causes the activation of tumor necrotic factor, interleukin 6, interleukin-beta, leading to destruction in the endothelial layer and connective tissue and disrupting of mucosal integrity. At the same time, the molecular pathway activates exacerbating mucosal destruction and ulcerations. Mucositis continues in a few weeks after the end of radiotherapy (26,31). This physiological process explains the cause of pain occurring in the 2nd and 5th time periods in both groups in our study. Kong et al. (2016) found that the use of honey delayed the onset of mucositis and decreased the pain score (22). However, no similar result could be reached in our study. The number of days with mucositis was similar in both groups and the use of honey did not have a significant effect on the number of days with mucositis.

Limitations of the Study

The limitation of the study is that it was conducted in a single hospital.

CONCLUSION

In our study, the use of honey was not found superior to the use of bicarbonate in head and neck cancer patients receiving radiotherapy in terms of the prevalence of mucositis and the grading of mucositis. In future studies, it may be suggested to increase the sample size and to conduct the study in a multi-centered manner.

Acknowledgement: The authors thank all participants.
Author contributions: Concept: Ö.U, F.A., Design: Ö.U., E.K., O.Ç., Data Collection: Ö.U., E.K., O.Ç., V.S.,
Analysis and/or interpretation: Ö.U, Literature Search: Ö.U., E.K., Writting: Ö.U, E.K, Critical Review: Ö.U, F.A.
Conflict of interests: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.
Ethical approval: The study was approved by Dokuz Eylul University, Clinical Research Ethics Committee (Date: 28.12.2017, Decision No: 2017/22-03).
Funding: Study was funded by Dokuz Eylul University Scientific Research Projects Coordination Unit (No: 2018.KB.SAG.052).
Peer-review: Externally peer-reviewed.

REFERENCES

1. Çıtlak K., Kapucu S. Kemoterapi ve Radyoterapi Uygulanan Baş- Boyun Kanserli Hastalarda Mukozit Yönetimine Yönelik Kullanılan Oral Ajanların Retrospektif Olarak İncelenmesi. Hacettepe Üniversitesi Hemşirelik Fakültesi Dergisi 2017; 4(1):15-27.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Coun tries. CA Cancer J Clin 2021;71(3):209- 249.
3. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. [Accessed date: 04 August 2021]. Available from: https://gco.iarc.fr/today.
4. Ardakani TM, Ghassemi S, Mehdizadeh M, et al. Evaluating the effect of Matricaria recutita and Mentha piperita herbal mouthwash on management of oral mucositis in patients undergoing hematopoietic stem cell transplantation: A randomized, double blind, placebo controlled clinical trial. Complement Ther Med 2016; (29):29-34.
5. Yang C, Gong G, Jin E, et al. Topical application of honey in the management of chemo/radiotherapy- induced oral mucositis: A systematic review and network meta- analysis. Int J Nurs Stud 2019; 89: 80-87.
6. Kongwattanakul S, Petchann N, Petroch P, et al. Prophylactic management of radiation induced mucositis using herbal mouthwash in patients with head and neck cancer: an assessor-blinded randomized controlled trial. J Complement Integr Med 2022;19(3):771-780.
7. Chattopadhyay S, Saha A, Azam M, Mukherjee A, Sur PK. Role of oral glutamine in alleviation and prevention of radiation-induced oral mucositis: A prospective randomized study. South Asian J Cancer 2014;3(1):8-12.
8. Sahebjamee M, Mansourian A, Hajimirzamohammad M, et al. Comparative Efficacy of Aloe vera and Benzydamine Mouthwashes on Radiation-induced Oral Mucositis: A Triple-blind, Randomised, Controlled Clinical Trial. Oral Health Prev Dent 2015;13(4):309-15.
9. Akagi S, Fujiwara T, Nishida M, Okuda A, Nagao Y, Okuda T. The effectiveness of rebamipide mouthwash therapy for radiotherapy and chemoradiotherapy-induced oral mucositis in patients with head and neck cancer: a systematic review and meta-analysis. J Pharm Health Care Sci. 2019; 25:5-16.
10. Hamzah MH, Mohamad I, Musa MY, Abd Mutalib NS, Siti-Azrin AH, Wan Omar WA. Propolis mouthwash for preventing radiotherapy-induced mucositis in patients with nasopharyngeal carcinoma. Med J Malaysia 2022;77(4):462-467.
11. Bulut KH, Tüfekçi GF. Honey prevents oral mocositis in children undergoing chemotherapy: A quasi-experimental study with a control group. Complement Ther Med 2016; 29:132-140.
12. Dastan F, Ameri A, Dodge S, Hamidi Shishvan H, Pirsalehi A, Abbasinazari M. Efficacy and safety of propolis mouthwash in management of radiotherapy induced oral mucositis; A randomized, double blind clinical trial. Rep Pract Oncol Radiother 2020;25(6):969-973.
13. Manoharan V, Fareed N, Battur H, Khanagar S, Praveena J. Effectiveness of mouthrinses in prevention and treatment radiation induced mucositis: A systematic review. J Can Res Ther 2020;16:1-10.
14. Charalambous M, Raftopoulos V, Paikousis L, et al. The effect of the use of thyme honey in minimizing radiation- induced oral mucositis in head and neck cancer patients: A randomized controlled trial. Eur J Oncol Nurs 2018; 34:89- 97.

15. Xu JL, Xia R, Sun ZH, et al. Effects of honey use on the management of radio/ chemotherapy-induced mucositis: a meta- analysis of randomized controlled trials. Int. J Oral Maxillofac. Surg 2016; 45:1618– 1625.
16. Bahramnezhad F, Nayeri DN, Bassampour SS, Khajeh M, Asgari P. Honey and Radiation-Induced Stomatitis in Patients With Head and Neck Cancer, Iran Red Crescent Med J 2015; 17(10):1-7.
17. Charalambous A, Lambrinou E, Katodritis N, et al. The effectiveness of thyme honey for the management of treatment- induced xerostomia in head and neck cancer patients:A feasibility randomized control trial. Eur J Oncol Nur 2017; 27:1-8.
18. Motallebnejad M, Akram S, Moghadamnia A, Moulana Z, S. The effect of topical application of pure honey on radiation-induced mucositis: a randomized clinical trial, J Contemp Dent Pract 2008;9(3):40-7.
19. Konishi M, Verdonschot RG, Shimabukuro K, Nakamoto T, Fujita M, Kakimoto N. The effectiveness of mouthwashes in alleviating radiation-induced oral mucositis in head and neck cancer patients: a systematic review. Oral Radiol. 2019;35(3):207-223.
20. Gouvêa de Lima A, Villar RC, de Castro G Jr, et al. Oral mucositis prevention by low-level laser therapy in head-and-neck cancer patients undergoing concurrent chemoradiotherapy: a phase III randomized study. Int J Radiat Oncol Biol Phys 2012;82(1):270-5.
21. Hasheminasab FS, Hashemi SM, Dehghan A, et al. Effects of a Plantago ovata-based herbal compound in prevention and treatment of oral mucositis in patients with breast cancer receiving chemotherapy: A double-blind, randomized, controlled crossover trial. J Integr Med 2020;18(3):214-221.
22. Kong M, Hwank DS, Yoon SW, Kim J. The effect of clove-based herbal mouthwash on radiation-induced oral mucositis in patients with head and neck cancer: a single-blind randomized preliminary study. Onco Targets Ther 2016;9:4533–4538.
23. Pour-Fard-Pachekenari A, Rahmani A, Ghahramanian A, Asghari Jafarabadi M, Onyeka TC, Davoodi A. The effect of an oral care protocol and honey mouthwash on mucositis in acute myeloid leukemia patients undergoing chemotherapy: a single-blind clinical trial. Clin Oral Investig 2019;23(4):1811-1821.
24. Co LJ, Mejia BMA, Que JM, Dizon MJR. Effectiveness of honey on radiation- induced oral mucositis, time to mucositis, weight loss, and treatment interruptions among patients with head and neck malignancies: A meta-analysis and systematic review of literature. Head Neck 2015; 38(7):1119-28.
25. Jaime CS, Martínez C, García FT, et al. Efficacy of Plantago major, chlorhexidine 0.12% and sodium bicarbonate 5% solution in the treatment of oral mucositis in cancer patients with solid tumour: A feasibility randomised triple-blind phase III clinical trial, Eur J Oncol Nurs 2017; 32:40-47.
26. Karadakovan A. Mukozit. Can G, editors. Onkoloji Hemşireliğinde Kanıta Dayalı Bakım, İstanbul Konsensusu, Nobel Tıp Kitabevi, 2015; 371-383.
27. Brozozowska A, Golebıowskı P. Acute radiation-induced oral mucositis in patients subjected to radiotherapy due to head and neck cancer. Pol J Public Health 2019;129(1):27-30.
28. Bossola M. Nutritional Interventions in Head and Neck Cancer Patients Undergoing Chemoradiotherapy: A Narrative Review. Nutrients 2015; 7:265-276.
29. Uğur Ö. Kemoradyoterapi Alan Baş- Boyun Kanserli Hastaların Beslenme Durumlarının Değerlendirilmesi. İzmir Kâtip Çelebi Üniversitesi Sağlık Bilimleri Fakültesi Dergisi 2019; 4(3):83-89.
30. Kurtuldu E, Miloğlu Ö, Derindağ G, Özdoğan A. Tat Duyusu Bozukluklarına Genel Bakış. Ataürk Üniv. Diş Hek. Fak. Derg. 2018; 28(2): 277- 283.
31. Alkhouli M, Laflouf M, Alhaddad M. Efficacy of Aloe-Vera Use for Prevention of Chemotherapy-Induced Oral Mucositis in Children with Acute Lymphoblastic Leukemia: A Randomized Controlled Clinical Trial. Compr Child Adolesc Nur.s 2020; 26:1-14.