Original Article

Effects of Henna-Violet Based Topical Preparation in Preventing and Reducing the Severity of Radiation-Induced Dermatitis in Breast Cancer Patients: A Randomized, Double-Blind Clinical Trial

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Abstract

Background: Radiation-induced dermatitis (RID) is a common side effect of radiotherapy. The present work attempts to examine the effect of using henna- violet based topical preparation to prevent and decrease the severity of RID in patients with breast cancer.

Materials and Methods: The study was carried out as a prospective, double-blind clinical study on 43 breast cancer patients aged 18-75 years. The subjects had undergone breast-conserving surgery, and radiotherapy was scheduled for them. The participants were categorized randomly into two groups; patients who received the henna- violet based topical preparation and patients who received a placebo twice a day for six weeks. The level of the RID score was measured every week based on the toxicity criteria of the radiation therapy oncology group (RTOG).

Results: The henna- violet based topical preparation decreased the severity of RID and delayed the development of grade 2 RID for two weeks. In addition, the initiation of grade 3 RID was deferred for one week. There was a significant decrease in grade 2 RID (20% vs. 56.52%) as well as grade 3 RID (10% vs. 26.09%) in the patients who received the henna- violet based topical preparation at the end of the 6th week (P=0.004).

Conclusion: This cream, which contained henna and violet, had no severe adverse effects, could prevent RID and decreased the grade of dermatitis in breast cancer patients compared to the placebo.

Keywords: Breast Cancer, Dermatitis, Radiotherapy, Prevention, Lawsonia inermis L, Viola odorata

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Introduction

The most prevalent cancer in women is breast cancer. It is also the second cause of cancer-related death in women. It accounts for many cancers, especially in developing countries, including Iran. Almost every advanced breast cancer patient needs radiotherapy as a part of the treatment[1]. Radiotherapy is a major part of treating patients with breast-conserving surgery[2]. Studies show that about two-thirds of cancer patients receive radiotherapy[3]. During radiotherapy or shortly after, patients suffer acute skin problems called

radiation-induced dermatitis (RID) (4). RID is the main side effect and troubles about 95% of patients[5,6]. The complication profoundly affects patients' quality of life because of the pain and discomfort. It can also lower adaptation to treatment and even stop or delay the process of radiotherapy. It can cause problems with disease control in the long term[6]. Therefore, RID treatment and prevention are important for healthcare providers. Finding effective health products to prevent and cure the disease is important. Numerous therapies for radiation dermatitis have been suggested. However, success in treating dermatitis during radiation therapy is not quite satisfactory, and there is no proven prophylaxis for it[7]. Most treatments are supportive to control pain and infection, including creams and lotions. In more severe cases, antibiotics and dressings are used to treat it[7]. Since no complete satisfaction exists with these treatments, a growing interest in using herbal medicine is evident. So, evidence-based investigations are needed to evaluate herbal medicines scientifically[8]. Studies have assessed various topical agents such as corticosteroids, vitamin E, hyaluronic acid, sucralfate, dexpanthenol, aloe Vera, and calendula on RID. However, most failed to provide an optimal effective agent for preventing RID. The evidence is insufficient to recommend a specific topical agent to prevent or treat this side effect[1,3,9].

Based on ancient Persian medicine resources like Rhazes' Liber Continens (865–925 AD) and the Canon of Medicine by Avicenna (980–1037 AD), henna (Lawsonia inermis L.) has medicinal effects like antimicrobial, an anti-inflammatory which is beneficial for individuals with radiation-induced dermatitis[10,11]. Moreover, studies have supported the plant's antimicrobial, anti-inflammatory analgesic, and wound-healing effects[12]. Violet (Viola odorata) seems to be effective in skin diseases. Also, this plant has exerted anti-inflammatory, analgesic, antioxidant and antibacterial activities in modern phytotherapy[13]. According to Persian medicine resources, combining henna and violet has been used in many skin disorders[1]. This research evaluated the efficacy of a topical henna- violet based topical preparation in preventing and reducing the severity of RID in breast cancer patients.

Methods

Trial design: The study was a double-blind, randomized, placebo-controlled clinical trial. The provisions of the Declaration of Helsinki (1989 revision) were observed as confirmed by the local committee of medical ethics, Shahid Beheshti University of Medical Science (Approval Code: IR.SBMU.RETECH.REC.1398.079) and registered in Iranian Registry of Clinical Trials (Approval Code: IRCT20191107045357N1)

The present research had two parallel arms: Henna-violet-based topical preparation and placebo. According to simple randomization through the randomizer software tool (Random Rx Ver.1), eligible subjects were allocated into two groups. A group received the henna- violet based topical preparation twice daily (experimental group), and another group received a placebo (control group) twice daily for six weeks.

Participants: This study was performed in the oncology department of Imam Hossein Hospital (Tehran, Iran) between October 2017 to October 2019. All participants signed an informed letter of consent to participate in the trial. The inclusion criteria were women aged 18-75 who had non metastatic invasive ductal breast carcinoma treated with breast conserving surgery (BCS) and were referred to the radiation therapy department after chemotherapy. Exclusion criteria were a history of allergy to henna, previous history of chest radiotherapy for any reason, skin involvement caused by breast cancer or inflammatory breast cancer, mastectomy for breast cancer, history of collagen vascular disease or diabetes mellitus or chronic renal failure, any skin lesion in the field of radiotherapy, concurrent chemoradiotherapy (except trastuzumab) and use of any other topical cream on the chest wall.

Plant material: Henna (Lawsonia inermis L.) dry leaves and common violet (Viola odorata) flowers were bought from an herbal market allotted at the herbarium of the Faculty of Pharmacy, Tehran University of Medical Sciences with the voucher specimen number (No) PMP-454 and PMP-573 respectively.

Preparation of henna-violet-based topical cream

One hundred grams of aerial parts of violet and 100 grams of henna leaves grind separately. Passed 20 mesh

and soaked 200 cubic centimeters (cc) of distilled water for 24 hours. After boiling the plant for 1 hour, strain them and add 100^{cc} of sweet almond oil to each one, and a mild temperature of 70-80 C° was given so that the water would come out and the oil would stay. After the oils were ready, violet oil and henna oil were added to 100 grams of cold cream base. The cold cream base was used to prepare the placebo. Its color was adjusted using brown color (khat zard, Tehran, Iran), similar to the color of medicine.

Cold cream contains white vaseline, glycerin, beeswax, lanolin, cetostearyl alcohol, stearic acid, purified Water, triethanolamine, and preservative. It creates therapeutic combination creams by adding variable effective drugs for various purposes. Henna and violet oils were prepared based on instructions from the Iranian medicine reference book[14-16].

Determination of total phenol changes: The changes in total phenol were measured with the Folin-ciocalteu method. This method transferred 0.5 millimeters (ml) of 5% ethanolic extract of cream into the test tubes. Their volumes were made up to 1 ml with ethanol. Four ml Folin–Ciocalteu reagent (1:10 diluted with distilled Water) was added. After incubation for 10 minutes in a dark place at room temperature, 4 ml aqueous Na2CO3 (75mg/ml) was added. The mixtures were allowed to stand for 30 minutes in a dark place at room temperature. The total phenols were obtained using colorimetry at 765 nanometers with Varian Cary 100 concentration UV-Vis Spectrophotometer. Total phenolics content (TPC) is expressed as mg GAE /100 grams of cream. The standard curve equations for gallic acid ($y = 0.0092x + 0.0212$) and the R2 value (0.9945) were calculated[17].

Intervention: The participants were randomly allocated to receive henna- violet based topical preparation as the experimental group or topical placebo as the control group. Both topical preparations were white and remained no color on the skin. Participants were asked to spread intervention preparation on the surfaces of the irradiated areas after radiotherapy and before bedtime. The intervention was started since the first session of radiotherapy. The cases were treated with radiotherapy five days a week (Saturday to Wednesday) with a prescribed fraction dose of 1.8-2 Gray (Gy) once daily. All the cases in both groups had conservative breast surgery, and none had bolus on the treatment fields. The total breast dose was 50 Gy, and the boost dose was 10-12 Gy. None of them was treated with a hypofunction schedule. The treatment energy was 6 MV with a linear accelerator (LINAC). They were treated with tangential fields with treatment planning. All the cases received just radiotherapy, and none received chemotherapy agents during radiotherapy except trastuzumab with every 3-week schedule.

Patients were advised to avoid using the cream for at least 6 hours before radiotherapy to avoid the effects of a bolus. Patients should not use any other topical medications during treatment.

All the cases had CT simulations. Computed tomography (CT) simulation is a special CT scan with the patient's position for radiotherapy, which is used for radiotherapy treatment planning with planning software. The breast, skin, and clinical target volume were contoured in the CT simulation. Treatment planning was done for each case with the Isogray planning system version 4.2.3.63L.

Outcome measures: The severity of RID symptoms, such as erythema, burning, itching, and pain, is set as the outcome measure. The RID grade was evaluated weekly based on the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) for six weeks. The grading system used for RID is shown in table 1.

Patients were monitored weekly during radiotherapy for the side effects of intervention and the dermatitis grade. In the case of dermatitis grade 3, routine topical creams such as flaming were also prescribed. All demographic data, radiotherapy and pathology information, and weekly grade of dermatitis by examination were recorded.

Sample size: Based on the mean comparison formula for two independent groups, with an error of 5 %, a study power of 80 %, and 20 % attrition, 25 patients were selected for each group (n = 50).

Safety assessment: All the participants were asked to report any new symptoms or serious or bothering side effects during the study. They were explained that they could withdraw from the study for any reason at any time.

Randomization and blinding: Fifty participants were randomized to 2 groups, double-blind, and the participants and researchers were not informed about

Table 1: RTOG scoring systems for acute radiation induced dermatitis.

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No change	Erythema; dry desquamation, epilation	Bright erythema, moist desquamation, edema	Confluent moist desquamation, pitting edema	Ulceration, hemorrhage, necrosis

the grouping. The placebo topical was identical to henna- violet based topical preparation in terms of color, viscosity, and weight. The physician, patients, and drug deliverer were blinded to the type of intervention.

Statistical methods: The data were described using mean ± SD or number. T-test was used, and the Chi-square test measured the relationships between qualitative variables to compare the mean score of quantitative variables between the groups ($P<0.05$). Data analyses were done in SPSS, version 21 (SPSS Inc., Chicago, IL, USA).

Results

Participants' enrollment: At the end of the study, 20 cases were in the experimental group, and 23 patients were in the placebo group.

Basic characteristics: The baseline demographic and clinical characteristics of the participants are illustrated in Table 2. There was no significant difference in age, breast size, the total dose of radiotherapy, and the number of days between the two groups observed between the end of chemotherapy till the start of radiotherapy. The mean age of the patients in the experimental group was 49.1, and 50.8 in the control group ($P = 0.325$).

Clinical response: At the end of the study, forty-three patients were included in the study and randomly assigned to the two groups receiving henna-violet-based topical preparation drugs (20 people) and placebo (23 people). In both groups, more than 80% of patients were treated by breast radiotherapy and supraclavicular lymph nodes. Diagram 1 summarizes the randomization of the patients. It should be noted that, in general, there was no significant difference in missed data, including the cases that did not continue the trial.

In this study, patients who received more than 110 percent doses of radiotherapy on breast skin in the planning were excluded from the study. The volume of breast receiving 107% of the radiotherapy dose was significantly higher in the case group compared to the placebo group (81.60 ± 46.55^{cc} versus 54.78 ± 37.83^{cc}, $p=0.043$). Also, the volume of the breast receiving 110% of the radiotherapy dose was significantly higher in the case group (19.70 ± 20.41 cc versus 7.68 ± 8.87cc, $p=0.014$). The percentage of breast volume that received 110% of the radiotherapy dose was significantly higher in the case group (2.06 ± 2.79^{cc} versus 0.78 ± 1.06 cc, $p=0.049$).

Skin doses of more than 105 and 107% of the prescribed

Table 2: Demographic and radiotherapy variables in two groups.

Variable	Group	Mean	p-value
Age (year)	Case	49.1±10.44	0.325
	Placebo	50.87±10.47	
Total dose of radiotherapy (Gy)	Case	61.16±1.92	0.912
	Placebo	61.22±1.57	
Breast size (cc)	Case	1107.25±370.41	0.852
	Placebo	1086.57±351.24	
Number of days *	Case	34.25±13.78	0.434
	Placebo	31.52±8.62	

*Number of days from the end of chemotherapy till the start of radiotherapy

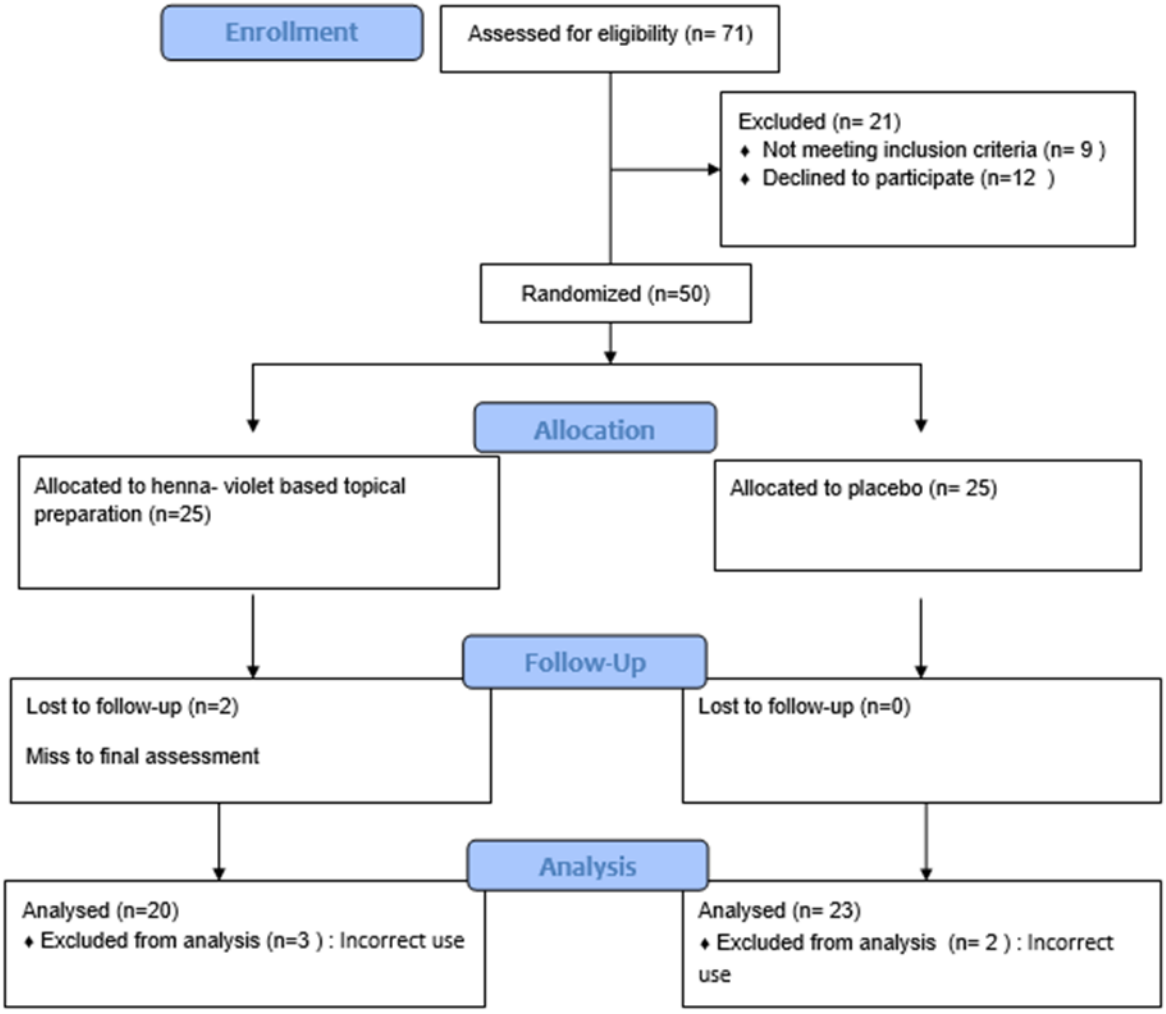

Figure 1. Randomization and allocation of the patients.

dose did not differ significantly in the two groups (P = 0.638 and P = 0.309, respectively). The results show that in the experimental group, 65% (13 people) had T2 cancer stages and 35% (7 people) had T3 cancer stages, and no patient was T1. In the placebo group, 17.39% (4 people), 60.87% (14 people), and 21.74% (5 people) were in the T1, T2, and T3 cancer stages, respectively. Lymph node involvement is shown in Table 3.

As shown in Table 4, most of the patients in both groups were treated by radiotherapy of breast and supraclavicular lymph node which was not significantly

Table 3: Involvement of lymph nodes in two groups.

		N				Total
		N0	**N1**	**N2**	**N3**	
Group	**case**	6 (30%)	10 (50%)	3 (15%)	1 (50%)	20 (100%)
	placebo	7 (30.43%)	10 (43.48%)	4 (17.39%)	2 (8.69%)	23 (100%)
Total		13 (30.23%)	20 (46.51%)	7 (16.28%)	3 (6.98%)	43 (100%)

Fisher's Exact Test=1.00

Table 4: The treatment radiation field in the two groups.

		Treatment field		Total
		Breast	**Breast and supraclavicular**	
Group	**Case**	4(20%)	16(80%)	20(100%)
	Placebo	3(13.04%)	20(86.96%)	23(100%)
Total		7(16.28%)	36(83.72%)	43(100%)

Chi-Square=0.538

Table 5: The grade of dermatitis in weeks.

Grade of dermatitis			**0**	**1**	**2**	**3**
Group		**Week**				
	drug	3	16 (80%)	4 (20%)		0
		4	10 (50%)	10 (50%)	0	0
		5	5 (25%)	10 (50%)	5 (25%)	0
		6	4 (20%)	10 (50%)	4 (20%)	2 (10%)
	placebo	3	10 (43.48%)	0	11 (47.83%)	2 (8.69%)
		4	2 (8.7%)	13 (56.52%)	8 (34.78%)	0
		5	0	8 (41.86%)	9 (39.13%)	6 (26.09%)
		6	0	4 (32.56%)	17 (39.53%)	6 (26.09%)

Number of cases in each group and percentage in each group are shown in column 4-7

different. Patients were visited and examined at the end of every week of radiotherapy. In the first week, all patients in the experimental group had no dermatitis. Nevertheless, in the placebo group, one patient (4.35%) had grade 1 dermatitis. At the end of the first week, there was no significant difference between the two groups (P = 0.345).

In the second week, a physical examination of the cases showed that all (100%) patients who used the henna-violet-based topical preparation had no dermatitis. In contrast, five cases (21.74%) had grade 1 dermatitis in the placebo group. This difference was significant (P = 0.027).

At the end of the third week, only four patients (20%) in the treated group (the cases treated with henna-violet based topical preparation) had grade 2 dermatitis. There was no patient with grade 3 dermatitis in this group. Nevertheless, in the placebo group, 47.83% (11 people) had grade 2, and 8.69% (2 people) had grade 3 dermatitis. The difference was again (P = 0.039). At the end of the fourth week, the patients did not have grade 2 dermatitis in the treated group, while in the other group, 34.78% (8 people) had grade 2 dermatitis; the difference between the two groups was significant (P = 0.001).

In the fifth week in the treated group, five patients (25%) had grade 0 dermatitis, ten people (50%) had grade 1 dermatitis, and 5 cases (25%) had grade 2 dermatitis. These results showed that the use of henna-violet based topical preparation could delay the onset of grade 2 dermatitis in 2 weeks compared to the placebo. There were no patients with grade 3 dermatitis in this group. In the placebo group, 34.78% (8 people) had grade 1 dermatitis, 39.13% (9 people) had grade 2 dermatitis and26.09% (6 people) had grade 3 dermatitis. This difference was again significant (P = 0.007). Whenever grade 3 dermatitis was observed during the study in each group, the participant was excluded from the study.

In the sixth week in the treated group, four patients (20%) had no dermatitis, ten patients (50%) had grade 1 dermatitis, four patients (20%) had grade 2 dermatitis,

and only two cases (10%) had grade 3 dermatitis. The results showed that henna- violet based topical preparation can delay the onset of grade 3 for one week compared to the placebo. The difference between the two groups was significant (P = 0.004). Grade 4 dermatitis was not seen in any patients during the six-week intervention. All the data about the grade of dermatitis in the third to sixth week of treatment are summarized in Table 5. None of the cases had allergic or any other adverse effect of henna cream or placebo.

Discussion

The efficacy of henna- violet based topical preparation to prevent and decrease the severity of RID in breast cancer patients was investigated. The present study showed that in the treated group, the most grade of RID was 0 and 1 until the fourth week of radiotherapy. In contrast, in the placebo group, 8.69% of patients had grade 2 RID from the third week. In the treated group, grade 2 RID was reported in 25% of patients from the fifth week of radiotherapy. Therefore, henna-violet-based topical preparation could delay the onset of grade 2 RID by two weeks compared to the placebo group. In the treated group, only 10% of patients in the fifth and sixth weeks of radiotherapy had grade 3 RID. In contrast, 26.09% of patients had grade 3 RID at the exact times in the placebo group. Therefore, henna-violet based topical preparation could delay grade 3 RID for one week compared to placebo. The six-week follow-up observed no grade 4 RID in either group.

In both groups, the average age of patients, tumor stage, the total dose of radiotherapy (61.16 ± 1.92 g versus 61.22 ± 1.57 g, p=0.912), breast volume (1107.25 ± 370.41cc versus 1086.57 ± 351.24cc, p=0.852) were not different significant.

We observed that in the case group, the volume of the breast that received 107% and 110% and the percentage of the total breast volume that received 110% of the radiotherapy dose were significantly higher than the placebo group (P = 0.043, P=0.014 and P=0.49, respectively).

Viola odorata contains an alkaloid, glycoside, saponins, methyl salicylate, mucilage, vitamin C, and anthocyanins[18]. The water extracts of flowers from Violet can scavenge free radicals and exert antioxidant effects[19]. In Koochek et al., the aqueous extract of Viola odorata showed anti-inflammatory properties compared with hydrocortisone in preventing and treating formalin-induced lung damage in the rat[20]. This cream was used topically and not orally. Therefore, there was little concern about the systemic absorbed vitamin C in it conferring with the mechanism of radiation therapy. Also, the patients use fruits and foods which contain minerals and vitamins. We cannot omit them from food. Therefore, this topical vitamin C in a topical cream can be negligible.

The aqueous extract of Lawsonia inermis contains carbohydrates, phenolic compounds, flavonoids, saponins, proteins, alkaloids, terpenoids, quinines, coumarins, xanthones, fat, resin, and tannins. One of the main compounds in henna is 2-hydroxy-1, 4-naphthoquinone (lawsone)[21, 22]. Henna and lawsone have revealed anti-inflammatory effects in lots of studies. Henna also contains luteolin, which possesses anti-inflammatory and anti-oxidative properties[12, 23, 24]. Khantamat et al. examined the antioxidant and anti-inflammatory activity of hot water extract. These effects were demonstrated by significant scavenging of ABTS (2, 2'-azinobis-(3-ethylbenzothiazoline-6-sulfonate) and DPPH radicals (2, 2′-diphenyl-1-picrylhydrazyl radical) and decreasing nitric oxide levels in lipopolysaccharide-induced RAW 264.7 cells. These abilities can be attributed to their phenolic and flavonoid contents[25].

There are limited research works on different types of topical henna formulations for dermatitis. These works have reported significant positive results consistent with the present study. For instance, Niazi et al. showed that a topical medication containing henna significantly reduced symptoms of contact dermatitis, such as skin swelling, itching, sweating, thinning of the skin, and pain in patients with used the prosthesis[12]. Hosseini et al. demonstrated that henna ointment (alpha ointment) was as effective as silver sulfadiazine ointment on wound healing[26]. The alpha ointment is a mixture of Lawson (natural Henna) and unsaturated fatty acids[1].

In addition, histological investigations showed that the tissue treated with henna increased well-organized bands of collagen, few inflammatory cells, and more fibroblasts compared to the controls. This indicates the benefits of using henna in wound healing management[27].

In another study, Ansari et al. appraised henna ointment for treating breast cancer patients with RID compared

to hydrocortisone ointment and showed that topical henna ointment was more beneficial than the topical hydrocortisone cream in the improvement of RID[1]. The difference between Ansari's study and our study was the intervention time; their intervention was after chest wall radiotherapy for treatment of grade 2 and 3 RID, while we evaluated the preventing effect and lowering the severity of RID in patients with breast cancer. They indicated that topical henna ointment for 3 weeks was more effective in the healing of RID than topical hydrocortisone cream. Although, Chan et al., by a systematic review, demonstrated that topical corticosteroids did not reduce the incidence of RID but reduced its severity[28].

Ulff et al. showed that grade 2 and 3 RID was less common in patients receiving topical beclomethasone than in the placebo group[29]. Also, Keshavarz et al. reported that henna was better than hydrocortisone cream on diaper rash treatment in infants[30].

Some evidence suggests that the anti-inflammatory and moisturizing effects of hydrocortisone cream are probable mechanisms in the healing of RID[1,31]. Henna has anti-inflammatory, analgesic, antimicrobial, and wound-healing effects[12]. Moreover, Lozza et al. showed that lawsone activates the aryl hydrocarbon receptor (AhR) transcriptional program and modulates skin homeostasis. These receptors (AhR) mediated signals have a key role in skin regeneration and recovery during long-term exposure to harmful environmental agents[12,32]. Thus, it seems that henna-violet based topical preparation can be effective in both preventing and healing RID.

There were some limitations in this study. It was supposed to end the study with 10% missing data. However, due to a lack of time to finish the study, we could include 20 cases in the henna cream group and 23 cases in the placebo group. This study did not have sponsorship, and the authors paid all the cost of preparing cream and placebo. We did not include other demographic factors like smoking, comorbidity, body mass index (BMI), and nutritional status. They can be considered for future studies with a larger sample size.

Conclusion

This cream, which contained henna and violet, had no severe adverse effects, could prevent RID and decreased the grade of dermatitis in breast cancer patients compared to the placebo. Still, well-designed, randomized controlled trials with long-time follow-up are needed to achieve more reliable findings.

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