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CORRESPONDENCE

The effects of Ankaferd hemostat on preventing oral mucositis in colorectal cancer patients receiving chemotherapy

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Abstract

Introduction New agents are introduced each day to be used in the prevention and treatment of mucositis in cancer treatment. One of those agents is the Ankaferd hemostat. Ankaferd hemostat has pleiotropic effects and anti-infective characteristics in tissue healing.

Methods The study was designed as a randomized controlled experimental study. The sample of the study comprised a total of 66 patients (33 patients in the Ankaferd hemostat group and 33 patients in the sodium bicarbonate group) with colorectal cancer who received FOLFOX combination chemotherapy treatment in the first cycle of chemotherapy to prevent mucositis. Participants who met the criteria were randomly assigned to the groups. Before the patient received chemotherapy, ECOG performance score and Oral Mucositis Grading Scale were applied on the 7th day and 15th day. The Ankaferd hemostat group brushed teeth at least twice a day for 2 min and gargled with Ankaferd hemostat twice for 2 min for 2 weeks. The sodium bicarbonate group brushed teeth at least 2 min a day and gargled with sodium bicarbonate 4 times for 2 min for 2 weeks. The Consolidated Standards of Reporting Trials diagram was used to illustrate the randomization of patients.

Results When the Ankaferd hemostat group is compared with the sodium bicarbonate group, there is a significant difference in favor of the Ankaferd hemostat group in the mucositis grade on the 7th day and 15th day after chemotherapy ($p < 0.05$). In the binary logistic regression analysis, among the factors affecting the formation of mucositis on the 7th day, only neutrophil and thyroid-stimulating hormone (TSH) were included in the model, while only the TSH variable is statistically significant.

Conclusions It was determined that Ankaferd hemostat is effective in preventing oral mucositis due to chemotherapy in adult patients diagnosed with colorectal cancer. In addition, it has been suggested to conduct new studies on the effectiveness of Ankaferd hemostat in the prevention of mucositis in different groups.

Trial registration The study was registered at ClinicalTrials.gov (ID: NCT05438771, Date: 25.06.2022).

Keywords Oral mucositis · Ankaferd hemostat · Bicarbonate · Oral care · Colorectal cancer

Introduction

Colorectal cancer treatment is performed as curative surgery, radiotherapy, and chemotherapy or by performing them together. Depending on these treatments, many problems may arise and these problems may cause changes in the treatment process or interruptions in the treatment [1]. One of those problems is oral mucositis (OM). OM-associated ulcers seen in individuals receiving chemotherapy negatively impact patients' eating status, cause pain that reduces tolerance for cancer treatment [2], cause problems in the oral intake of food and medications, and lead to the risk of local and systemic infection. All these negative effects may lead to worsening of the patient's quality of life. OM due to chemotherapy begins to develop 3–5 days after drug administration and gets worse on days 7–14. It can heal spontaneously

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without any intervention in 5–10 days with the effect of the individual's immune system [3].

5-Fluorouracil (5-FU), which is used as a chemotherapeutic agent in the treatment of colorectal cancer today, can cause serious hematological and gastrointestinal symptoms [4] and toxic effects such as hand-foot syndrome as it causes myelosuppression [5]. One of these effects in the gastrointestinal system is oral mucositis. Oral mucositis development is seen at a rate of 22–73% [6] in fluorouracil-based FOLFOX (Folinic acid + Fluorouracil + Oxaliplatin) regimen protocol in which drugs are used in combination [7].

The basic principle of mucositis treatment involves protection and treatment. Approaches to the Multinational Association of Supportive Care in Cancer (MASCC) guidelines, which include evidence-based practices, are used in the protection of the mucosa [8]. The basic approach in the prevention of mucositis in cancer patients includes rearranging the diet, evaluating the oral mucosa and teeth prior to treatment, treating periodontal diseases, and educating the patient/family about daily routine oral care. Bicarbonate and saline mouthwash for standard oral care is included as an expert opinion in the MASCC 2020 guidelines. Recommended oral care includes brushing the teeth twice a day and rinsing the mouth with 0.9% saline or sodium bicarbonate. Additionally, methods such as benzydamine hydrochloride, oral glutamine, chlorhexidine gluconate, low-level laser therapy, and oral cryotherapy are used in the prevention and treatment of mucositis. New agents (such as irsogladine maleate, misoprostol) are added to these agents every day [9]. One of these new agents is Ankaferd hemostat [10].

Ankaferd hemostat (ABS; Ankaferd Blood Stopper®) is a plant-based product. Ankaferd hemostat contains standardized plant extracts comprising Alpinia officinarum, *Glycyrrhiza glabra*, *Thymus vulgaris*, *Urtica dioica*, and *Vitis vinifera* [11]. The mechanisms of action of the plants in it are similar to each other and have an impact on the endothelium, blood cells, angiogenesis, cell proliferation, vascular dynamics, apoptosis, inflammation, and mediators. It does not include any inorganic or synthetic additives. This product is licensed for external and dental use as well as post-surgical major or minor bleeding. Additionally, Ankaferd hemostat has anticancer, anti-angiogenesis, antifungal, antimicrobial antioxidant, and antimutagenic properties. During experimental or clinical topical applications, neither local nor systemic adverse effects and/or toxicities are encountered [10]. There is a limited number of studies testing the efficacy of Ankaferd hemostat in the treatment of mucositis. These studies were conducted with pediatric patients, and patients with hematological malignancies, in small groups, and Ankaferd hemostat was found to be effective in the treatment of mucositis [10, 12]. The aim of this study is to evaluate the effectiveness of the Ankaferd hemostat in the prevention of oral mucositis due to chemotherapy in adult patients diagnosed with colorectal cancer.

Material and methods

Study design

The study was designed as a randomized controlled experimental study. In sampling, a preliminary power analysis was performed based on the findings of the study conducted by Sattari et al. [13]. The patients to be assigned to the study or control group were determined with the support of a person who was independent of the study and had no knowledge of the research. This person, who had no knowledge of the research, was asked to specify a number, and in the next process, patients were assigned to the study or control group depending on whether the random number was even or odd. Study and control group patients were first evaluated in terms of inclusion criteria. The Consolidated Standards of Reporting Trials [14] diagram was used to illustrate the randomization of patients. The consort diagram was used to improve the conduct and reporting of randomized controlled trials and allowing for the inclusion of the study in future meta-analyses [15] (Fig. 1).

Inclusion Criteria of the Study

- Being between the ages of 18–75
- Having completed primary education at minimum
- Not having communication problems
- Not having mouth sores/mucositis (Mucositis grade = 0)
- Having been diagnosed with colorectal cancer
- Planned for receiving Folfox (5-Fluorouracil, oxalplatin, folinic acid) combination therapy as first-line therapy
- Not having received chemotherapy or radiotherapy with any other diagnosis before
- Accepting to participate in the study
- Having an ECOG performance of 0–2

Exclusion Criteria of the Study

- Using dentures
- Having oral herpes simplex lesion
- Smoking
- Using Glutamine Research®
- Receiving G-CSF support
- Having a physical disability that prevents using the correct tooth brushing technique

Exclusion Criteria During Research

- Requesting to withdraw from the study
- Not performing oral care in accordance with the study protocol/performing irregular oral care
- Starting G-CSF
- Inability to continue in the study due to worsening of general condition during monitoring
- Being inaccessible (Not being able to be contacted via phone, not continuing the same treatment in the same center, etc.)
- Death

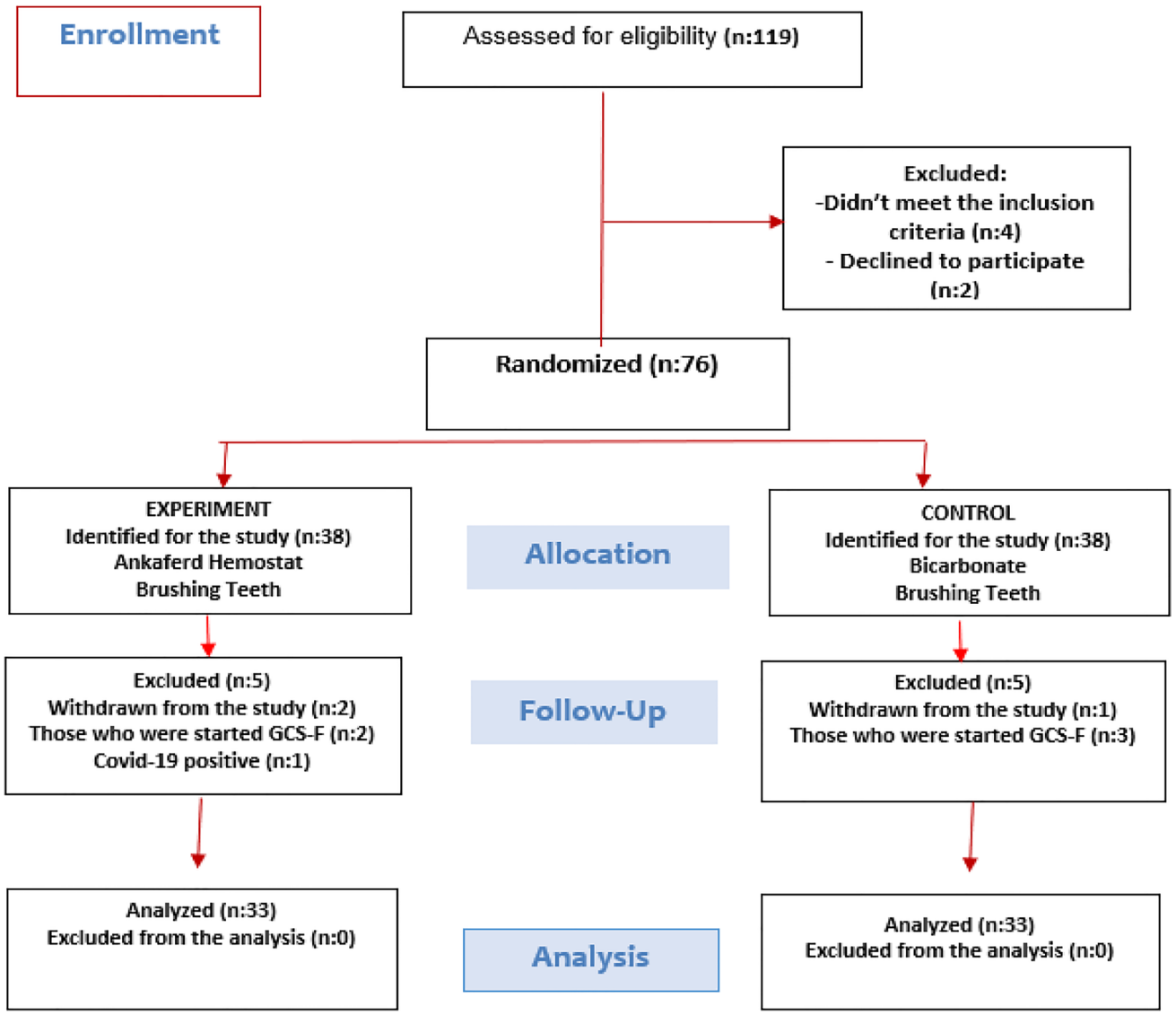

Fig. 1 CONSORT 2010 flow diagram

Study population

The population of the study consists of all patients diagnosed with colorectal cancer who received FOLFOX [16] combination chemotherapy treatment in the first cycle of chemotherapy. Sample size calculation is based on the day 7 World Health Organization (WHO) Oral Mucositis Grading Scale of the control and experimental groups. Since chemotherapy-induced oral maximum expression occurs 7–10 days after chemotherapy, patients were evaluated for mucositis on the 7th day [17]. It was calculated as $n=33$ per group and the power of the study was estimated as 0.80 and the alpha value as 0.05 for a total of 66 participants. Power analysis was performed in GPower 3.1. (http://www.gpower.hhu.de/). The patients included in the sample were divided into 2 groups (group 1: 33 patients receiving the 1st course of treatment and using sodium bicarbonate; group 2: 33 patients receiving the 1st course of treatment and using Ankaferd hemostat). Patients included in the experimental group with the approval of the physician were excluded from the routine mucositis prevention protocol of the unit.

Study procedures

The study was conducted between March 2020 and October 2021 at the outpatient chemotherapy unit of the oncology department of a university hospital in Bursa. Data were collected using a personal information form, Eastern Cooperative Oncology Group (ECOG) Performance Score, WHO Oral Mucositis Assessment Scale, laboratory findings and

body mass index (BMI), and oral care control chart. Study procedures were followed with the research follow-up plan chart (Fig. 2).

Personal information form

This form developed by the researchers as a result of a review of the literature at the beginning of the study consists of 12 questions on socio-demographic information (date of birth, gender, marital status, education level, employment status, people living with them, income level, a habit of brushing teeth, and the person responsible for care) and characteristics related to health status and habits (having other chronic diseases, smoking, and consuming alcohol) of patients both in the study and in the control group within the scope of the sample.

ECOG performance score

The ECOG Performance Scale, also known as the WHO or Zubrod performance score, was developed in 1960. 0 refers to normal health and 5 refers to death in the ECOG Performance Scale. Low scores indicate good general condition, while high scores indicate poor prognosis. "0" normal is evaluated as being able to continue pre-disease normal activities, "1" as being able to continue daily life with bearable tumor findings, "2" as having a disturbing level of tumor findings but spending more than 50% of the time up, "3" as having severe

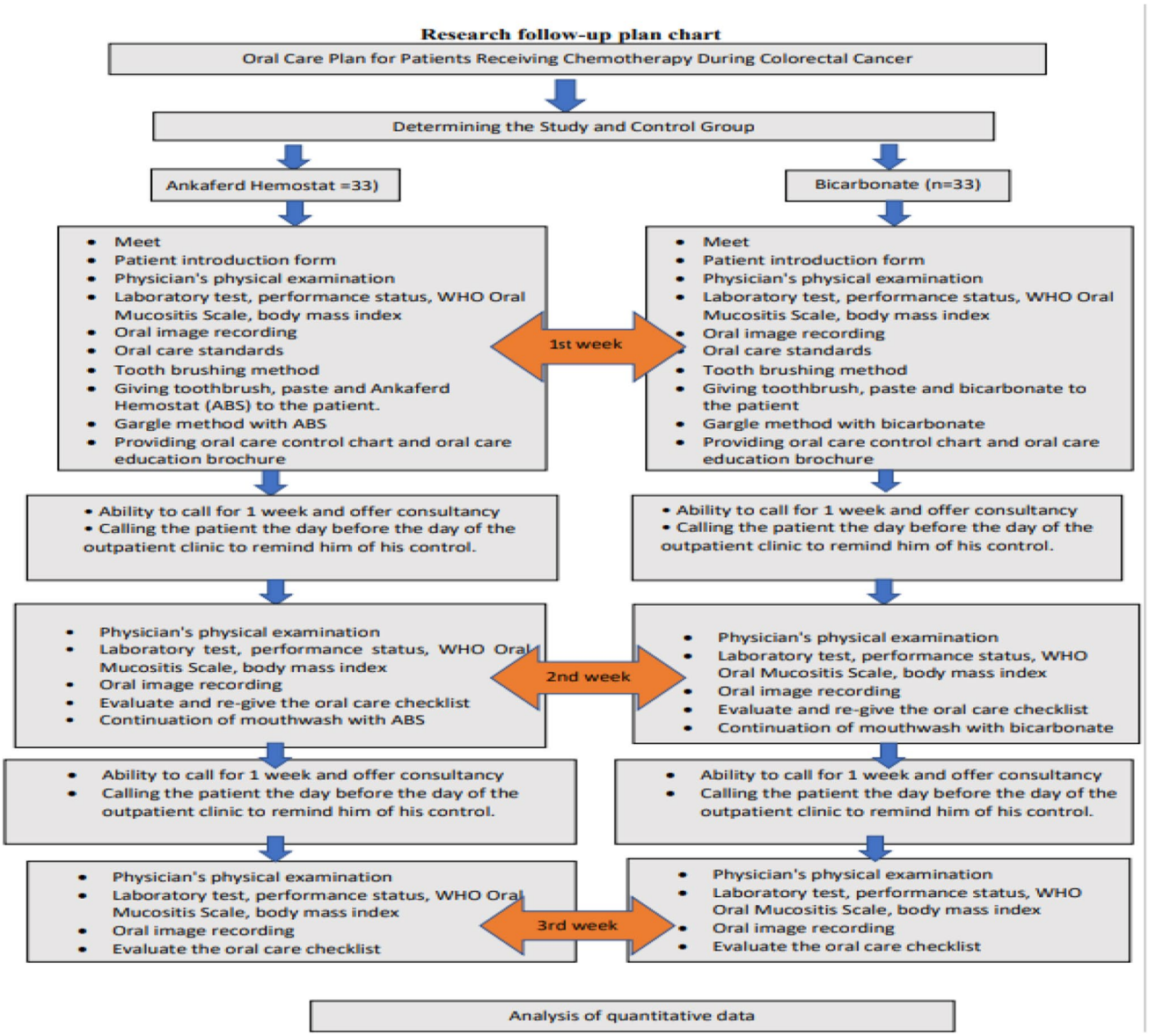

Fig. 2 Research follow-up plan chart

disturbance and being confined to bed more than 50% of the time, "4" as completely disabled and totally confined to bed, and "5" is evaluated as dead [18].

World health organization oral mucositis grading scale

This is a grading system developed by WHO according to the clinical appearance and functional status of mucositis. WHO evaluates oral mucositis (OM) as subjective (patient-described pain), objective (presence of erythema and ulcerations), and functional (ability to consume liquid/solid foods orally or inability to eat anything orally. The classification is as follows: OM grade 0 (normal), grade 1 (mild focal changes (erythematous areas) no pain and tenderness yet, can be fed orally), grade 2 (painless ulcers, erythema, mild pain sensation), grade 3 (painful erythema, edema or ulcers) (depth of > 2 mm and less than half of the mucosa) no bleeding, can only be fed orally with liquid diet), and grade 4 (erythema, edema or ulcers (more than half of the mucosa), severe pain, bleeding, no nutrition, parenteral, and enteral nutrition support may be required) [19].

Laboratory findings and body mass index

Hemoglobin (HGB), hematocrit (HCT), leukocyte (WBC), neutrophil, platelet, total protein, albumin, vitamin B12 (cobalamin), folate, and thyroid function test values were obtained from patient files. BMI was calculated by measuring current height and weight [20]. The BMI formula is [(Body weight kg) / (Height m)^2] [21]. BMI was assessed at the first interview, on the 7th day and 15th day.

Oral care control chart

This form was developed by the researchers to ensure patients' oral care intervals, that tooth brushing and mouthwash are done, and to prevent them from being forgotten. The form was used to record the oral care performed by the patients in the intervention and control groups during the monitoring period. The form is a checklist filled by clicking after oral care. This form was assessed at the first interview, on the 7th day and 15th day.

Patient education

To standardize the materials patients use in oral care, all patients were provided with the same brand of toothbrush (round-headed, soft bristle) [22] and toothpaste (triclosan active ingredients 0.3%, sodium fluoride 0.32%, aqua, sorbitol, hydrated silicate, sodium lauryl sulfate, PVM/Ma copolymer, aroma, carrageenan, sodium hydroxide, sodium saccharin, CI 77891, limonen) [22, 23] that are recommended in the literature.

Patients were informed about the importance of oral hygiene. The patients were instructed to brush their teeth at least twice a day, mornings and evenings. Modified Stillman method for brushing tooth was taught. It was explained that the bristles of the brush should be placed in the apical direction, against the cervical part of the teeth, and partially against the adjacent gingiva (activation of the brush with a back-and-forth motion at least 4 times at a 45° angle, and simultaneous movement in the coronal direction [22] (from down to up, from right to left).

To evaluate the suitability of the written educational material, opinions were obtained from 9 experts in the field, 2 patients, and 1 patient relative. These individuals were asked to evaluate the educational booklet by using Demir et al.'s (2008) "Evaluating the Suitability of the Written Material" [24] form and DISCERN (Quality Criteria for Consumer Health Information) measurement tool [25, 26]. The data obtained from the evaluation of the educational material by experts were evaluated according to the Lawshe content validity ratio calculation method [27, 28] and the mean scores were determined to be 22.33 ± 0.50. As a result of expert evaluation, it was determined that the prepared educational material was suitable for its purpose (71.77 ± 4.02). The content validity ratio was calculated as 0.74 which indicates that the content validity is sufficient.

In the booklets prepared for the experimental and control groups, the preparation and usage information about the mouthwash that the group will use is given. It is recommended to prepare and use Ankaferd hemostat [12] and bicarbonate solution [29] as follows.

Experiment group: Ankaferd hemostat group

Preparation of mouthwash with Ankaferd hemostat

- 100 °C boiled and cooled water.
- Putting 4 ml of water in the 5-ml measuring cup given to the patient.
- Putting Ankaferd hemostat on the remaining 1 ml portion of the 5-ml beaker.

Making and using the mouthwash

- Use on an empty stomach 2 h before meals in the morning and at least 2 h after dinner.
- After preparing 5 ml of Ankaferd hemostat 2 times a day, he/she can gargle for 2 min and swallow the solution in his/her mouth.
- Due to solution-related discoloration in the mouth and teeth, therefore, he/she is necessary to brush his/her teeth.

Control group: sodium bicarbonate group

- Preparation of mouthwash with sodium bicarbonate.
- 100 °C boiled and cooled water.

- Putting boiled and cooled water in the supplied 100-ml measuring cup.
- Adding 6 g of sodium bicarbonate to the water.

Making and using the mouthwash

- After rinsing with 20 ml of bicarbonate mouthwash, spitting up without swallowing, 4 times a day for 2 min.

Analysis

The statistical analysis of the data was performed using IBM SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) package program. A Shapiro–Wilk test was completed to check whether the data were normally distributed. Descriptive statistics are provided as mean and standard deviation, and median (minimum–maximum) for quantitative data, and as frequency and percentage for qualitative data. A *t*-test was completed for the comparison of two groups with normally distributed data, while a Mann–Whitney *U* test was completed for the comparison of two groups with not-normally distributed data. Comparison of repeated measurements between groups was performed by calculating the percent change value (percent change = (last measurement – first measurement) / first measurement) compared to the initial measurement. Additionally, repeated measures analysis of variance

Table 1 Personal characteristics of individuals in the Ankaferd hemostat and bicarbonate group

Personal characteristics/agent		Ankaferd hemostat ($n=33$)	Bicarbonate ($n=33$)	t/χ^2	p value
Age (years) (mean ± SD)		58.15 ± 8.76	58.82 ± 10.32	−0.283	0.778
BMI (mean ± SD)		26.27 ± 4.58	26.65 ± 4.80	0.532	0.597
		n (%)	*n* (%)		
Gender	Female	14 (42.4)	15 (45.5)	0.062	0.804
	Male	19 (57.6)	18 (54.4)		
Education level (school)	Elemantary	15 (45.5)	22 (66.7)	3.379	0.348
	Secondary	6 (18.2)	5 (15.2)		
	High	8 (24.2)	4 (12.1)		
	University	4 (12.1)	2 (6.1)		
Marital status	Married	29 (87.9)	28 (84.8)	–	1.000
	Single	4 (12.1)	5 (15.2)		
Income level	High income	11 (33.3)	17 (51.5)	3.286	0.193
	Medium income	10 (30.3)	10 (30.3)		
	Low income	12 (36.4)	6 (18.2)		
Employment status	Private sector	5 (15.2)	5 (15.2)	0.331	1.000
	Public employee	4 (12.1)	3 (9.1)		
	Not working	9 (27.3)	10 (30.3)		
	Retired	15 (45.5)	15 (45.5)		
The person responsible for care	Spouse	15 (45.5)	16 (48.5)	1.564	1.000
	Brother	2 (6.1)	2 (6.1)		
	Parents	1 (3.0)	0 (0.0)		
	Child	13 (39.4)	14 (42.4)		
Diagnosis	Colon ca	27 (81.8)	22 (66.7)	1.981	0.159
	Rectal ca	6 (18.2)	11(33.3)		
Other chronic diseases	No	29 (88.0)	29 (88.0)	4.223	1.000
	Behçet and Crohn's	0 (0.0)	1(3.0)		
	Diabetes mellitus	1(3.0)	0 (0.0)		
	Hypertension	1(3.0)	1 (3.0)		
	CAD	1(3.0)	1 (3.0)		
	Neuropathy	0 (0.0)	1 (3.0)		

BMI body mass index, *cad* coronary artery disease

Descriptive statistics were provided as mean ± standard deviation, median (minimum–maximum), *n*, and %. Pearson chi-square, Fisher-Freeman-Halton, Fisher's exact, and *t* tests were used

Table 2 Individual risk factors causing oral mucositis development

Risk factors		Ankaferd hemostat ($n=33$)		Bicarbonate ($n=33$)		U/χ^2	p value
		n	%	n	%		
ECOG	Grade 0	22	66.7	20	60.6	2.447	0.311
	Grade 1	9	27.3	13	39.4		
	Grade 2	2	6.1	0	0.0		
Smoking	Never	15	45.5	16	48.5	0.061	0.805
	Previously	18	54.5	17	51.5		
Smoking previously (year)	Mean ± SD	12.5 (0.10–34)		20 (0.10–40)		153.50	0.509
Alcohol	Never	27	81.8	27	81.8	–	1.000
	Previously	6	18.2	6	18.2		
Alcohol previously (year)	Mean ± SD	6 (0.10–30)		8.5 (0.20–40)		18.00	0.662
A habit of brushing teeth	Yes	13	39.4	14	42.4	0.063	0.802
	No	20	60.6	19	57.6		
Regular dental check-ups (year)		2 (0.02–30)		2.5 (0–20)		517.00	0.723

ECOG The Eastern Cooperative Oncology Group

Descriptive statistics are provided as mean ± standard deviation, median (minimum–maximum), *n*, and %

Pearson chi-square, Fisher-Freeman-Halton, Fisher's exact, and Mann Whitney *U* tests were used

Table 3 Laboratory findings before the treatment

	Ankaferd hemostat ($n=33$)	Bicarbonate ($n=33$)	t/U	p value
Hgb g/dl	11.42 ± 1.46	11.53 ± 1.72	−0.270	0.788
HCT%	34.98 ± 3.98	35.82 ± 4.89	−0.765	0.447
Neutrofil %	4150 (1200–12,000)	4300 (2150–10,370)	612.0	0.387
WBC 10^6 hcr/μL	6770.91 ± 2386.62	8025.758 ± 2621.32	**−2.038**	**0.046***
PLT 10^6 /μL	249,300 (85,080–472,400)	284,000 (78,850–87,000)	611.50	0.390
Total protein g/dl	71 (56–79)	69 (50–77)	479.5	0.403
Albumin g/dl	40 (27–47)	40 (23–46)	541.5	0.969
Vitamin B12 ng/L	270 (115–1138)	304 (132–825)	498.5	0.555
Folate ug/L	8 (2–53)	7.5 (2.1–20)	514.0	0.696
fT3 ng/L	2.3 (1.18–3.9)	2.3 (1.07–3.46)	540.0	0.954
fT4 ng/L	1.02 (0.35–2.5)	1.07 (0.64–2.8)	492.5	0.505
TSH mU/L	0.97 (0.04–3.12)	1.36 (0.24–5.59)	396.0	0.057

Descriptive statistics were provided as mean ± standard deviation or median (minimum–maximum). Mann Whitney *U* and *t* tests were used. *Hgb* hemoglobin, *HCT* hematocrit, *WBC* leukocyte, *PLT* platelet, *TSH* thyroid-stimulating hormone, *fT3* free T3(triiodothyronine), *fT4* free T4(thyroxine), *$p<0.05$

(ANOVA) and Friedman test were performed for in-group comparisons. The Bonferroni correction was applied in paired comparisons when there was a significance. Pearson chi-square test, Fisher's exact chi-square test, and Fisher-Freeman-Halton test were used in analyzing the categorical data. Forward stepwise binary logistic regression analysis was completed to examine the factors affecting mucositis formation. Odds ratios (ORs) with 95% confidence interval are given because of binary logistic regression analysis. The significance level was accepted as $\alpha=0.05$. During the analysis of the data, support was received from a statistician.

Results

The findings of the study conducted to compare the effectiveness of Ankaferd hemostat protocol and standard oral care to prevent oral mucositis in individuals with colorectal cancer who underwent FOLFOX chemotherapy protocol were examined under six headings that are personal characteristics, disease-related characteristics, risk factors affecting the oral mucosa, and characteristics related to the development of oral mucositis.

Table 4 Comparison of oral mucositis grades of individuals in the Ankaferd hemostat and bicarbonate groups

Status of mucositis (WHO scale)		Ankaferd hemostat ($n=33$)		Bicarbonate ($n=33$)		χ^2/p value
		n	%	*n*	%	
7th day	No mucositis	33	100.0[a]	16	48.5[b]	**$\chi^2=25.161$; $p<0.001$**
	Grade 1	0	0.0[a]	15	45.5[b]	
	Grade 2	0	0.0[a]	2	6.1[b]	
	Grade 3	0	0.0	0	0.0	
	Grade 4	0	0.0	0	0.0	
15th day	No mucositis	31	93.9[a]	19	57.6[b]	**$\chi^2=11.879$; $p=0.002$**
	Grade 1	2	6.1[a]	9	27.3[b]	
	Grade 2	0	0.0[a]	4	12.1[b]	
	Grade 3	0	0.0	1	3.0	
	Grade 4	0	0.0	0	0.0	

[a,b]As a result of pairwise comparisons, different symbols were assigned to the groups with differences

WHO scale World Health Organization Oral Mucositis Grading Scale

Descriptive statistics were provided as *n*, and %. Fisher-Freeman-Halton test was used

Table 5 Comparison of ECOG performance levels between the groups

Control	ECOG	Ankaferd hemostat ($n=33$)		Bicarbonate ($n=33$)		χ^2/p value
		n	%	*n*	%	
7th day	Grade 0	6	18.2	7	21.2	$\chi^2=1.436$; $p=0.504$
	Grade 1	24	72.7	20	60.6	
	Grade 2	3	9.1	6	18.2	
15th day	Grade 0	11	33.3	8	24.2	$\chi^2=1.449$; $p=0.541$
	Grade 1	19	57.6	19	57.6	
	Grade 2	3	9.1	6	18.2	

ECOG The Eastern Cooperative Oncology Group

Descriptive statistics were provided as *n*, and %. Fisher-Freeman-Halton test was used

Personal characteristics

Socio-demographic characteristics of individuals in the study and control groups are presented in Table 1. The sociodemographic characteristics of the groups were similar ($p>0.05$). Table 1 shows the distribution of individuals in the study and control groups by the characteristics of the disease diagnosis and co-morbidities. The characteristics of the individuals in the study and control groups in terms of disease diagnosis and comorbidities were similar ($p>0.05$).

Risk factors affecting oral mucosa

The distribution of the performance scores of the individuals in the study and control groups on the first day of treatment, smoking, alcohol use, regular tooth brushing, and dental check-up is presented in Table 2. Grade 0 performance was determined in 66.7% of the individuals in the Ankaferd hemostat group on the first day of chemotherapy, and in 60.6% of the individuals in the bicarbonate group in the first control. The relationship between the pre-treatment performance levels of the individuals in the study and control groups was similar ($p>0.05$). Smoking and alcohol use and quitting times and dental characteristics of the groups were similar ($p>0.05$).

Table 3 shows the distribution of the mean/median of the laboratory findings of the individuals in both groups on the first day of pre-treatment. Of the hemogram results, the median values of Hgb, HCT mean, PLT, the median of neutrophil, biochemically total protein, albumin, vitamin B12, folate, free T3(triiodothyronine) (fT3), free T4(thyroxine) (fT4), and thyroid-stimulating hormone (TSH) were similar ($p>0.05$). This difference between the mean results of WBC (6900) in the Ankaferd hemostat group and WBC (7150) in the bicarbonate group was statistically significant ($p=0.046$).

Table 6 Examination of laboratory findings within and between groups

	Ankaferd hemostat ($n=33$)	Bicarbonate ($n=33$)	U/t	p value
Hemoglobin 1	11.42 ± 1.46	11.53 ± 1.72	−0.270	0.788
Hemoglabin 2	11.44 ± 1.5	11.33 ± 1.63	0.780	0.438
Δ	0.0 ± 0.07	−0.01 ± 0.1		
Hemoglabin 3	11.39 ± 1.46	11.15 ± 1.4	0.986	0.328
Δ	0.0 ± 0.07	−0.02 ± 0.12		
Test statistics/p value	$F=0.056$; $p=0.946$ww	$F=1.754$; $p=0.181$		
Hematocrit 1	34.98 ± 3.98	35.82 ± 4.89	−0.765	0.447
Hematocrit 2	34.83 ± 4.26	34.88 ± 4.5	0.994	0.324
Δ	0 ± 0.08	−0.02 ± 0.08		
Hematocrit 3	35.05 ± 4.36	34.6 ± 4.22	0.507	0.238
Δ	0 ± 0.08	−0.03 ± 0.12		
Test statistics/p value	$F=0.126$; $p=0.882$	$F=2.328$; $p=0.106$		
Neutrophil 1	4150 (1200–12,000)	4300 (2150–10,370)	477.0	0.387
Neutrophil 2	2810 (1040–7190)	3100 (1048–7300)	462.0	0.290
Δ	−0.26 (−0.82–2.17)	−0.37 (−0.81–0.51)		
Neutrophil 3	2990 (920–10,000)	3260 (420–9510)	506.0	0.621
Δ	−0.17 (−0.82–5.68)	−0.18 (−0.88–1.59)		
Test statistics/p value	**$\chi^2=18.606$; $p<0.001$**	**$\chi^2=19.697$; $p<0.001$**		
Leukocyte 1	6770.91 ± 2386.62	8025.76 ± 2611.33	**−2.038**	**0.046***
Leukocyte 2	4129.7 ± 1627.7	4888.06 ± 1897.47	0.849	0.399
Δ	−0.27 ± 0.53	−0.36 ± 0.24		
Leukocyte 3	5419.15 ± 2607.06	5481.55 ± 2410.07	1.756	0.084
Δ	−0.09 ± 0.59	−0.29 ± 0.28		
Test statistics/p value	**$F=11.989$; $p<0.001$**	**$F=27.428$; $p<0.001$**		
Platelet 1	249,300 (85,080;472,400)	284,000 (78,850;587,000)	477.50	0.390
Platelet 2	240,900 (70,200;434,000)	241,000 (32,700;480,000)	394.00	0.054
Δ	−0.1 (−0.68;0.54)	−0.19 (−0.76;0.34)		
Platelet 3	246,000 (71,400;704,500)	250,000 (32,400;500,000)	**382.00**	**0.037**
Δ	−0.08 (−0.65;2.27)	−0.2 (−0.61;1.34)		
Test statistics/p value	$\chi^2=3.697$; $p=0.157$	**$\chi^2=16.424$; $p<0.001$**		
Total protein 1	71 (56–79)	69 (50–77)	479.50	0.403
Total protein 2	68 (60–81)	68 (49–78)	540.00	0.954
Δ	−0.03 (−0.14–0.45)	−0.03 (−0.19–0.06)		
Total protein 3	70 (55–78)	68 (46–79)	460.50	0.280
Δ	−0.01 (−0.22–0.36)	−0.03 (−0.3–0.22)		
Test statistics/p value	**$\chi^2=11.241$; $p=0.004$**	**$\chi^2=8.228$; $p=0.016$**		
Albumin 1	40 (27–47)	40 (23–46)	541.50	0.969
Albumin 2	40 (26.3–47)	40 (25–45)	530.50	0.857
Δ	−0.02 (−0.23–0.28)	0 (−0.25–0.31)		
Albumin 3	40 (27–68)	39 (22–44)	480.00	0.408
Δ	0 (−0.17–0.58)	−0.03 (−0.24–0.41)		
Test statistics/p value	$\chi^2=0.117$; $p=0.943$	$\chi^2=3.409$; $p=0.182$		

ΔComparison of repeated measurements between groups was made by calculating the percentage change value (percentage change = (last measurement − first measurement)/ first measurement) according to the baseline measurement). Mann–Whitney U and t tests were used for comparison of percentage change values. Friedman test and repeated measures ANOVA were used for repeated measures within group comparison, *$p<0.05$

Characteristics of oral mucositis development

Oral mucositis grades on the follow-up days of the individuals in the Ankaferd hemostat and bicarbonate groups are presented in Table 4. In the individuals included in the study, it was observed that mucositis did not develop in the Ankaferd hemostat group on day 7 of the treatment, and grade 1 level mucositis developed on day 15 at a rate of 6.1%. In the

bicarbonate group, mucositis developed at a rate of 45.5% at grade 1 level on the day 7 control, and 27.3% at grade 1 level on the day 15 control. In the Ankaferd hemostat and bicarbonate groups, the difference between the mucositis symptom findings on the 7th day and 15th day follow-up after chemotherapy was statistically significant ($p < 0.001$).

The distribution of the performance scores of the individuals in the Ankaferd hemostat and bicarbonate groups on days 7 and 15 after the treatment is presented in Table 5. 72.7% of the individuals in the Ankaferd hemostat group on day 7 control and 57.6% on day 15 control, 60.6% of the individuals in the bicarbonate group on day 7 control and 57.6% on day 15 control were found to be grade 1 symptomatic but completely up. The relationship between the performance levels of the individuals in the study and control groups on days 7 and 15 after treatment was similar ($p > 0.05$).

Table 6 shows the in-group and between-group comparisons of laboratory findings on the first day of treatment, and on days 7 and 15 after the treatment of the patients who received chemotherapy. The common laboratory values of the patients in the Ankaferd hemostat and bicarbonate groups in 3 time intervals are hemoglobin (hgb), hematocrit

Table 7 Examination of the effects of socio-demographic variables on the development of oral on the 7th day and 15th day in the bicarbonate group

Descriptive characteristics/agent		7th day (2nd control)				15th day (3rd control)			
		No mucositis ($n=16$)	Oral mucositis ($n=17$)	χ^2	p	No mucositis ($n=19$)	Oral mucositis ($n=14$)	χ^2	p
Gender	Female	6 (37.5)	9 (52.9)	**0.793**	0.373	8 (42.1)	7 (50.0)	0.203	0.653
	Male	10 (62.5)	8 (47.1)			11 (57.9)	7 (50.0)		
Education level (school)	Elemantary	11 (68.8)	11 (64.7)	2.809	0.503	11 (57.9)	11 (78.6)	2.167	0.637
	Secondary	1 (6.3)	4 (23.5)			4 (21.1)	1 (7.1)		
	High	3 (18.8)	1 (5.9)			3 (15.8)	1 (7.1)		
	University	1 (6.3)	1 (5.9)			1 (5.3)	1 (7.1)		
Marital status	Married	14 (87.5)	14 (82.4)	–	1.000	17 (89.5)	11 (78.6)	–	0.628
	Single	2 (12.5)	3 (17.6)			2 (10.5)	3 (21.4)		
Income level	High income	6 (37.5)	11 (64.7)	3.933	0.154	8 (42.1)	9 (64.3)	1.571	0.570
	Medium income	5 (31.3)	5 (29.4)			7 (36.8)	3 (21.4)		
	Low income	5 (31.3)	1 (5.9)			4 (21.1)	2 (14.3)		
Employment status	Private sector	3 (18.8)	2 (11.8)	2.265	0.602	3 (15.8)	2 (14.3)	2.336	0.516
	Public employee	2 (12.5)	1 (5.9)			3 (15.8)	0 (0.0)		
	Not working	3 (18.8)	7 (41.2)			5 (26.3)	5 (35.7)		
	Retired	8 (50.0)	7 (41.2)			8 (42.1)	7 (50.0)		
The person responsible for care	Spouse	7 (43.8)	9 (52.9)	1.437	0.924	9 (47.4)	7 (50.0)	1.063	1.000
	Brothers	1 (6.3)	1 (5.9)			1 (5.3)	1 (7.1)		
	Parents	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)		
	Child	7 (43.8)	7 (41.2)			8 (42.1)	6 (42.9)		
	Friends	1 (6.3)	0 (0.0)			1 (5.3)	0 (0.0)		
Diagnosis	Colon ca	10 (62.5)	12 (70.6)	0.243	0.622	12 (63.2)	10 (71.4)	–	0.719
	Rectal ca	6 (37.5)	5 (29.4)			7 (36.8)	4 (28.6)		
Other chronic diseases	No	15 (93.8)	14 (82.4)	–	0.601	18 (94.7)	11 (78.6)	–	0.288
	Yes	1 (6.3)	3 (17.6)			1 (5.3)	3 (21.4)		
Smoking	Never	6 (37.5)	10 (62.5)	1.500	0.221	8 (50.0)	8 (50.0)	0.730	0.393
	Previously	10 (58.8)	7 (41.2)			11 (64.7)	6 (35.3)		
Alcohol	Never	13 (48.1)	14 (51.9)	–	1.000	13 (48.1)	14 (51.9)	–	**0.027***
	Previously	3 (50.0)	3 (50.0)			6 (100.0)	0 (0.0)		
A habit of brushing teeth	Yes	5 (35.7)	9 (64.3)	1.588	0.208	7 (50.0)	7 (50.0)	0.571	0.450
	No	11 (57.9)	8 (42.1)			12 (63.2)	7 (36.8)		
Regular dental check-ups (year)		3 (0.4;10)	2 (0;20)	116.50	0.488	4(0.4;20)	1.5(0;10)	80.00	0.055
Age (years)		57.31 ± 11.28	60.24 ± 9.45	0.809	0.425	57.26 ± 10.80	60.93 ± 9.60	1.009	0.321
BMI		27.29 ± 3.96	23.92 ± 5.13	**2.121**	**0.042**	26.41 ± 4.65	25.09 ± 4.96	0.775	0.444

Descriptive statistics were provided as mean ± standard deviation, median (minimum–maximum), n, and %. Pearson chi-square, Fisher-Freeman-Halton, Fisher's exact, and t tests were used, *$p<0.05$

(hct), neutrophil (neu), leukocytes (wbc), thrombocyte (plt), total protein (tot protein), and albumin (alb). A significant decrease was found in the group between total protein 1 (71)-total protein 2 (68) and total protein 1 (71)-total protein 3 (70) compared to the baseline level ($p=0.004$). A negative decrease between Neu 1 (4150)-neu 2 (2180) and neu 1 (4150)-neu 3 (2990), between wbc 1 (6770.91)-wbc 2 (4129.7) and wbc 1 (6770.91)-wbc 3 (5419.15) was found compared to the baseline levels, and the relationship in between is significant ($p<0.001$). A negative decrease between plt 1 (284,000)-plt 2 (241,000) and plt 1 (284,000)-plt 3 (250,000), between neu 1 (4300)-neu 2 (3100) and neu 1 (4300)-neu 3 (3260), between wbc 1 (8025.76)-wbc 2 (4888.06) and wbc 1 (8025.76)-wbc 3 (5481.55) was found compared to the baseline levels and the in-group relationship is significant ($p<0.001$). A significant decrease was found in the group between total protein 1 (69)-total protein 2 (68) and total protein 1 (69)-total protein 3 (68) compared to the baseline level ($p=0.016$).

Ankaferd hemostat wbc 1 (6770.91) and bicarbonate wbc 1 (8025.76) value were found to be significantly correlated between groups ($p=0.046$). Again, the relationship between thrombus 3 (246,000) and thrombus 3 (250,000) values, respectively, was significant between the two groups ($p=0.037$).

Characteristics related to mucositis development

Socio-demographic variables, hb, hct, neu, wbc, platelet, total protein, albumin, vitamin B12, folate, fT3, fT4, and TSH and ECOG performance status variables were included in the model created to determine the factors affecting the oral mucositis development in the 2nd and 3rd controls in the bicarbonate group.

The factors that may cause the development of mucositis in the 7th day controls of the individuals in the bicarbonate group after chemotherapy are presented in Table 7. It was seen that the mucositis grades were variable and not significant in terms of analysis; thus, the classification was stated as mucositis present and not present. Table 4 shows that the mucositis grade in the 7th day control is 45.5% grade 1 and 6.1% grade 2. When the characteristics presented in Table 7 are examined, it is seen that the relationship between age, gender, education, marital status, employment status, family support, diagnosis, comorbidity, smoking and alcohol use, regular tooth brushing, and mean year of dental check-ups between individuals with and without mucositis are similar ($p>0.05$). The factors that may cause the development of oral mucositis are listed in Table 7 in groups as having mucositis and no mucositis on the 7th day and 15th day. Considering the characteristics examined, it is seen that the relationship between the individuals who did not develop mucositis and those who developed mucositis with age, BMI, gender, education, marital status, employment status, family support, diagnosis, comorbidity, smoking, regular tooth brushing, and the average year of dental check-ups is similar ($p>0.05$). In patients without mucositis, mucositis was not observed in all patients who consumed alcohol and quit. Among the patients who developed mucositis, 51.9% of 27 patients who never consumed alcohol developed mucositis. Regarding the alcohol consumption and quitting, the difference between the groups with and without mucositis on day 15 after chemotherapy in patients using bicarbonate was significant ($p=0.027$). No significant relationship was found between the history of not consuming alcohol and mucositis development.

The BMI (27.29) was higher on day 7 in patients without mucositis, while the BMI (23.92) was lower in patients with mucositis. The difference between the groups with and without mucositis in the development of mucositis is significant in terms of BMI on day 7 after chemotherapy in individuals using bicarbonate ($p=0.042$).

According to the results of the binary logistic regression analysis, examining the factors affecting the development of mucositis on day 7 showed that only neutrophils and TSH were included in the model, and only the TSH variable was statistically significant while other variables included in the model were not significant. A 1-unit increase in TSH measurement increases the risk of mucositis development (OR = 2.2) ($p=0.047$). When the factors affecting the mucositis development on the 15th day at the 3rd control were examined, it was found that free T3, thrombocyte, and neutrophil were included in the model while only free T3 and neutrophil were statistically significant. While a 1-unit increase in the free T3 measurement increases the mucositis development by 8.106, a 1-unit increase in the neutrophil measurement decreases the mucositis development risk on day 7 control ($p<0.05$) (Table 8).

Table 8 Factors affecting the oral mucositis development in the bicarbonate group

Variables	7th day			
	p	OR	Hazard ratio 95% CI	
			Lower limit	Upper limit
Neutrophil	0.059	0.031	0.001	1.136
TSH	**0.047***	2.205	1.009	4.817
15th day				
fT3	**0.048***	8.016	1.021	62.958
Platelet	0.118	17.003	0.485	595.723
Neutrophil	**0.020***	0.010	0.000	0.494

A forward stepwise binary logistic regression analysis was completed

CI confidence interval, *OR* odds ratios, *TSH* thyroid-stimulating hormone, *fT3* free T3, *$p<0.05$

Mucositis images

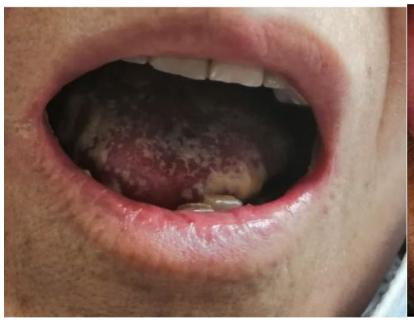

Image 1. Grade 3 OM

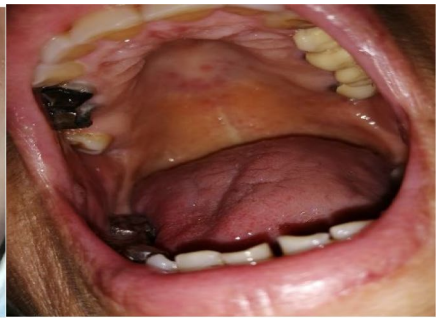

Image2. Grade 2 OM

Discussion

This study aimed to determine the effectiveness of bicarbonate mouthwash and Ankaferd hemostat in preventing OM in patients with colorectal cancer receiving chemotherapy. Comorbidities such as DM and obesity, leukocyte count, nutrition, oral hygiene, tobacco use, and poor ECOG performance are described as potential risk factors in the literature for OM development [22, 30]. It is seen in this study that ECOG score, smoking, alcohol consumption, a habit of tooth brushing regularly, and the intervals of dental checkups are similar in both groups (Table 2). In a study by Suresh et al. conducted to determine the risk score of OM in 218 patients with head and neck cancer (HNC) who received chemoradiotherapy, the probability of developing grade 3 or 4 mucositis was determined to be 17% in patients with an ECOG score of 3 or less, while it was 76% in patients with a score of 6 or more. Additionally, poor oral hygiene and tobacco use increases the potential of mucositis [30]. In a phase III study by Niikura et al. it was observed that OM due to everolimus used in the treatment of breast cancer developed at the rate of 58%, but with professional oral care including tongue and tooth cleaning, a 12% decrease was found in grade 1 mucositis and a 20% decrease in grade 2 mucositis. Niikura et al. recommended that professional oral care should be used in other diseases in which everolimus is indicated [31]. Table 2 shows that 60.6% of the patients in the Ankaferd hemostat group and 57.6% in the bicarbonate group did not brush their teeth regularly, and the relationship between the two groups is similar. It is seen that the individuals included in the study do not have the habit of brushing their teeth, and more than half of them do not have regular dental check-ups. It was found that there are patients who did not have dental check-ups between 2 months and 30 years in the Ankaferd hemostat group, and between 2 months and 20 years in the bicarbonate group. According to the Turkey Oral and Dental Health Profile Research report (2018), 4.8% of individuals in the 35–44 age group do not have a toothbrush, 25.1% of those who have a toothbrush brush their teeth at least twice a day, and even though they have a toothbrush, the participant do not brush their teeth; its rate is 1.8%. In this study conducted in Turkey, it is seen that the rate of tooth brushing is higher. This difference may be due to the sample group, as well as the fact that patients do not prioritize brushing with the diagnosis of cancer, because they do not have enough information on this subject or they do not receive education. Saito et al. reported that professional prophylactic oral care before chemotherapy decreases both the deterioration of oral flora and the incidence of oral mucositis in patients with breast cancer receiving adjuvant chemotherapy to prevent mucositis [20]. It is important to resolve oral problems before cancer treatment begins, and to educate patients about the potential risks, side effects, and complications of the treatment. In cases where cancer treatment is not urgent, referring to a dentist to resolve issues such as broken teeth, loose crowns or fillings, or gum problems at least 4 weeks before the chemotherapy reduces the complication risk [32]. It is recommended to use a soft toothbrush that is changed regularly, to use reliable and validated scales to regularly evaluate oral health, and to maintain regular dental treatment and follow-up by dentists during the chemotherapy process as well [8]. Minor invasive procedures should be completed at least 2 weeks before chemotherapy, and major surgical procedures should be completed 4–6 weeks before the start of chemotherapy [33]. Although the importance of oral hygiene for patients receiving chemotherapy is emphasized, it is seen in this study that, unlike the literature,

patients did not apply to the dentist at long intervals for 4.3 years (min: 0–max: 30 years). It is thought that this is because of the poor oral care habits in Turkey due to socioeconomic factors, and the inability of individuals to benefit from preventive and therapeutic services [34].

Plasma albumin, which reflects the human protein level, is an important nutrient for the human body. The amino acid produced by the breakdown of plasma albumin can be used for the synthesis of tissue proteins, energy supply, or conversion to other nitrogenous substances. Early nutritional intervention can reduce the incidence and level of severe oral mucositis [35]. For this purpose, albumin and total protein evaluation was performed in this study (Table 3). Vitamin B12 and folate induce erythrocyte production and are important for hematopoiesis. As the thyroid is the main regulator of metabolism, all body functions, including the mouth, are affected in any thyroid disease. Oral cavity is adversely affected by hypothyroidism and hyperthyroidism. These effects include deterioration of periodontal health, salivary gland changes, delayed bone resorption, glossitis, mouth breathing, tooth enamel hypoplasia, burning mouth syndrome, tooth eruption, maxillary and mandibular osteoporosis, and connective tissue diseases such as Sjogren's [36]. Similar to the literature [37, 38], it is seen in this study that a 1-unit increase in free T3 measurement increases the risk of mucositis formation OR = 8 times (Table 8).

Mucositis more commonly affects non-keratinized mucosa. The chemotherapy-induced maximum expression occurs 7–10 days after chemotherapy and can progress from erythema to ulceration. The immunosuppression experienced during this period gradually decreases without leaving a trace for 2–3 weeks after the infusion of the drug [17]. In this study, it was seen that no mucositis developed in the Ankaferd hemostat group on day 7, and that mucositis developed as grade 1 at a ratio of 6.1% on day 15. In the bicarbonate group, grade 1 mucositis developed at a rate of 45.5% on day 7, and at a rate of 27.3% on day 15 while grade 2 mucositis developed at the rate of 6.1% on day 7 and 12.1% on day 15, and grade 3 mucositis developed at a rate of 3% on day 15 (Table 4). In a study by Rodrigues et al. comparing the standard oral care and cryotherapy in cancer patients receiving 5-FU, it was observed that grade 1 mucositis developed at a rate of 23.3% and grade 2 mucositis at a rate of 3.3% on day 7, and 13.3% grade 1 mucositis on day 14 after chemotherapy in the group of oral care with saline [39]. A study by Fatimah et al. reported that the prevalence of oral mucositis in cancer patients receiving 5-FU chemotherapy was 60.98%, and the rate of grade1 oral mucositis was 52.0%, and the location of OM in the oral cavity was completely in non-keratinized mucosa [40]. In this study, similar to the study of Rodrigues and Fatimah, it was observed that the patient developed grade 1 and grade 2 mucositis on day 7 after chemotherapy, but the rates were higher (grade 1: 45.5%; grade 2: 6.1%). In the study by Ameen et al. comparing ice cube and sodium bicarbonate mouthwash, 15 (60%) of the 25 patients had mucositis at varying grades before using the sodium bicarbonate mouthwash, a total of five patients (20%) reported mucositis, four (16%) reported grade 1, and one patient (4%) reported grade 2 mucositis after using the bicarbonate mouthwash [29]. In this study, the OM development in the bicarbonate group was 51.5%, which is higher than the study of Rodrigues and Ameen. The reason for this is thought to be because only 5-Fu treatment was used in Rodrigues' study, while patients with solid tumors were included and different chemotherapies were applied in Ameen's study. Additionally, the differences in the educational status, professional years, experience in chemotherapy, and the level of knowledge on the prevention and care of oral mucositis of nurses working in the chemotherapy unit may have also contributed to these results. In the study, OM was not observed in the control on day 7 in the Ankaferd hemostat group. In their study addressing the grade of oral mucositis in early childhood cancer, Paturoglu et al. applied standard oral care (brushing teeth, bicarbonate mouthwash, nystatin, and chlorhexidine) before the start of the treatment and added oral care with Ankaferd hemostat to the standard oral care in the second cure treatment of the same patients. In the results of the study, it was stated that the grade of oral mucositis never increased to grade 4 and that Ankaferd hemostat was safe in the prevention and treatment of oral mucositis [12].

In the study, there is not a difference between the ECOG performances of both groups which was similar on days 7 and 15 (Table 5). After chemotherapy, patients with a low ECOG performance score experience both self-care and nutritional problems, as their fatigue increases and their quality of life decreases [14]. Therefore, the patient's inability to perform self-care may cause deterioration of oral hygiene and mucositis. In a study evaluating the OM grade after radiotherapy in patients diagnosed with HNC by comparing the placebo and oral glutamine, Huang et al. found a similar relationship between the ECOG performance score and the OM grade in the groups [41]. In their study evaluating modified FOLFOX therapy phase II toxicity in patients with stomach cancer, Oh et al. determined that chemotherapy is safe and applicable despite poor performance (grade 2) [42]. Similar to [41] Oh et al.'s study, a change was observed in performance level in both groups in this study; however, toxicity such as dose adjustment of OM or interruption of treatment did not occur. However, it is thought that the low grade of oral mucositis in patients allowed the patient's oral intake and nutrition to be maintained at an adequate level, thus causing no significant difference in ECOG parameters between the first evaluation

and subsequent evaluations due to BMI [42]. In Pattanayak et al. (2016), 57% of patients who had an ECOG performance score of 1 compared with 51% patients who had an ECOG performance score of 0 developed mucositis at the fourth week [43].

Mucosal barrier damage is a very important factor in the emergence of inflammatory complications after cytotoxic therapy and is characterized by infection, inflammation, and fever [44]. Additionally, comorbidities such as neutrophil count, kidney diseases, thyroid disease, and age, BMI, smoking, neutropenia, lymphopenia, and low hemoglobin levels are listed among OM risk factors [45]. Recovery of peripheral blood neutrophil counts and migration of neutrophils to the oral cavity contributes to the reduction of neutropenia, the rate of infection, and thus the duration and severity of OM [46]. In their retrospective study, Satheeshkumar et al. compared two groups—with and without mucositis—in patients receiving chemotherapy, and found a significant difference in pancytopenia, anemia, and fluid-electrolyte balance [45]. In a study by Kazemian et al. comparing benzodiazepine and standard oral care (brushing teeth and mouthwash with saline/bicarbonate twice a day) and oral mucositis development in head and neck cancers, they found that smoking was significant in the development of grade ≥ 3 mucositis [47]. In this study, it is thought that acetaldehyde secretion in saliva may have decreased because smoking cessation occurred at least 1 month ago and there is no smoking currently (Table 2). However, the relationship between smoking and mucositis is controversial. Tobacco smoke can damage the mucous lining of the oral mucosa, partly because it raises the temperature inside the mouth and burns the tissues [48]. Also, due to the proinflammatory activity of smoking, a higher risk of OM has been reported in smokers, which may increase mucosal damage [49]. Alcohol can destroy the lipid composition that the protective layer of the oral mucosa covers the acanthosis granules and disrupt the normal arrangement of epithelial lipid molecules, causing a space between epithelial cells and increased oral mucosal permeability. In other words, alcohol creates a pathway for deep soft tissues [50]. Chronic alcohol consumption induces cytochrome P450 2E1 enzyme activity in mucosal cells, resulting in increased activation of reactive oxygen species and various dietary and environmental carcinogens [51]. However, although there is a similar effect in smoking, smoking is not shown to affect the OM development. As gingival pockets are a source of leukocytes in the oral cavity [52], it is thought that OM develops due to a decrease in the number of oral leukocytes. Suresh et al. define a positive relationship between local immune markers (total white blood cell count, comorbid conditions, markers of inflammation and tobacco use, nutritional status as reflected by albumin levels), mucositis severity and incidence, and healing capacity (performance, nutritional status, and comorbid conditions). Poor oral hygiene and tobacco use increase the likelihood of mucositis [30]. In the study of Saito et al., in which they examined OM in breast cancer patients, there was a significant difference between the group that did self-care and the group that was taught professional oral care before and 2 weeks after chemotherapy [20]. In this study, standardized tooth brushing and training were performed for both groups in terms of oral hygiene. Although we chose the same toothpaste and toothbrush to be used, a difference in OM was observed in the bicarbonate and Ankaferd hemostat groups. The recommendations in the literature to brush the teeth and gums at least twice a day and to use high fluoride toothpaste and a soft-bristled toothbrush [53] were determined to be followed by all patients verbally and by looking at the control charts in their hands.

In the bicarbonate group, socio-demographic variables affecting mucositis development are seen to be BMI and alcohol consumption on days 7 and 15, respectively (Table 7). However, the mucositis grade was determined to be 0 in the 3 controls of these patients. Although there was a significance between the BMIs on day 7 in this study, this significance was not found to be related to the OM development. In this study, although a significance was found on the 7th day between BMIs, this significance could not be found to be related to the development of OM in the model studied (Table 8). In their comparative study of standard oral care and cryotherapy in cancer patients who received 5-FU, Rodrigues et al. found no difference between the 2 groups when evaluated by factors such as having and not having regular dental check-ups, income level, marital status, and gender [39]. Gebri et al. stated that female sex hormones predominantly have a negative effect on oral immunity and play a role in the etiopathogenesis of OM [54]. In this study, it was seen that mucositis developed more in women in terms of mucositis development between men and women in terms of genders, but the difference was not significant. It was thought that this was due to the sample group. On the contrary, the study by Fatimah et al. found the oral mucositis prevalence as 60.98% in cancer patients receiving 5-FU chemotherapy, and it is 40% higher in the 46–55 age range, 56% in women, and 44% higher in those with low BMI [40]. The reason for this difference is thought to be the weight loss in cancer patients with low BMI, that there is no nutrition problem as indicated by total protein and albumin levels, and that the BMI may be similar prior to treatment.

When the factors affecting mucositis development on day 7 at the 2nd control were examined because of the binary logistic regression performed for a detailed analysis of OM in the bicarbonate group in the study, it was found that only one unit increase in neutrophil and TSH and TSH measurement in the model increased the risk of

mucositis development by OR = 2.2 times (Table 8). Thyroid hormones regulate metabolic processes necessary for normal growth and development and regulate metabolism in adults. It is known to have an important role in the regulation of lipid metabolism and metabolic rate. It regulates weight gain and fat balance by stimulating lipolysis and increasing the conversion of fatty acids into energy. Additionally, TSH activates the secretion of fT3 and fT4 by the thyroid gland. TSH also plays an important role in weight gain and regulating the energy balance. Changes in thyroid hormone levels occur due to malignancy and chemotherapy used [55]. In a posttraumatic stress disorder (PTSD) study conducted by Loo et al. on individuals with breast cancer, it was observed that individuals who underwent chemotherapy and surgery experienced PTSD for a long time and their serum fT3 and fT4 levels were high. Patients experienced more severe pain and longer-lasting oral ulcers in mucositis compared to healthy individuals in the control group [37]. In this study, it was found that the increase in the amount of TSH affects the fat metabolism, affecting weight loss, and malnutrition and suggests that it is a precursor to mucositis. When the factors affecting the formation of mucositis on day 15 were examined, while free T3, thrombocyte, and neutrophil were included in the model, only free T3 and neutrophil were found to be statistically significant. A 1-unit increase in free T3 measurement increases the risk of mucositis formation OR = 8 times, while a 1-unit increase in neutrophil measurement decreases the risk of mucositis formation. Similar to the literature, this suggests that thyroid dysfunction contributes to the development of OM by causing oral cavity changes [36], and neutropenia causing oral mucosal damage [44]. Schmidberger et al., in their study examining the relationship between radiotherapy, chemoradiation, and the development of OM in a healthy volunteer, found that OM developed during low oral neutrophils after radiotherapy, but differently, the decrease in oral neutrophils in the mouthwash was not associated with radiation-induced mucositis [56]. In a randomized controlled three-group comparison by Cabrera-Jaime et al. for the treatment of mucositis in cancer patients with grade II–III mucositis, although healing of mucositis was observed in 5 days in the bicarbonate-bicarbonate group, 7 days in the chlorhexidine-bicarbonate arm, and 7 days in the Plantago major-bicarbonate group, there was no significant difference between them. Additionally, it was reported that no neutropenia development occurred in any of the patients [57]. In this study, as the prevention of OM development was aimed, similar patients were observed for 2 weeks, and neutropenia development occurred, and mucositis developed in the bicarbonate group in the day 7 and 15 controls constituted a significant relationship with only the Ankaferd hemostat group. This showed that Ankaferd hemostat is an effective agent in preventing OM.

Strengths and limitations of the research

Strengths

- Randomized controlled experimental design type was used in the study.
- The study was carried out on a homogeneous group diagnosed with colorectal cancer.

Limited aspects

- The fact that the study was conducted in a single center limits the generalization of the results of the study to all colorectal cancer patients.
- Since it was carried out in a single center with the participation of patients who met the sample selection criteria and accepted to participate in the study, the data obtained are generalized only to patients with the characteristics in this sample group.
- Oral care practice and monitoring of the patients by the investigator during 1 treatment course are limiting in terms of evaluation of late side effects.
- Due to the pandemic, it was spread over a 19-month implementation.

Conclusion

In our study, it was observed that the rate of mucositis development in the group using Ankaferd hemostat was lower than that in the bicarbonate group. The results of the advanced statistics performed determined that Ankaferd hemostad reduced mucositis development by 93.9% and the severity of mucositis was limited to grade 1. In preventing the development of oral mucositis, it is recommended to teach Ankaferd hemostat and toothbrushing with the Modified Stealman technique in colorectal cancer patients treated with FOLFOX. It is thought that more studies should be conducted to evaluate the effectiveness of Ankaferd hemostat in preventing oral mucositis that the study should be repeated with a larger sample, and that not having an autoimmune disease should be added to the exclusion criteria when the study is repeated.

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Author contribution YK participated in the study design, data collection, data analysis, and implementation of the study; HY participated in the study design, analysis, and manuscript revision and supervised the research; YK provided an initial draft of the manuscript and

participated in analysis, interpretation of data, and manuscript revision; HY, TE, and ICH participated in the study design and data analysis; ICH participated in the study design, analysis, and interpretation of data. All authors have read and approved the final manuscript.

Data availability All data generated during this study are included in this published article.

Declarations

Ethics approval and consent to participate This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Bursa Uludag University (Date.2020/ No.4/21–1). Informed consent was obtained from all individual participants included in the study.

Consent for publication Patients signed informed consent regarding publishing their data and photographs.

Competing interests The authors declare no competing interests.

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