

Research Article

Henna Application in the Prevention of Capecitabine-Induced Hand-Foot Syndrome in Breast and Colorectal Cancer Patients

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Abstract

AIM: This study investigates the prophylactic effect of henna on the occurrence of hand-foot syndrome (HFS) in patients receiving capecitabine for breast and colorectal cancer.**METHOD:** This experimental study was carried out between May 2014 and May 2015. In this self-control experimental study, 52 patients with breast and colorectal cancer were included on the first day of capecitabine treatment and had a minimum follow-up of 3 cycles. One hand/foot of each patient constituted the study hand/foot, whereas the others constituted the control. Henna was administered to the study hand/foot on the first day of treatment and application renewed weekly. Development of grade 1–3 toxicity was set as the termination criterion for study.**RESULTS:** Painful skin changes such as rawness, intumescence and bulla formation, blocking the daily activities or self-care were observed in 26.9% of the patients in the 3rd or 4th cycles of treatment. Development time and severity of skin changes over time did not differ significantly between the study and the control hand/foot.**CONCLUSION:** Further studies with a larger sample size are needed to conclude on the prophylactic effect of henna in the management of the HFS.**Keywords:** Cancer, capecitabine, henna, hand-foot syndrome

Introduction

Cancer is one of the common diseases currently. Parallel to the increase in the incidence of cancer, important advances have been made in its treatment (American Cancer Society, 2016; Centers for Disease Control and Prevention, 2015). According to the individual characteristics and disease progression, different treatment techniques such as surgery, radiotherapy, and chemotherapy are being used alone or in combination in the treatment of cancer. Although these treatment methods can cure the disease, they may lead to many adverse effects that impair the duration of survival as well (Wild et al., 2019). One of these adverse effects is the hand-foot syndrome (HFS) induced by capecitabine treatment in breast and colorec-

tal cancer patients. The incidence of HFS among patients receiving capecitabine is 10%-60% and is as an important factor impairing the quality of life of the individual (Nishida, 2003; Smorenburg et al, 2001).

HFS, also known as palmar-plantar erythrodysesthesia (PPE) syndrome, affects the palmar and plantar regions of the patients and may lead to dysesthesia, erythema, or edema of varying degrees. As the severity of the reaction progresses, dry or wet desquamation, ulceration, and serious pain develop in the hands and feet. This in turn negatively affects the daily activities and quality of life of the individuals and may lead to a pause in, cessation or even termination of the treatment (Chidharla & Kasi, 2019; Miller et al., 2014; Nikolaou et al., 2016).

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Till date the efficacy of many approaches including moisturizing creams, systemic and local corticosteroids, vitamin E, pyridoxine, cyclooxygenase inhibitors and henna application have been investigated in the management of HFS (Kara et al., 2006; Lin et al., 2002; Vail et al., 1998; Zhang et al., 2011). The studies have reported some of these approaches as being effective (Chin et al., 2001; Hofheinz et al., 2015; Kara et al., 2006; Lyass et al., 2001; Mangili et al., 2008) and some as ineffective or controversial in the management of HFS (Bresalier et al., 2005; Chen et al., 2013; Mortimer et al., 2003; Nussmeier et al., 2005; Solomon et al., 2005; Yap, et al., 2017; Zhang et al., 2011; Zhou et al., 2013). Currently, there is no approved approach for the management of this problem; however, physicians generally pause drug administration or reduce the dosage in patients who develop severe HFS (Blum et al., 2001). During capecitabine treatment our priority is to prevent the development of HFS. Henna application, which is one of our traditional approaches, has been reported as being an effective intervention in the management of HFS (Ilyas et al., 2014; Yucel & Guzin 2008).

Henna has been traditionally used in Islamic and Indian cultures in religious ceremonies or weddings in to color the hair, hands, feet and nails as a permanent tattoo. Henna has wide usage as folk tradition, such as its use in constipation after boiling it with sweeteners, locally in the treatment of burns, pressure ulcers or application onto the hair for headaches (Rafiei, 2019; Tortumluoglu, 2006). Studies have demonstrated the antibacterial, anti-fungal, analgesic, and anti-inflammatory effects of henna. Furthermore, the antifungal and antioxidant effects have been demonstrated in studies on mice (Ali et al., 1995; Elzayat, 2018; Mikhaeil et al., 2004; Mutluoglu & Uzun, 2009; Rahmoun et al., 2013).

Efficacy of henna application in the management of HFS has been investigated in two small-sized studies, one of which was a case report. Both studies concluded that henna application was effective in the treatment of capecitabine-related HFS (Ilyas et al., 2014; Yucel & Guzin, 2008).

In addition to the studies mentioned above, the present study was planned to investigate the efficacy of henna application in the prevention of HFS in patients diagnosed with breast or colorectal cancer who have newly begun taking capecitabine.

Hypotheses

Hypothesis 1

H0: Prophylactic henna application in patients with breast and colorectal cancer does not prevent the development of HFS associated with capecitabine treatment.

H1: Prophylactic henna application in patients with breast and colorectal cancer prevents the development of HFS associated with capecitabine treatment.

Hypothesis 2

H0: Prophylactic henna application in patients with breast and colorectal cancer does not reduce the severity of HFS associated with capecitabine treatment.

H1: Prophylactic henna application in patients with breast and colorectal cancer reduces the severity of HFS associated with capecitabine treatment.

Hypothesis 3

H0: Prophylactic henna application in patients with breast and colorectal cancer does not delay the development of HFS associated with capecitabine treatment.

H1: Prophylactic henna application in patients with breast and colorectal cancer delays the development of HFS associated with capecitabine treatment.

Method

Study Design

This is a prospective experimental study.

Sample

This self-control experimental study was performed at the oncology hospital in Istanbul in Turkey, between May 2014 and May 2015. Patients with breast and colorectal cancer who had recently undergone capecitabine treatment (as monotherapy or combined therapy) were included in the study. Those who had received capecitabine previously, those who had lost cutaneous integrity on the hands and feet, and those who refused to participate in the study were excluded.

A total of 100 patients admitted to the outpatient clinic were reached out to during the data collec-

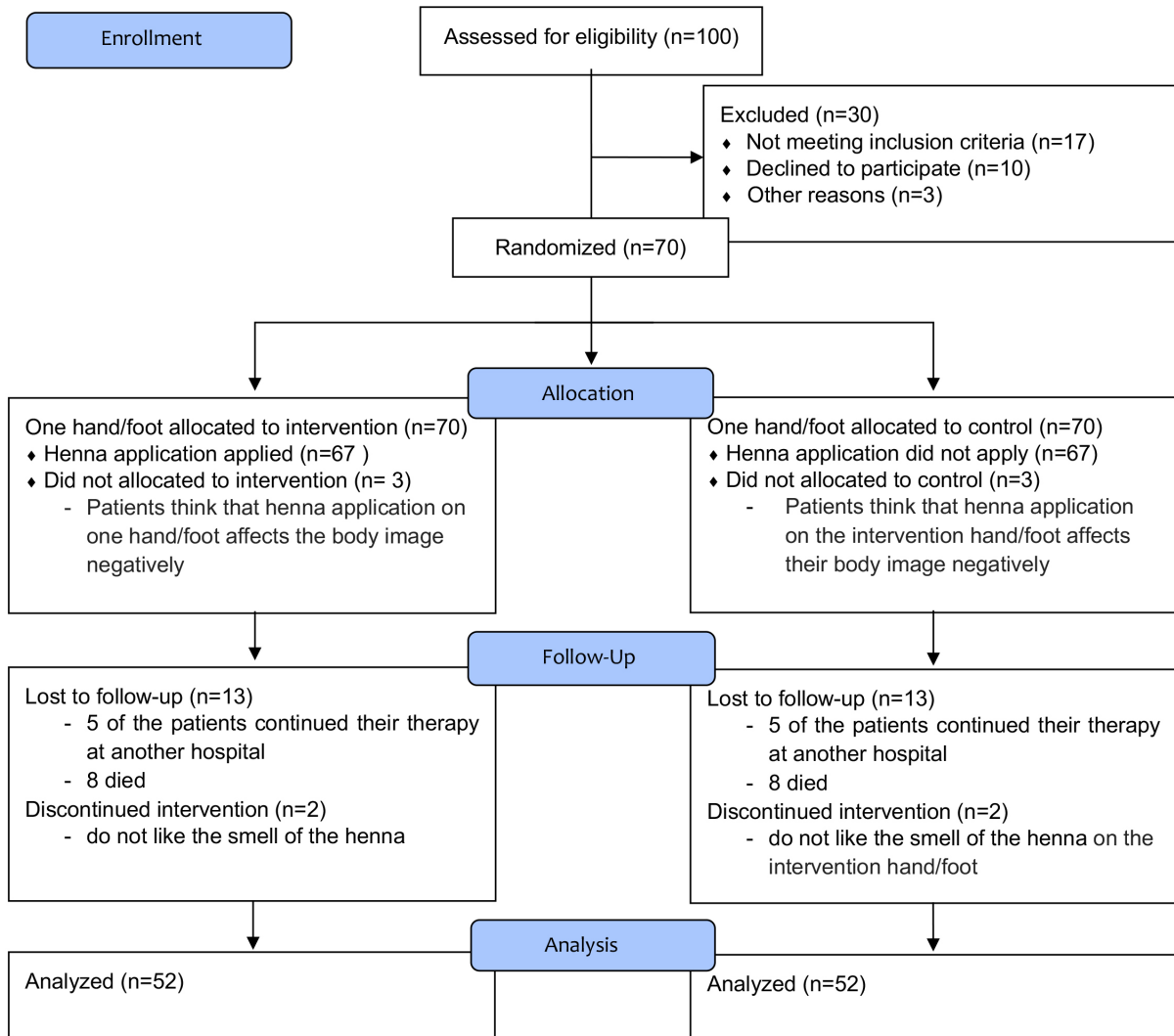


Figure 1
The Flow Diagram for This Study (CONSORT Statement)

tion process. After an explanation of the study, 30 patients were excluded because they did not meet the inclusion criteria, and the study started with the participation of 70 patients. A total of 70 patients who had presented to our clinics between 2014 and 2015 constituted the patient universe for the sample size calculation. α and β were defined as 0.05 and 0.20, respectively, during the calculation. On the basis of this calculation, a sample size comprising 74.2% of 70 patients was accepted as sufficient for statistical analyses.

All the 70 patients met the inclusion criteria for the study. Three patients stated that one-side henna application would affect their body image negatively and were excluded. The study commenced with 67

patients. During the study, 13 patients were lost to follow-up: five patients continued their therapy at another hospital and eight died. Two patients discontinued henna application. So, the study was completed with 52 patients (Figure 1).

Data Collection

First Interview with the Patient

In the first interview with the patients, the Patient Information Form was used to assess factors affecting the occurrence and severity of HFS.

Patient Information Form. The Patient Information Form prepared by the investigators was used to assess the personal (sex, age, educational status, occupation,

marital status, economic status, working status, and health insurance), disease/treatment (cancer diagnosis, stage of disease, previous and current treatment interventions, history of chronic disease, or concomitant drug), and cutaneous (structure, skin changes, and sensitivity of the skin) characteristics suggested as factors affecting the occurrence and severity of HFS.

Patient Follow-Up

The prophylactic effect of henna was assessed weekly over phone and three-weekly during the patient's visit.

Between treatment cycles, the weekly phone call with the patient was done by the nurse researcher, and capecitabine use, weekly renewal of henna and skin change on the hands and feet were assessed by asking questions of the patients.

At the treatment approval visit of the patients, capecitabine-related adverse effects and visual skin changes on their hands and feet were evaluated by the medical oncologist.

The national cancer institute common terminology criteria for adverse events - version 4.03 (NCI-CTCAE v4.03) - and The Hand-Foot Syndrome-14 (HFS-14) were used during the follow up.

National cancer institute common terminology criteria for adverse events - version 4.03.

The national cancer institute common terminology criteria for adverse events - version 4.03 (NCI-CTCAE v4.03) were used as the baseline for the follow up study data for capecitabine-related cutaneous changes. NCI-CTCAE v4.03 is a classification tool used to assess and report cancer treatment related adverse events in oncology (CTCAE, 2010). NCI-CTCAE version 4.03 consists of about 700 descriptive terms. Each term is assessed using a 5-point verbal descriptor grading scale, with each grade following a similar grading convention (i.e. 0 = not present, 1 = mild, 2 = moderate, 3 = severe and/or requiring medical intervention but not life-threatening, 4 = life-threatening consequences, and 5 = death). The severity of the chemotherapy related HFS is classified as a PPE term between 0 and 3 because it not a life-threatening adverse event.

- Grad 0: None,
- Grade 1: Minimal cutaneous changes or dermatitis without pain (eg. erythema, edema, or hyperkeratosis).

- Grade 2: Painful cutaneous changes that block daily activities (eg. rawness, intumescence, bleeding, edema, bulla formation, or hyperkeratosis).
- Grade 3: Painful serious cutaneous changes that block self-care (eg. rawness, intumescence, bleeding, edema, bulla formation, or hyperkeratosis).

Hand-Foot Syndrome-14. The HFS-14 was used for patients who had HFS development. HFS-14, developed by Sibaud et al. (2011), is an evaluation tool with 17 items used to assess the effect of HFS on the quality of life. The permission for use was taken from the authors.

The first question in the scale evaluated the type of the affected limb [hand or foot alone, or both (both hand and foot)]. This question was scored as "1" if only the hands or the feet were affected and as "3" if both were affected.

The second question of the scale evaluated if the HFS was painful or not. This question was scored as "1" in case of no pain, as "2" in case of moderate pain, and as "3" in case of severe pain.

The third question asked the patient to mark his/her HFS-related pain on the Visual Analog Scale between 0 and 10.

The last 14 items of the scale evaluated the degree of HFS-related contagion in 3 subdimensions with a Likert-type scale [hand (1-8), foot (3 and 5-11) and social (12-14)]. Questions on hand and foot subdimensions evaluated the disease related inabilities of the hands and feet of the patients, and the questions on the social subdimension evaluated the effects of HFS on social life. Each item was scored using the triple Likert classification, which was "0" if the answer was "no, never", "3" if the answer was "yes, sometimes", and "6" if the answer was "yes, always".

All the answers were collected, and the total score related to the HFS-14 scale was obtained. The minimum total score was 2 and the maximum was 100. The higher the score, the more negatively affected was the quality of life.

In 2015, the validity and reliability of the Turkish version of the scale was performed by Ozdemir and Can. The internal consistency coefficient (Cronbach

Alpha) of the HFS-14 scale was 0.81 (Ozdemir & Can, 2015).

Intervention

One hand and foot of each patient were used as the study hand-foot, and the remaining were used as control.

The control hand-foot did not undergo any intervention, and the standard protocol of the clinic was followed.

The first henna application on the study hand-foot was done by the investigator on the day of capecitabine treatment, and the patient was trained to renew it once weekly.

Four spoons of lyophilized henna were mixed in about 100 cc water and applied on the plantar region of the study foot and palmar region of the study hand to cover the fingers, and then covered with bandage. The patient was told to take off the bandage 6 hours later and to wash the hand and foot in water.

Pure henna was used in the study. It was obtained from a spice and chemical substances company that had ISO 22,000 and ISO 9001 quality certificates. Certificates that declared the harmless nature of the henna and the ingredients were also obtained from this company.

Following completion of the henna application and training, a training brochure about the application of henna at home and the henna packaged in proper quantities for each week were given to the family of the patient. The patient and the family were then sent home.

Termination Criteria for Patient Follow-Up

Development of drug-related Grade 1-3 HFS or cessation of capecitabine treatment were set as the termination criteria for patient follow up. The decision was made by the medical oncologist depending on patient's self-report or examination. Patients who reported a skin change were asked to take a picture and send to us.

The types of skin changes observed in the pictures were evaluated and recorded according to the NCI-CTCAE v4.03 – PPE form. Henna application was stopped in patients who developed Grade 1, 2, or 3

HFS, and the standard clinical protocol was followed to manage it. Furthermore, the effect of the skin changes on the quality of life was assessed for these patients using the HFS-14 scale.

The color change because of henna did not affect or complicate the interpretation of HFS-related erythema and pigmentary changes, and hand/foot skin changes were easily noticed.

Statistical Analysis

The Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA) client program package was used for statistical analyses of the data. Descriptive statistics such as percentage, mean, standard deviation and median were used for evaluation of the descriptive data. The Chi-square test was used to evaluate the efficacy of henna application in the development of HFS. Comparative tests like the Mann-Whitney U test that investigates the difference between the groups were used to define important parameters in HFS. A p value of <0.05 was accepted as statistically significant.

Ethical Considerations

This study was approved by the Istanbul University – Istanbul Medical Faculty Clinical Research Ethics Committee (Decision No. 812). Written consent was obtained from Sibaud by mail to use his HFS-14 scale in our study. Written and verbal consents of the patients were obtained.

Results

The mean age of the patients was 56.23±12.29 [range: 35-82]. Many of the patients had primary school of education (63.5%). Most of them were women (71.2%) and housewives (63.5%) (Table 1).

Most of the patients had metastatic disease (73.1%), some of them had previous surgery (92.3%) and radiotherapy (57.7%). Some patients had been treated with a number of chemotherapy protocols in the past ($x=2.73\pm 1.88$, range: 0-7). Capecitabine treatment was started as monotherapy within the chemotherapy protocol for 48.1% and as combined therapy for 51.9%. No chemotherapy related adverse effect was observed in 42.3%. The most frequent adverse effect reported by the patients was HFS, which was reported by 32.6%. Only 3.8% of patients had HFS, and 23.1% had peripheral neuropathy related to previous chemotherapy and all patients

Table 1
Socio-Demographic Characteristics of the Patients (n=52)

	n	%
Gender		
Female	37	71.2
Male	15	28.8
Educational status		
Primary school	33	63.5
Secondary school	7	13.5
High school	5	9.6
University or higher	7	13.5
Occupational status		
Working	2	3.8
Housewife	33	63.5
Retired	14	26.9
Other	3	5.8

reported they had had no skin sensitivity in the past. Moreover, 32.7% of patients had concomitant chronic disease with cancer, and 34.6% were taking medication for non-cancer chronic health disease concurrently with cancer treatment (Table 2).

Hand-Foot Syndrome-Related Characteristics

The median duration of follow-up was 3 cycles ($\bar{x}=3.44\pm 1.60$, range: 0-8). HFS was commonly observed in the 3rd or 4th cycle of the therapy. HFS developed in 17 patients. Painful skin changes that blocked the daily activities and self-care of the patients (eg. rawness, intumescence, bleeding, edema, bulla formation, or hyperkeratosis) were observed in 25.0% (n=13) as Grade 2 and 3. In 3 patients the drug dose was reduced, in 1 patient it was interrupted, and in 4 patients the drug therapy was discontinued. No changes were made in the treatment of other patients (Table 3).

Effect of HFS on the Quality of Life

Many of the patients stated that the severity of the HFS-related pain was moderate. Standing (25%), walking (21.2%) and performing everyday actions (23.1%) were the commonly affected daily activities of patients. The mean HFS score of the patients was 26.41 ± 12.58 (Table 4).

Table 2
Disease-and Treatment-Related Characteristics (n=52)

	n	%
Diagnosis		
Breast cancer	28	53.8
Colon-rectum cancer	24	46.2
Disease stage		
Stage II	3	5.8
Stage III	11	21.2
Stage IV	38	73.1
Surgical treatment		
Not performed	4	7.7
Performed	48	92.3
Radiotherapy		
Not recieved	22	42.3
Recieved	30	57.7
Chemotherapy protocol		
Capecitabine monotherapy	25	48.1
Combined therapy	27	51.9
Chemotherapy- related adverse effect		
Not observed	22	42.3
HFS	17	32.6
Constipation	9	17.3
Nausea-vomiting	9	17.3
Loss of appetite	7	13.4
Diarrhea	4	7.7
Fatigue	1	1.9
HFS in previous chemotherapy		
Not developed	50	96.2
Developed	2	3.8
Peripheral neuropathy in previous chemotherapy		
Not developed	40	76.9
Developed	12	23.1
Presence of a concomitant chronic disease		
No	35	67.3
Yes	17	32.7
Concomitant drug usage except for cancer treatment		
Yes, using	18	34.6
No, not using	34	65.4
Skin sensitivity		
None	52	100.0
\bar{x} \pm SD		
Treated with a number of chemotherapy protocols in the past	2.73	1.88

Note. HFS: Hand-Foot Syndrome

Table 3
Hand-Foot Syndrome-Related Characteristics (n=52)

	n	%
HFS		
Not developed	35	67.3
Developed	17	32.7
Cycles of treatment in which HFS was developed		
2nd cycle	1	1.9
3rd cycle	7	13.5
4th cycle	7	13.5
5th cycle	2	3.8
Severity of HFS		
Grade 0 No cutaneous change	35	67.3
Grade 1 Minimal skin changes or dermatitis (eg. erythema, edema. or hyperkeratosis) without pain	4	7.7
Grade 2 Skin changes with pain. limiting instrumental activities of daily living ¹	12	23.1
Grade 3 Severe skin changes with pain. limiting self-care activities of daily living ¹	1	1.9
Management of HFS		
Capecitabine dose was reduced	3	5.7
Capecitabine treatment was interrupted	1	1.9
Capecitabine treatment was discontinued	4	7.6
	\bar{x}	$\pm SD$
The median duration of follow-up	3.44	1.60

Note. HFS: Hand-Foot Syndrome; SD: Standard deviation
¹(e.g. peeling, blisters, bleeding, edema, or hyperkeratosis)

Prophylactic Effect of Henna Application in the Prevention of HFS

It was observed that the development of HFS in both hands and feet was similar and there were no statistical differences (Table 5).

Factors Affecting the Development of HFS

The incidence of HFS was higher in young patients ($z_{MWU}=-3.66$; $p=.0001$), in women (OR 6.48, 95% CI, 0.94-44.65), in patients with breast cancer (OR 13.71 95% CI, 1.96-95.94), and in those who had

previously had several different chemotherapy treatments ($z_{MWU}=-3.87$; $p=.0001$). Capecitabine combination or monotherapy was not an important variable in the development of HFS ($p=0.28$) (Table 6).

Discussion

Breast and colorectal cancers are major diseases affecting the population in our country. Although important advances have been made in the early diagnosis and treatment of these two cancer types (Tuncer, 2009), the antineoplastic agents used in the systemic treatment of the disease still lead to many adverse effects that impair the quality of life of the patients (Wild et al., 2019). One of these adverse effects is HFS, observed secondary to capecitabine used in the treatment of breast and colorectal cancers (Liu et al., 2002; Nishida, 2003; Smorenburg et al., 2001).

The incidence of capecitabine-related HFS in our study was 32.6%, which is lower than that reported in the literature. Capecitabine-related HFS is caused by dose-dependent toxicity. In our country capecitabine doses in the chemotherapy regimens are lower than those in other countries. The FDA recommended dose is 1250 mg/m² twice a day; however, 1000 mg/m² is better tolerated (Bajetta et al., 2005). However, it is generally recommended twice daily (850-1000 mg /m²) in our country (Sezgin et al., 2007; Ustaalioglu et al., 2018).

Two studies in the literature, one being a case report, have reported the beneficial effects of henna in relieving this syndrome (Ilyas et al., 2014; Yucel & Guzin, 2008). The first study conducted by Yucel and Guzin in 2008 included 10 patients with capecitabine-related HFS. Six of these patients had grade 3 and 4 had grade 2 HFS. The investigators applied henna to the hands and feet of the patients who developed HFS without cessation of the drug therapy and evaluated the efficacy of henna application at the end of one week. The evaluation revealed complete cure in 8 of 10 patients with henna application and regressed the grade from 3 to 1 in 2 patients (Yucel & Guzin, 2008). A similar effect has been reported in the case report of Ilyas et al. In this case, capecitabine-related grade 2 HFS developed in the 2nd cycle of the treatment. Two weeks after the investigators applied henna to the patient, the grade 2 HFS regressed to grade 0 (Ilyas et al., 2014). This study, which was planned considering these earlier studies demonstrating the

Table 4
Hand-Foot Syndrome-Related Quality of Life (n=17)

	n	%
HFS region		
Hand or foot	4	7.7
Hand and foot	13	25.0
HFS-related pain		
No pain	4	7.7
Moderate pain	11	21.2
Severe pain	2	3.8
Visual Analog Scale (0-10)		
3	4	7.7
6	11	21.2
10	2	3.8

Because of my HFS.	No, never		Yes, from time to time		Yes, always	
	n	%	n	%	n	%
1. I find it hard to turn the key in my door	11	21.2	6	11.5	-	-
2. I find it hard to prepare my meals	13	25.0	4	7.7	-	-
3. I have difficulty performing everyday actions	4	7.7	12	23.1	1	1.9
4. I have difficulty washing myself, putting on makeup (or shaving)	10	19.2	6	11.5	1	1.9
5. I find it hard to drive my car	16	30.8	1	1.9	-	-
6. I find it hard to put on my stockings/tights (or my socks)	15	28.8	2	3.8	-	-
7. I take longer than usual to get dressed	16	30.8	1	1.9	-	-
8. I have difficulty putting on my shoes	7	13.5	9	17.3	1	1.9
9. It is hard for me to stand	3	5.8	13	25.0	1	1.9
10. I have difficulty walking, even over quite short distances	5	9.6	11	21.2	1	1.9
11. I tend to stay seated or lying down	12	23.1	4	7.7	1	1.9
12. I find it hard to fall asleep	7	13.5	9	17.3	1	1.9
13. My work is suffering	17	32.7	-	-	-	-
14. My relationships with others are less amicable	17	32.7	-	-	-	-
		Median	Mean	±SD	Min.	Max.
HFS Score		27	26.41	12.58	0	7

Note. HFS: Hand-Foot Syndrome; SD: Standard deviation; Min: Minimum; Max: Maximum

Table 5
Henna in Prevention of the Hand-Foot Syndrome (n=52)

	Control hand/foot (n=52)		Study hand/foot (n=52)		χ^2	p
	n	%	n	%		
Hands						
No HFS development	40	76.9	42	80.8	0,23	0.63
HFS development	12	23.1	10	19.2		
Feet No HFS development	39	75.0	42	80.8	0,50	0.47
HFS development	13	25.0	10	19.2		
Affected site						
No HFS development	38	73.1	40	76.9	0,66	0.71
HFS development on hand or foot	3	5.8	4	7.7		
HFS development on hand and foot	11	21.1	8	15.4		

Note. HFS: Hand-Foot Syndrome

Table 6
Factors Affecting the Development of Hand-Foot Syndrome (n=52). The effect of Gender, Disease Diagnosis, Chemotherapy Protocol, Chemotherapy Change Count, Age on the HFS (n=52)

Gender	Women (n=37)		Men (n=15)		χ^2	p		
	n	%	n	%				
No HFS development	21	56.8	14	93.3	4.93	0.03		
HFS development	16	43.2	1	6.7				
Disease Diagnosis								
Disease Diagnosis	Breast cancer (n=28)		Colorectal cancer (n=24)		χ^2	p		
	n	%	n	%				
No HFS development	12	42.9	23	95.8	16.48	0.0001		
HFS development	16	57.1	1	4.2				
Chemotherapy Protocol								
Chemotherapy Protocol	Combine therapy (n=27)		Monotherapy (n=25)		χ^2	p		
	n	%	n	%				
No HFS development	20	74.1	15	60.0	1.17	0.28		
HFS development	7	25.9	10	40.0				
Chemotherapy Change Count								
Number of chemotherapy changes	No HFS development (n=35)			HFS development (n=17)			zMWU	p
	\bar{x}	\pm SD	med	\bar{x}	\pm SD	med		
Number of chemotherapy changes	2.03	1.65	2.00	4.18	1.47	4.00	-3.87	0.0001
Age								
Age	No HFS development (n=35)			HFS development (n=17)			zMWU	p
	\bar{x}	\pm SD	med	\bar{x}	\pm SD	med		
Age	60.60	11.60	61.00	47.41	8.34	47.00	-3.66	0.0001

Note. HFS: Hand-Foot Syndrome; SD: Standard deviation; Med: Median; MWU; Mann-Whitney U

beneficial effect of henna in HFS, was aimed at investigating if henna had a preventive effect for HFS. The design of our prospective experimental study was planned based on these two studies, as the previous studies had not evaluated the prophylactic efficacy of henna (Ilyas et al., 2014; Yucel & Guzin, 2008). Yucel and Guzin applied a henna and water mix to both hands- feet of the patients, covered them with bandage, and washed under water 5-6 hours later. They repeated the application once a week (Yucel & Guzin, 2008). Ilyas et al. prepared the henna with water and applied it to both hands and feet of the cases, banded the extremities, and different from the previous study, they washed the limbs in the morning. The patient repeated the application twice a week (Ilyas et al., 2014). We formed our protocol based on these studies.

It was observed that henna was not an effective approach to the prevention of HFS in this study. The syndrome commonly developed in the 2nd or later cycle as grade 2. When the studies in the literature on the severity and timing of HFS development were investigated, it was observed that they generally developed as grade 2 and commonly in the 2nd cycle or later (Abushullaih et al., 2002; Blum et al., 2001; Son et al., 2009; Tortumluoglu, 2006). The severity and timing of HFS development observed in our study were in compliance with the results in the literature.

Although the antibacterial, antifungal, analgesic, anti-inflammatory, and the antioxidant effects of henna have been reported in different studies in the literature (Ali et al., 1995; Elzayat, 2018; Mikhaeil et al., 2004; Mutluoğlu & Uzun, 2009; Rahmoun et al., 2013), the prophylactic effect of henna could not be demonstrated in this study. This may possibly be related to the effect of capecitabine on epidermal cells that lead to cutaneous changes and formation of necrotic keratinocytes (Miller et al., 2014). The reason for the disease being regional at the palmar and plantar regions is not known; however, it is believed that the thick nature of stratum corneum, heat gradient, absence of sebaceous glands and hair follicles, high eccrine gland concentration, and wide dermal papilla may have a role in the development of the disease (Baack & Burgdorf, 1991; Miller et al., 2014; Susser et al., 1999).

As the capecitabine dose is increased, when used in combination with other chemotherapeutic agents

(eg. docetaxel-capacitabine treatment), this effect is increased and the risk of HFS is increased. Studies have reported a higher incidence of HFS in the combined use of docetaxel and capecitabine, compared to other combined therapies (Heo et al., 2004). In our study, no significant difference was observed in the incidence of HFS in combined capecitabine regimens ($p>0.05$). This may be because of the low dose use of capecitabine in combined regimens in our country.

It has been reported in the literature that use of capecitabine as monotherapy or in combination shows a difference with regard to the development of HFS. In our study, no difference was observed between the incidence of HFS in patients receiving capecitabine as monotherapy or combined therapy.

The studies in the literature have also reported that the capecitabine-related syndrome is more severe in the feet than hands since the feet are exposed to higher pressures (Abushullaih et al., 2002; Son et al., 2009). Development of the syndrome in hands and feet were similar in this study. Our patients reported problems in standing and walking related to the development of HFS, and it was observed that the quality of life of the patients had been negatively affected.

It has been reported in the literature that age, sex, high performance score, chemotherapy protocol, drug dose, and presence of stomatitis are important variables in the development of HFS therapies (Heo et al., 2004). The statistical analysis performed in our study revealed that age, sex, diagnosis and the number of chemotherapy exchanges were important parameters in the development of HFS.

It has been reported in the literature that age and sex are not important variables in the development of capecitabine-related HFS (Ali et al., 1995; Blum et al., 2001; Ilyas et al., 2014; Liu et al., 2002; Macedo et al., 2014; Mikhaeil et al., 2004; Mutluoğlu & Uzun, 2009; Rahmoun et al., 2013; Tortumluoglu, 2006; Yucel & Guzin, 2008), and that they are important in the development of intravenous fluorouracil application-related HFS (Baack & Burgdorf, 1991). It has been reported in previous study that the risk is higher in the elderly and female patients receiving intravenous fluorouracil (Levy et al., 1998). In our study group, it was observed that the mean age of the patients with HFS was lower than those with-

out HFS and that the syndrome was more frequent among women. The reason for this may be the application of more aggressive treatment in young patients compared to the elderly. Furthermore, the skin of palmar and plantar regions of women is thinner than in men, easily damaged during housework because of exposure to cleaning agents, and is more susceptible to high and low temperatures, which may be the reason for a higher incidence among women (Lammintausta et al., 1987; Meh & Denislic, 1994; Seidenari et al., 1994).

Conclusion and Recommendations

It was concluded that henna application had no preventive effect on the development of HFS, did not reduce its severity and had no effect on its progression.

The results of this study can be used to update the interventions for management of the HFS in booklets and guides. Further studies with a larger sample size are needed to conclude on the prophylactic effect of henna in the management of the HFS.

Ethics Committee Approval: This study was approved by Istanbul Medical Faculty Clinical Research Ethics Committee (Decision No. 812).

Informed Consent: Verbal and written informed consent was obtained from the patients who agreed to take part in the study.

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