DARU Journal of Pharmaceutical Sciences (2022) 30:117–125
https://doi.org/10.1007/s40199-022-00438-8

RESEARCH ARTICLE

Topical henna and curcumin (Alpha®) ointment efficacy for prevention of capecitabine induced hand-foot syndrome: A randomized, triple-blinded, placebo-controlled clinical

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Received: 21 September 2021 / Accepted: 17 February 2022 / Published online: 23 March 2022

Abstract

Purpose In this clinical trial, we evaluated Alpha® ointment efficacy in prevention of capecitabine induced hand-foot syndrome (HFS) in patients with gastrointestinal or breast cancers, for the first time.

Methods During this pilot, randomized, triple-blinded, placebo-controlled clinical trial, the effect of Alpha® ointment (*Lawsonia inermis* 3 g and *Curcuma longa 0*.15 g/ 30 g*)* was assessed. It was applied on the palms and the soles, two times daily starting at the first day of chemotherapy for 4 consecutive courses. The severity of HFS was assessed at the end of the chemotherapy courses based on World Health Organization (WHO) scale and scored between 0–4.

Results Ninety eligible patients were included randomly in the treatment or placebo group. Median WHO HFS grade was not significantly different between the two groups, during the follow-up period ($P > 0.05$). In the weekly assessment, the scores increased meaningfully in both the placebo and treatment groups, but there was a delay in HFS occurrence and deterioration in Alpha ointment group based on post hoc analysis.

Conclusion Administration of Alpha® ointment containing henna and curcumin could not significantly prevent capecitabine induced HFS during 4 courses of treatment, but can somewhat delay its occurrence in patients with gastrointestinal or breast cancer.

Keyword Hand-foot syndrome- Capecitabine- Henna- *Lawsonia inermis*- Curcumin

Introduction

It is estimated that annually 19.3 million cancer cases and over 10 million cancer deaths happen all over the world [1]. Based on World Health Organization (WHO) report in 2019, cancer is the first or second important cause of death before the age of seventy in most countries [2].

Capecitabine is an oral prodrug of 5–fluorouracil (5-FU) which prevents cell replication through thymidylate synthase inhibition. It produces 5-FU exactly at the tumor site, reducing systemic drug distribution. Better safety profile beside acceptable efficacy compared with 5-FU infusion as well as more convenient administration make capecitabine an attractive option for the treatment of various kinds of cancers, including breast, head and neck, gastrointestinal and genitourinary tracts [3–5].

Capecitabine is mostly well tolerated. The dose limiting adverse reactions are hyperbilirubinemia, diarrhea, and hand-foot syndrome (HFS). HFS is more common with capecitabine in comparison with 5-FU and is happened in at least half of the patients. The severe form of HFS occurred in about 10–20% of the patients [6, 7].

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It is initially manifested as dysesthesia and tingling in the palms and the soles. Then, symmetric edema and redness of the skin with pain or burning sense can occur. If proper dose adjustment based on available guidelines do not perform, blistering or scaling of the skin and sometimes secondary infections, can take place [4, 8].

Although HFS is not typically a serious and fatal reaction, but it can decrease quality of life of patients and interfere with their daily activities. Moreover, patients who experienced National Cancer Institute Common Toxicity Criteria (NCI-CTC) toxicity grade 2 or higher, need capecitabine dose adjustment during the current course and/or for the next cycle and maybe temporarily discontinuation of capecitabine [9–11].

No definite preventive or therapeutic measure has been established for HFS. However, numerous supportive or experimental interventions are mentioned based on available studies including local cooling of the hands and feet, prevention of considerable temperature variations, pressure, or skin abrasion, wound care, use of emollients like urea-based creams, silymarin gel, topical or oral corticosteroids, antibiotics for secondary infection prophylaxis, vitamin B6 and E, cyclo-oxygenase-2 (COX-2) inhibitors, and amifostine [3, 4, 9, 12]. However, well-designed clinical trials assessing their effectiveness are missing.

The pathogenesis of HFS is not fully understood, but direct toxic effect is suggested as the utmost possible mechanism. Drug metabolite accumulation in the skin, resulting from high levels of the thymidine phosphorylase and dihydropyrimidine dehydrogenase (DPD) enzymes in keratinocytes is related to HFS occurrence [13]. Besides, the augmented number of eccrine glands on the palms and soles may play an important role, as capecitabine may be removed by this system [14]. The dense stratum corneum of the palms and soles plays an important role as a reservoir, which could cause an oxidative injury and produce toxic free radicals. Chemokines mediating this reaction include interleukin (IL)-1a and b, 6, 8, growth-related oncogene (GRO) and fractalkine (CX3CL1) [12, 14].

Henna is a dye extracted from the dried leaves and the skin of *Lawsonia inermis* branches, a member of lythracea family. It is widely used in some Asian countries particularly India, Pakistan, Turkey, Bangladesh, and some part of Middle East for cosmetic purposes like decorative paintings of the hands, feet, and nails as well as a dye for hair [14, 16–18]. It also can be used for medical purposes like as a preservative, an astringent, and an abortifacient. Its topical formulation was used for management of seborrhea and fungal infections [17]. The precise mechanism of action has not been clarified but based on animal studies antioxidant and immune-modulatory effects are suggested [18–20]. There are some case reports from Indian and Turkish patients with breast, colon or pancreatic cancers who received henna topically and experienced its therapeutic effects against HFS. This clinical improvement proposed to be due to anti-inflammatory, antipyretic and analgesic effects of henna [14, 18].

Curucumin, the main component of turmeric, is also famous for its anti-inflammatory and anti-oxidant activities. It could prevent the activation of prostaglandin biosynthesis and also c-Jun/AP-1, protein kinases and COX-2 expression and activity. It is also an oxygen scavenger and an inhibitor of lipid peroxidation [21]. In a clinical trial on 40 patients with gastrointestinal and breast cancer, turmeric with dose of 4 g/d for 6 weeks significantly reduced the rate of HFS and also serum level of c-reactive protein (CRP) and inflammatory biomarkers including tumor necrosis factor (TNF)-α and IL-6 [22].

As in our previous research on patients with gastrointestinal cancer, silymarin topical formulation was significantly effective in reduction of the capecitabine-induced HFS severity and delayed its occurrence after 9 weeks of use possibly via antioxidant and anti-inflammatory effects, in this study we tried to evaluate the effects of Alpha® ointment, including henna and curcumin, administration on hand-foot syndrome induced by capecitabine in a triple-blind randomized clinical trial.

Method

Study design

This study was a pilot, prospective, triple-blind, randomized, placebo-controlled clinical trial performed from April 2018 to December 2020, at the Oncology Department of Imam Reza Hospital affiliated to Mashhad University of Medical Sciences, Iran.

Study population

The inclusion criteria involved these items: Patients with colorectal, gastric, pancreatic or breast cancers who received capecitabine for the first time in XELOX regimen including oxaliplatin 130 mg/m^2 on first day and capecitabine (Xeloda®) 2000 mg/m^2 on days 1–15, every three weeks for gastrointestinal cancers or in dose of 1000 mg/m^2 twice daily on days 1 to 14 of a 21-day treatment cycle ± lapatinib in breast cancer, age higher than 18 years, Eastern Cooperative Oncology Group (ECOG) performance scale of 0–1, and normal bone marrow function. Patients with 1) hepatic failure (liver function tests > 5 times of upper limit normal, or > 3 times of upper limit normal and symptoms), 2) renal failure (GFR < 60 mL/min/1.73 m^2), 3) severe infection requiring antibiotic therapy, 4) dissatisfaction of patient, 5) history of allergy to curcumin or henna or Alpha® ointment, 6) history of autoimmune disease, diabetes mellitus,

concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and other immunosuppressive drugs and warfarin, and 7) patients suffering from mental illness were not included in the study.

Ethics

The study protocol was approved by the local Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1397.624) and was registered at the Iranian Registry of Clinical Trials (IRCT20181230042179N1). All participants signed a written consent forms.

Study protocol

Patients were randomly allocated to either the treatment (Alpha® ointment) or the placebo group. The treatment ointment used in this trial was a commercially available ointment, produced by Alpha development Company, Tehran, Iran for more than 10 years (production license: 61,305). This medication is covered by the national insurance and presented in all pharmacies in Iran. It is produced in 30 g tubes and included *Lawsonia inermis* extract 3 g and *Curcuma longa* extract 0.15 g in each tube. The Alpha® ointments were bought from one of the teaching pharmacy of Mashhad University of Medical Sciences, Iran.

Patients in treatment group received Alpha® ointment twice daily. Half fingertip unit of the ointment was applied on the soles and one fingertip unit on the palms from the first day of chemotherapy with capecitabine and continued consecutively for 4 courses. The placebo ointment was produced identically, containing all ingredients of Alpha® ointment except active components and colored (with food coloring) to match it.

All of the patients received capecitabine (Xeloda®) with abovementioned amount, in two divided doses morning and evening, 12 h apart after breakfast and dinner for 4 courses of chemotherapy. The total capecitabine dose was almost identical for all patients per cycle. Patients did not receive any other medication or supportive measure for HFS prevention or management. It is worth to mention that capecitabine dose was reduced or temporarily discontinued based on available guideline [11], if high grade HFS occurred.

Outcomes

Based on former studies that have reported HFS occurrence peaks within the first three cycles of chemotherapy [23], patients were examined by the oncologist regarding HFS occurrence at the beginning of chemotherapy and at the end of each chemotherapy course based on WHO HFS grading scale [24], for 4 cycles.

The WHO grading system scores the severity of HFS considering dysesthesia/ paresthesia, tingling, discomfort in holding items or upon walking, painless/ painful swelling and erythema of the palms and soles, desquamation, ulceration and blistering between 0 to 4. This is one of the two most frequent used HFS scoring systems beside the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale [23, 24]. However, as WHO scoring system puts severe cases in two separate groups (grade 3 or 4) instead of one (grade 3) in NCI CTCAE, we could have more accurate evaluation and comparison between the placebo and medication groups.

Liver and kidney function tests were also assessed at the end of each course.

Additionally, patients' drug administration compliance and adverse events were followed through the study. They were considered to be adherent to their treatment if they consumed one tube of drug/placebo ointment (30 g) every three weeks. Common Terminology Criteria for Adverse Events version 4 was used to assess the adverse events [11].

Sample size

Since to the best of our knowledge, there was no clinical trial on topical formulation including *Lawsonia inermis* and *Curcuma longa* extracts efficacy for prevention and management of hand-foot syndrome induced by capecitabine, we defined this study as a pilot one. Based on Whitehead et al. [25] recommendation, for a main trial designed with 90% power and two-sided 5% significance, pilot trial sample sizes per treatment arm of 75, 25, 15 and 10 is enough for standardised effect sizes that are extra small (≤ 0.1), small (0.2), medium (0.5) or large (0.8), respectively. So, assuming that the effect size of Alpha® ointment is small, the sample size is defined 40 patients in each group. However, 55 patients are included in each arm to increase the study's accuracy.

Randomization and blinding

A computer generated list of sequential random allocation was produced by using randomization.com site. Then, block randomization of four patients was used to ensure balanced allocation of eligible patients in the placebo and treatment arms. Alpha® and placebo ointments were filled in the boxes with same appearance by an unrelated person to the study (one of the pharmacists working in the teaching pharmacy that we bought Alpha® ointments from there) which were marked with letter A (treatment) or B (placebo) by the clinical pharmacist and delivered to the oncologist. Each box filled with 30 g of Alpha® or placebo ointment which was enough for a period of 3 weeks. Patients who fulfilled the inclusion criteria were selected by the oncologist. She

entered patients randomly in two groups (A or B) based on randomization list and gave them boxes marked A or B. Patients' assessment during the chemotherapy course regarding HFS occurrence and its severity were done by the oncologist. The clinical pharmacist analyzed the data. Patients, the oncologist and the clinical pharmacist were all not aware of the group allocation of the patients.

Statistical methods

SPSS software, version 21 was used for data analysis. Results have been presented as mean ± standard deviation or median (range) for normally and non-normally distributed continuous variables, respectively and number (percentages) for nominal variables. Kolmogorov–Smirnov test was used to evaluate the normality of the variables distributions. Independent sample t-test and Mann–Whitney U-test were used respectively to compare normally and non-normally distributed variables between the two groups at the initiation and at the end of the study. Friedman test and Wilcoxon signed rank test were used for multiple comparisons in each group during the study. Fisher exact test was used to compare proportions between the groups; $p < 0.05$ was proposed as significant. It should be mentioned that data were analyzed per protocol.

Results

Out of the 135 screened patients, 110 subjects were eligible to be enrolled in the study based on the inclusion criteria. Forty-six patients in the treatment group and 44 patients in the placebo group finally completed the study (Fig. 1). All these patients received the same cumulative dose of capecitabine during the study course. One-hundred and ten patients with average age of 56.25 ± 11.51 years completed the study. All of them were adherent to treatment/placebo ointment during the two months follow-up. About 66% of patients were female. Colorectal cancer was the most common diagnosis in the treatment and placebo groups (50.1% vs. 56.8%; p value = 0.29). Most of the patients in the treatment group experienced metastatic cancer (58.7%), in contrast to the placebo group (47.7%). However the difference was not significant (P = 0.38). XELOX was the most common prescribed chemotherapy regimen in both groups (91.4 vs. 83.8, treatment vs. placebo group). It is worth to mention that the mean daily number of capecitabine 500 mg capsule (per m^2) was not significantly different between two groups (3.45 ± 0.46 vs. 3.44 ± 0.5, treatment vs. placebo groups) (P = 0.93).

Patients' demographics including age, sex and weight in both groups are summarized and compared in Table 1. There were no significant differences between groups regarding these characteristics.

Moreover, WHO HFS score was 0 for all patients of both groups at the beginning of the study.

The median grade of HFS was not significantly different between two groups at the end of all four assessed courses of chemotherapy (Table 2).

As it is obvious in Table 3, no patients in both groups experienced grade 4 HFS at the end of the first course; however the rate of grade 1 involvement was about two times higher in the placebo group. At the end of the second course, one patient in each arm experienced grade 3 and the rate of grade 2 HFS was higher in the placebo group. At the end of the third course, the rate of grade 3 involvements was about two times higher in the placebo group. Finally at the end of fourth course, we found grade 4 HFS in both groups with similar rate. No significant difference was found between two groups at the end of all four courses of chemotherapy (Table 3).

Comparing the WHO HFS scores in each group, the scores have increased significantly in both treatment and placebo groups during 4 courses of chemotherapy ($\chi 2 = 55.83$, p value < 0.001). Post hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction, resulting in a significance level set at p value < 0.008. Based on Table 4, there was no significant difference between WHO HFS scores of patients in the treatment group in any two consecutive weeks until the third course. But in the placebo group, the difference was significant between all consecutive weeks. So, it seems that despite the progressive trend of HFS in both groups during the chemotherapy course, Alpha® ointment may cause a delay in HFS occurrence and also decelerate its progression (Table 4).

Intention-to-treat analysis was not performed, as the data related to the patients who had not completed the study is not available.

Alpha® and the placebo ointment were well tolerated and no adverse effects were reported by the participants related to their use.

Discussion

In the present study, based on findings of the previous case reports, we evaluated Alpha® ointment efficacy for prevention of capecitabine induced HFS. There was no significant difference between WHO HFS scores among Alpha® ointment and the placebo group at the end of four chemotherapy courses. Moreover, in both groups the median grade increased meaningfully during the follow-up period. Therefore, it seems that topical henna and curcumin use with available doses in Alpha® ointment is not effective in prevention of capecitabine induced HFS. However, as the differences between two consecutive weekly courses were not significant in treatment group in contrast to the placebo

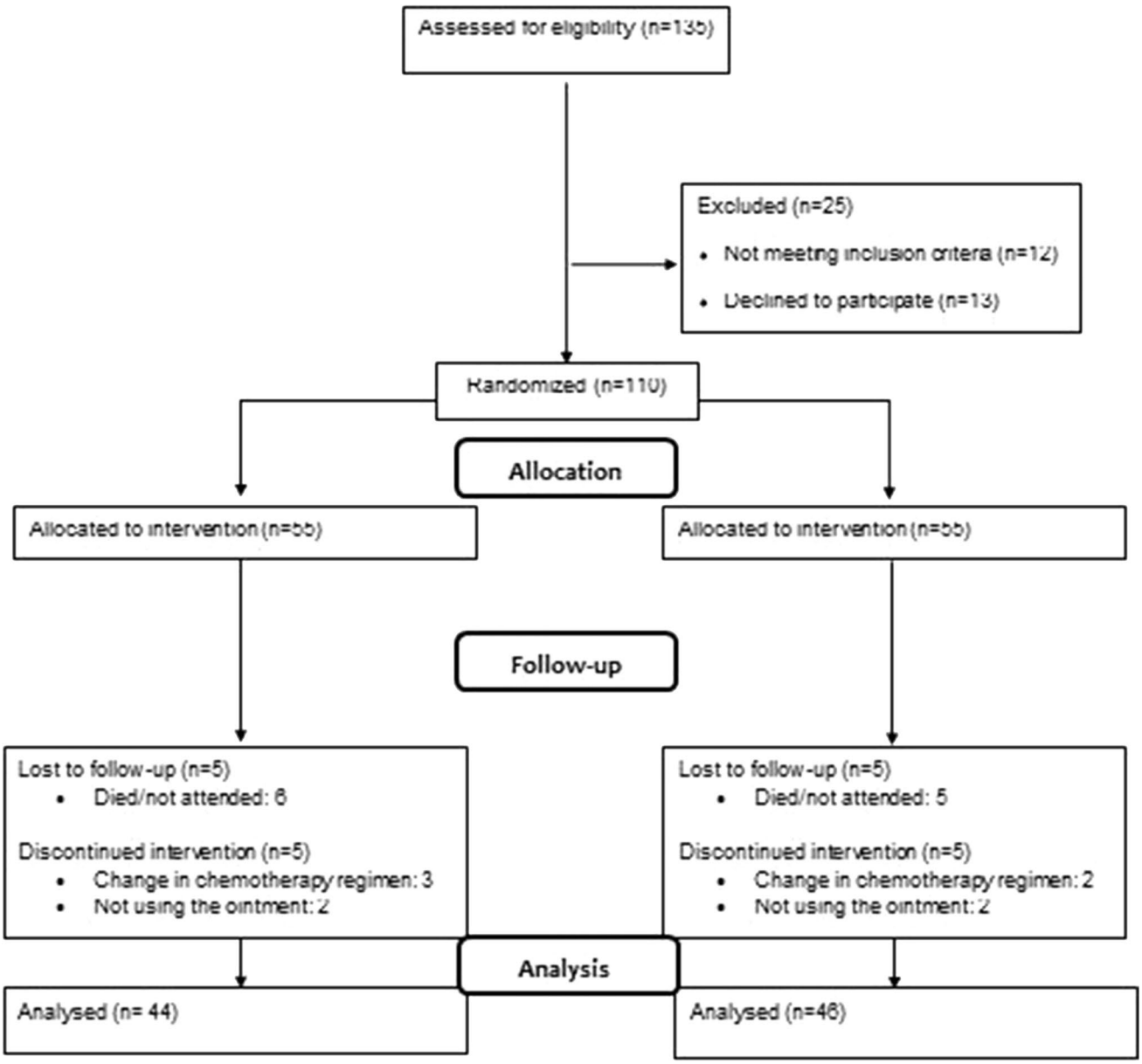

Fig. 1 Flow diagram of the study design

group, Alpha® ointment may slow down the progression of HFS.

Lawsonia inermis (henna) is a plant which is traditionally applied on the hands and feet in Middle-East since many years for cosmetic purposes. It was also used for treatment of fungal infections and seborrheic dermatitis [18]. There was also some case reports [14, 18] on its use for management of HFS in patients on chemotherapy, but to the best of our knowledge, this randomized clinical trial is the first study on the probable protective role of henna against capecitabine induced HFS in a topical formulation.

More than half of cancer patients who received capecitabine experience different grades of hand-foot syndrome [15, 23]. Capecitabine and its metabolites proposed to cause HFS by direct toxic effect. Thymidine phosphorylase is available in high concentration in keratinocytes of the palms and soles. This subject, beside high concentration of the eccrine system on these body regions which eliminates capecitabine is responsible for drug accumulation in the palms and soles. The thick stratum corneum of these areas also plays a role as a pool, resulting in the production of toxic free radicals and oxidative stress [4].

Table 1 Comparison of the patients' baseline characteristics between the treatment and placebo groups

Characteristics		Treatment group (n = 46)	Placebo group (n = 44)	*P*-value
Male:female (N)		16:30	14:30	**0.88**[a]
Age (year) (mean ± SD)		55.4 ± 12.9	57.1 ± 9.9	**0.49**[b]
Weight (kg) (mean ± SD)		59.5 ± 9.31	64.35 ± 10.53	**0.13**[b]
Body surface area (m^2)		1.6 ± 0.145	1.61 ± 0.144	**0.8**[b]
Daily number of capecitabine 500 mg capsules used each patient (per m^2)		3.45 ± 0.46	3.44 ± 0.5	**0.93**[b]
Cancer Type N (%)	Gastric N (%)	3 (6.5)	6 (13.6)	**0.29**[a]
	Colorectal N (%)	23 (50.1)	25 (56.8)	
	Pancreatic N (%)	8 (17.4)	5 (11.3)	
	Breast N (%)	8 (18.3)	12 (26)	
Regimen type N (%)	XELOX	42 (91.4)	37 (83.8)	**0.28**[a]
	Capecitabine N (%)	4 (8.6)	4 (9)	
	Capecitabine + lapatinib N (%)	0	3 (7.4)	

XELOX: oxaliplatin 130 mg/m2 on first day and capecitabine (Xeloda®) 2000 mg/m2 on days 1–15, every three weeks

[a]Chi-squared test

[b]Independent sample t-test

Lots of therapeutic measures are evaluated for prevention and management of HFS, but no completely effective agent was found and temporary pause of treatment and dose reduction are still the main measures for capecitabine induced HFS control [23, 26]. Some anti-inflammatory agents including celecoxib have revealed several encouraging findings in some studies [23, 26]. However, lots of trials on celecoxib have been postponed at this time, since there are some reports suggesting cardiovascular risks in relation with this medication [27–29].

Table 2 Comparison of the median WHO HFS scores of patients in the treatment and placebo groups

WHO HFS score	treatment Group (n = 46)[b]	Placebo Group(n = 42)[b]	*P*-value[a]
Baseline	0	0	-
At the end of the first course	0 (0–2)	0 (0–2)	0.35
At the end of the second course	0 (0–3)	0 (0–3)	0.75
At the end of the third course	0 (0–3)	0 (0–3)	0.39
At the end of the fourth course	1 (0–4)	1 (0–4)	0.43

WHO, World Health Organization. HFS: hand-foot syndrome

*Mann–Whitney test

[a]Median (range)

Topical high potency steroids have shown some desirable effects in the treatment of HFS [30]. However possible long-standing local adverse reactions, such as skin thinning should be checked carefully [26]. Limited studies are also available on antioxidant agents like vitamin E and silymarin with promising findings regarding prevention of HFS in patients treating with capecitabine [4, 31, 32].

Henna is a cheap natural herbal agent with anti-inflammatory, antipyretic, and pain-relieving properties. Besides, it acts as an antioxidant and immunomodulatory agent with no significant short-term and long-term side effects like corticosteroids [17, 33]. Guha et al. showed its antioxidant effects [34]. Philip Jacob et al. also defined antioxidant and radical scavenging activity of henna derivatives [20]. Moreover, there is some promising data on safety and efficacy of henna in accelerating wound healing [19, 20, 33, 34].

In a report by Yucel and Guzin, six patients with grade 3 HFS and four cases with grade 2 used henna topically weekly during chemotherapy with capecitabine with or without docetaxel for colorectal or breast cancer. Full recovery was found in four of grade 3 and all of grade 2 HFS; and two other patients with grade 3 HFS improved to grade 1. No dose reduction was necessary in all cases and also no side effect was reported. They proposed henna efficacy in management of HFS based on a patient's experience with grade 3 HFS in her feet after the first cycle of chemotherapy. As she used henna on her hand for cosmetic purpose and her hands were free of HFS, they suggested to her to use henna on her feet and the lesions disappeared after 1 week of henna use [18].

Table 3 HFS severity based on WHO scores in treatment and placebo groups during the study period

WHO HFS score grade	(%)0	(%)1	(%)2	(%)3	(%)4	P value[a]
Course 1						0.41
Treatment	86.96	10.87	2.17	0	0	
Placebo	77.27	20.45	2.28	0	0	
Course 2						0.67
Treatment	71.74	15.22	10.87	2.17	0	
Placebo	70.45	9.1	18.18	2.27	0	
Course 3						0.51
Treatment	60.87	17.39	13.04	8.7	0	
Placebo	61.36	9.1	13.64	15.9	0	
Course 4						0.78
Treatment	47.83	19.55	15.22	8.7	8.7	
Placebo	47.73	15.91	13.63	15.91	6.82	

WHO, World Health Organization; HFS, Hand-foot syndrome

[a]Chi-squared test

In another report, an Indian woman with pancreatic cancer receiving capecitabine, experienced grade 2 HFS at the end of the second course of chemotherapy. She decided to use henna on her feet and soles twice weekly and after two weeks, HFS resolved completely [14].

Curcumin, as the main component of turmeric also showed anti-inflammatory effects by reducing inflammatory cytokines and also inhibiting COX enzyme. It also acts a radical scavenging agent. Golmakani et al. evaluated the turmeric ointment efficacy on the wound healing of episiotomy in nulliparous women, however found no noteworthy change in pain severity between the treatment and control groups [35]. However, in another study performed by Chipodiora et al., curcumin was effective in the pain reduction [36]. Moreover, oral use of turmeric in dose of 4 g/d for 6 weeks beside capecitabine significantly reduced rate of HFS occurrence in gastrointestinal and breast cancer patients [22], but its topical efficacy is not assessed yet.

Alpha® ointment contains a combination of Lawson (Henna, 2-hydroxy-1,4-naphthoquinone) and curcumin. Henna is extracted from *Lawsonia inermis*, as its main component. Some previous studies evaluated this ointment in wound healing and found encouraging findings. According to the manufacturer, it is proposed to stimulate epithelialization and angiogenesis in the involved area and increase the elasticity of the tissue during its repair course. It also reduces inflammation and edema and prevents the infection spread [37]. Hoseini et al. showed its effectiveness in comparison with topical silver Sulfadiazine in grade 3 burn wounds infected by Pseudomonas aeruginosa. In another study, Alpha® ointment (n = 30) stimulated healing process of radiodermatitis more effectively than topical hydrocortisone cream (1%) (n = 30) in the second week of treatment and considerably reduced the patients' complaints including pain, pruritus, and discharge, when applying two times daily [38].

However, in another randomized trial Alpha® ointment did not significantly reduce the pain after episiotomy in 35 nulliparous women who used it once daily during 2–10 days after delivery, in comparison with the placebo [35].

There are some hypothetical explanations for the ineffectiveness of Alpha® ointment in present study, in contrast to the previous case reports. First, in those cases reports patients used henna directly on their hands and feet. Poured henna powder was mixed with lemon juice to facilitate its release from the plant or water and covered the mixture with

Table 4 Comparison of the median scores of WHO scale HFS scores during the chemotherapy in the treatment and placebo groups

WHO scale HFS score	First and second course[a]	First and third course[a]	First and fourth course[a a]	Second and third course[a]	Second and fourth course[a]	Third and fourth course[a]
Treatment group	0.008	0.01	< 0.001*	0.05	< 0.001*	< 0.001*
Placebo group	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*

WHO, World Health Organization; HFS, Hand-foot syndrome

[a]p-value Wilcoxon signed rank test

significance level: < 0.08

a plastic wrap and let it remain for about 24 h in Indian case and 5–6 h in Turkish cases [18]. So, the amount of henna penetrated to the skin may be much higher in those cases. Moreover, those patients used henna as a therapeutic measure and in current study its prophylactic use was assessed. After HFS occurrence, the damaged skin may have higher henna absorption rate and consequently better efficacy. On the other hand, as henna could not prevent accumulation of capecitabine in hands and feet it may not be effective in prevention of HFS, but by means of its anti-inflammatory and anti-oxidant properties, it may be useful in slowing the progression of lesions. Besides, as Vaseline was used as a base in the placebo ointment and based on previous data, that emollient creams and ointments can also have preventive role against HFS, it could somewhat blunted Alpha® ointment effects.

Moreover, another hypothesis is that henna topical formulation preventive effects may be more evident if we prescribed it a while before chemotherapy beginning, which should be assessed in future studies.

It is also worth to mention that in abovementioned studies on Alpha® ointment [35, 37, 38] no adverse reaction was reported. However, in some other studies on topical henna use, particularly for cosmetic purposes, various types of allergic reactions including erythematous scaly plaques, vesicular reactions, angioneurotic edema, contact urticaria and anaphylaxis and keloidal reaction are reported [39]. In present study, no patients in both groups reported any adverse reaction. So, it seems that henna and curcumin in topical form with doses available in Alpha® ointment are almost safe.

This study had some limitations. First, the sample size could be larger. However, because of the hard inclusion criteria it was not possible. Second, it may be better to prolong the follow-up period, as capecitabine induced HFS is a delayed adverse reaction. Moreover, we did not assess the Alpha® ointment stability outside its tube. Although we did not have any report of instability during the study period from the patients, it may be problematic for its efficacy. The last but the most important limitation is that we used a commercially available product contains a fixed value of henna and curcumin. It is suggested to use preparations with various amount of henna in future studies for better evaluation of its efficacy in HFS prevention and also treatment.

Conclusion

This study showed that use of Alpha® ointment including henna and curcumin twice a day for 4 courses of chemotherapy cannot prevent capecitabine induced HFS in patients with breast or gastrointestinal cancers but may slow down its progression. Larger clinical studies particularly on topical formulations with different amount of henna and curcumin are recommended for better judgment.

Acknowledgements This study is part of a research thesis for a MD degree at Mashhad University of Medical Sciences

Author Contributions Conceptualization: SE; Methodology: SE, SH; Formal Analysis: SR, SE; Investigation: SH, SR, ATK; Data Curation: SR; Writing–Original Draft: SE; Writing–Review & Editing: SH, ATK; Funding Acquisition: SH.

Funding This study was supported by Mashhad University of Medical Sciences, Mashhad, Iran.

Data availability statement The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics The study protocol was approved by the local Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1397.624) and was registered at the Iranian Registry of Clinical Trials (IRCT20181230042179N1). All participants signed written consent forms.

Conflict of Interest Nothing to declare.

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