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ORIGINAL ARTICLE

Topical silver sulfadiazine for the prevention of acute dermatitis during irradiation for breast cancer

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Abstract
Purpose This study aimed to evaluate the effectiveness of topical silver sulfadiazine (SSD) in preventing acute radiation dermatitis in women receiving radiotherapy for breast cancer.
Methods A randomized controlled clinical trial was conducted on patients with breast cancer referred for radiotherapy after treatment with mastectomy and chemotherapy. The patients were randomized into the intervention (n=51) and control (n=51) groups and were instructed on general skin care during radiotherapy. The intervention group received SSD cream 1%, three times a day, 3 days a week, for 5 weeks during radiotherapy and one week thereafter. A blinded observer assessed the severity of dermatitis weekly (for 6 weeks) and graded it from 0 to 4 according to the Radiation Therapy Oncology Group criteria.
Results The two groups were similar in baseline characteristics. Two patients in the control group discontinued the radiotherapy course because of severe skin injuries (grades 3 and 4). The intervention group encountered significantly less severe dermatitis during radiotherapy compared to the controls. The total score of skin injury was also lower in the intervention group compared with controls (5.49±1.02 vs. 7.21±1.76, $p<$ 0.001). A multivariate analysis found that the use of SSD cream ($p<0.001$) and flat chest wall anatomy ($p=0.008$) were significantly associated with a decreased skin injury.
Conclusions SSD cream reduced the severity of radiation-induced skin injury compared with general skin care alone. Further studies in patients with other types of cancer and also comparing SSD cream with other topical agents are warranted.

Keywords Radiation dermatitis · Breast cancer · Radiotherapy · Skin toxicity · Silver sulfadiazine · Skin care

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Introduction

Radiotherapy, with or without chemotherapy, plays an important role in the current management of breast cancer. Radiotherapy has become an essential adjunctive therapeutic modality for women with early-stage breast cancer who are candidates for breast conservation therapy [1]. In those with more advanced breast cancer requiring mastectomy, adjuvant radiotherapy has been shown to improve the overall survival [2]. However, despite a considerable progress in therapeutic strategies, radiation-induced skin injury, varying from mild erythema to ulceration and necrosis, remains a common and serious adverse effect of radiotherapy. Up to 90% of patients treated with radiotherapy for breast cancer develop various degrees of dermatitis, which can affect the activities of daily living and quality of life. In severe cases,

these side effects often limit doses of therapy or disrupt the treatment, which may negatively affect the treatment outcome [3, 4].

Skin injuries after radiotherapy are commonly categorized to acute reactions, which tend to occur within 1 to 5 weeks after radiation, and chronic changes, which may develop months or years after the initial exposure [4]. The intensity of skin reactions depends on the radiotherapy method, fraction schedules of radiation, the total dose, the treated surface area of the skin, concurrent chemotherapy, and also individual variations [4]. The pathophysiology is complex with a combination of direct radiation injury and a subsequent inflammatory response contributing to impairment of skin barrier function, bacterial colonization, superinfection, and superantigen production [4].

While chronic skin injuries are hard to treat, mild acute dermatitis is usually treated symptomatically. Skin washing, including gentle washing with water alone with or without mild soap, wearing loose and nonbinding clothing, and avoidance of irritants and ultraviolet exposure can be helpful [5]. When erythema and dry desquamation occurred, creams, ointments, and other topical agents such as aloe vera, D-panthenol, and chamomile can be tried. However, the use of these agents is suggested mostly by uncontrolled studies and anecdotal evidence. The value of topical antioxidants is not established and topical steroids are controversial. According to conflicting results of various therapeutic regimens proposed for the prevention/treatment of radiation dermatitis and lack of well-designed controlled trials, to date there is no general agreement about how to prevent/treat radiation dermatitis [6, 7]. A suitable preventive/therapeutic regimen should provide a lean and moist environment with adequate oxygenation, controlling inflammation, and preventing infection. The goal of the treatment is to minimize patient discomfort and to prevent the progression of mild dermatitis to a more severe skin injury [6, 7].

Silver sulfadiazine (SSD) is a sulfa derivative topical antibacterial used primarily as a topical burn cream for second- and third-degree burns [8]. It is typically delivered in a 1% solution suspended in a water-soluble base. It also has anti-inflammatory and barrier-enhancing functions and thus can protect the skin from entry of infectious and antigenic agents [9–12]. These characteristics, in addition to providing a moist environment to the irradiated area, make SSD cream a potential preventive/therapeutic agent for acute radiation dermatitis. Controlled trials are available on the use of silver-leaf nylon dressing (SLND) [13, 14] and case series on SSD cream [15] for the prevention of radiation dermatitis, but no controlled trial has been reported about the effectiveness of topical SSD. The purpose of this controlled trial was to assess the effectiveness of topical SSD as a prophylactic agent for acute radiation dermatitis in women who underwent radiotherapy for breast cancer.

Methods

Patients and settings

This randomized controlled study was conducted in the Isfahan Radiation Therapy Center which is a referral center for radiotherapy in Isfahan province (central Iran). The study population was selected from consecutive patients who had pathologically proven breast cancer referred for radiotherapy after treatment with modified radical mastectomy and subsequent to six to eight courses of chemotherapy. There was at least a 3-week interval between the end of chemotherapy and start of radiotherapy. Those with history of prior radiotherapy to the same area, diabetes mellitus, severe deformity of the chest wall after surgery, or allergic reaction to sulfa compounds were not included. Not having allergic reaction to topical SSD was confirmed by patch test 1 week before starting the intervention. Also, patients with inadequately healed surgical scars within the radiation field, those with dermatologic conditions that are known to be associated with a barrier defect or would preclude the evaluation of the skin (e.g., infection, trauma, collagen vascular disease, etc.), those receiving systemic corticosteroids during the 2-week period prior to or during radiotherapy, and cigarette smokers were excluded from the study. The calculated sample size per group was 51, considering α=0.05, study power=90%, effect size=0.5, and 20% drop-out. The Ethics Committee of Isfahan University of Medical Sciences approved the study and written consent was obtained from all patients after a full explanation of the study aim and protocol.

Irradiation

Each week, the patients received 10 Gy of radiation to the chest wall by external beam electrons (9–10 MeV). The radiation energy was generated by a linear accelerator (Saturn 20, CGR, France). Doses were applied in single fractions of 200 cGy (per day), five times a week (from Saturday to Wednesday) for 5 weeks. Radiation field arrangement included chest wall field for all patients and posterior axillary boost field for 60 patients. Chest wall field arrangement included the area between the midsternal line medially, midaxillary line laterally, 2 cm below the contralateral inframammary fold inferiorly, and supraclavicular–axillary field superiorly.

Topical agents and treatment schedule

Patients were randomized into the intervention and control groups by random allocation software [16]. Because the anatomy of the irradiated site is a known factor influencing the severity of radiation dermatitis [4], the two groups were matched in this regard (flat or not flat chest wall based on

the investigator's observation). Starting with radiotherapy, patients in the intervention group received SSD cream 1% (SobhanDaru Co., Tehran, Iran) and were instructed to apply the cream to the irradiated field every 8 h for three consecutive days; at least 2 h after the end of the radiotherapy session on Wednesday and then on Thursday and Friday. The patients were instructed to clean the radiation area from the cream gently with water and baby soap before starting the irradiation schedule of each week and not to use the cream during the irradiation days. Using the SSD cream was continued for 1 week after completion of radiotherapy course.

Both groups received verbal instructions and a leaflet about standard skin care at the start of radiotherapy, including gentle washing of the area with baby soap and not applying a powerful soap directly to the skin, patting the area dry with a soft towel, and wearing loose clothes, preferably cotton, next to the skin. Also, they were advised not to use cosmetics, perfume, cologne, or deodorant on the area. No other prophylactic creams/lotions/gels were to be applied to the radiation field during the radiotherapy course. The compliance in applying the SSD cream and general skin care instructions was evaluated weekly by treating physician.

Clinical assessment

Skin within the irradiation field was examined at weekly intervals during radiotherapy and 1 week thereafter. The observer was a radiation oncologist who was unaware to which groups the patients belong to. Skin injury was scored according to the Radiation Therapy Oncology Group (RTOG) criteria [17]—grade 0: no change over baseline; grade 1: follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating; grade 2: tender or bright erythema, patchy moist desquamation, moderate edema; grade 3: confluent, moist desquamation, other skin folds, pitting edema; and grade 4: ulceration, hemorrhage, necrosis.

Statistical analyses

Data were analyzed using SPSS version 16.0. Baseline characteristics were compared between the two groups using independent sample *t*-test and chi-square test. The outcomes used for analysis were the frequency and severity of skin injuries compared between the two groups with chi-square and Mann–Whitney tests. Multivariate analysis was done to assess the factors associated with more severe skin injury. A p value of <0.05 was considered statistically significant.

Results

Patient and treatment characteristics

During the study period, 119 patients were evaluated and 104 patients who were eligible for the study were enrolled. Two patients in the control group discontinued the radiation treatment at 18th and 21st fractions because of severe skin injury (grades 3 and 4) and two other new patients were enrolled instead of them; so, data of 102 patients (51 patients in each group) were considered for analyses (Fig. 1). As presented in Table 1, the two groups were similar in baseline characteristics.

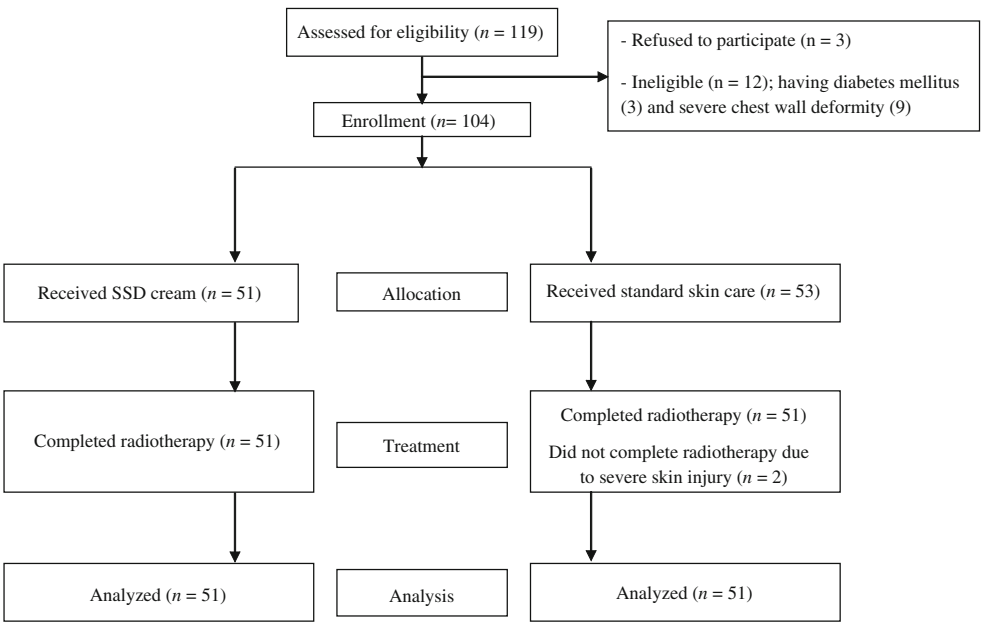

Fig. 1 Flow chart of participating patients

Table 1 Comparison of baseline characteristics between the two groups

	SSD n=51	Control n=51	p
Age	48.7±10.3	48.1±9.9	0.785 *
Chest wall, flat/not flat	40/11	40/11	–
Energy, E8/E10	1/50	4/47	0.181 **
Radiation fields, one/two	42/9	45/6	0.289 **
Post. axillary field, no (%)	29 (56.8)	31 (60.7)	0.420 **

Data are shown as mean±SD or number (percent)

* Independent sample t-test

** Chi-square test

Comparison between the treatment arms

The severity of skin injuries in each week is presented in Table 2. Skin injury was limited to grade 3 in both groups. The intervention group encountered significantly less severe dermatitis during radiotherapy compared to the controls. The total score of skin injury was also lower in the intervention group compared with controls (5.49±1.02 vs. 7.21±1.76, $p<0.001$; Fig. 2). As expected, the severity of skin injury increased with increasing radiation dose (Fig. 3). A multivariate analysis found that the use of SSD cream ($p<0.001$) and flat chest wall anatomy ($p=0.008$) were significantly associated with decreased skin toxicity.

Discussion

Radiotherapy is a critical component in the treatment of breast cancer but is often associated with bothersome skin reactions that can cause significant discomfort, disruption to daily life, and treatment interruption [3]. Reducing skin toxicity and preventing the progression of mild dermatitis to severe skin injuries (moist desquamation) is therefore a central objective in radiation oncology [5].

There has been a growing interest in identifying a topical agent that would prevent or decrease the acute adverse effects of radiation to skin. In this regard, numerous trials using different compounds such as aloe vera, antioxidants, biafine, sucralfate, hyaluronic acid, antibacterial agents, and corticosteroids have been done, but the results were contradictory and few of them demonstrated an effective prevention of skin injury. Moreover, many of these trials were not randomized controlled studies and the sample sizes were often not enough [4, 6, 7]. Hence, there is no current evidence-based consensus guideline regarding the optimal management of radiation dermatitis and physicians continue to treat, most commonly with powders or emollients, based on clinical experience and availability of the topical agents.

The pathophysiology of radiation-induced skin injury is complex. Bacterial colonization, superinfection, superantigen production, and subsequent inflammatory responses play important roles [4]. There is a report on the role of *Staphylococcus aureus* in the pathogenesis of severe radiation dermatitis [18]. Evidence also exists for the positive effects of antibacterial strategies in alleviating radiation-induced skin injury. Two controlled studies reported the efficacy of washing with soap in reducing the duration, severity, and incidence of grade 3 dermatitis in patients treated for breast cancer [19, 20]. In another controlled trial, Vuong et al. administered silver-leaf nylon dressing for prevention of radiation dermatitis in patients with anal canal or gynecologic cancer. The authors found that SLND significantly reduced radiation dermatitis and

Table 2 The severity of skin injury in detail through the study

		Severity of skin injury					p*
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
1st wk	SSD	51 (100)	0	0	0	0	–
	Control	51 (100)	0	0	0	0	
2nd wk	SSD	51 (100)	0	0	0	0	< 0.001
	Control	40 (78.4)	11 (21.5)	0	0	0	
3rd wk	SSD	0	51 (100)	0	0	0	0.003
	Control	0	43 (83.3)	8 (15.6)	0	0	
4th wk	SSD	0	51 (100)	0	0	0	< 0.001
	Control	0	29 (56.8)	22 (43.1)	0	0	
5th wk	SSD	0	31 (60.7)	18 (35.2)	2 (3.9)	0	0.002
	Control	0	15 (29.4)	26 (50.9)	10 (19.6)	0	
6th wk	SSD	0	8 (15.6)	32 (62.7)	11 (21.5)	0	0.001
	Control	0	1 (1.9)	23 (45.1)	27 (52.9)	0	

Data are shown as number (percent)

* Chi-square test

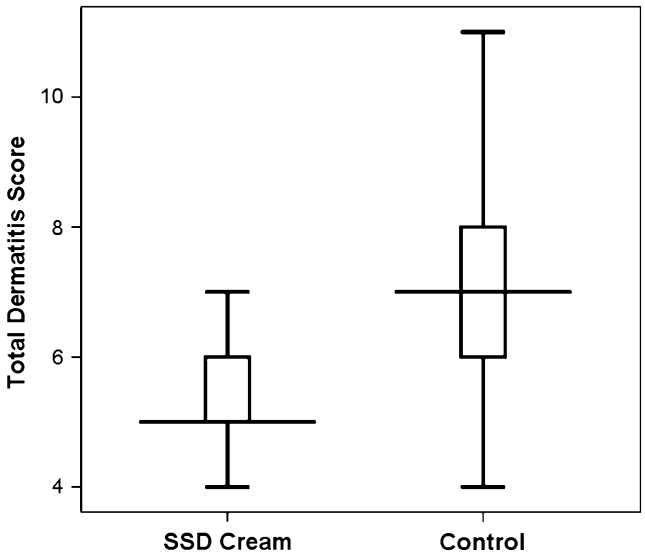

Fig. 2 Comparison of the total dermatitis score between the two groups; $p<0.001$

attributed their results to the antibacterial properties of SLND [13].

SSD cream is a topical antibacterial used primarily as a topical burn cream which prevents the growth of a wide array of bacteria, as well as yeast, on the damaged skin [8]. According to anti-inflammatory and barrier-enhancing functions, SSD can protect the skin from entry of infectious and antigenic agents [9–12]. Evidence has shown the ameliorating effects of formulations with putative barrier-enhancing activity on radiation dermatitis [21, 22]. The use of topical lidocaine in a vehicle of SSD cream for patients

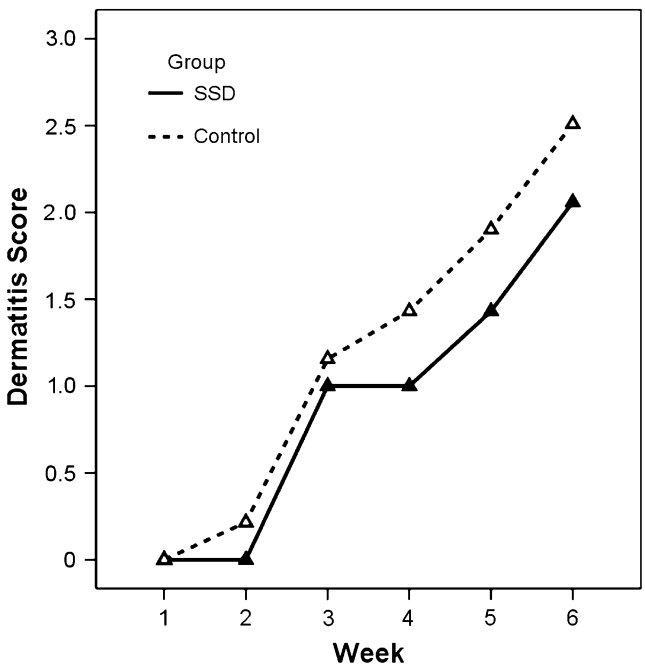

Fig. 3 Severity of skin injury through the study in the two groups

with radiochemotherapy-related painful skin conditions (vulvitis with erythema and desquamation) has been reported in a case series [15]. In contrast, Vavassis et al. compared SNLD with SSD for the treatment of RTOG grade 2 dermatitis in 20 patients presenting with cancers of the head and neck region and found no improvement in RTOG grade skin toxicity [14]. However, the sample size and design of these reports are not conclusive. To our knowledge, the present study is the first large-enough, controlled trial demonstrating a reduction in severe radiation-induced dermatitis in patients with breast cancer using SSD cream. As the results showed, patients who received SSD cream experienced severe skin injuries (moist desquamation) less frequently compared to controls. SSD cream also delayed the development of various degrees of skin injury. Moreover, the treatment was well tolerated by patients, and no treatment delays were necessary because of skin reactions while two patients of the control group discontinued the radiotherapy course because of severe skin injuries. The incidence of RTOG grade 3 skin injury in our study (3.9% at the 5th week and 21.5% at 1 week after the end of radiotherapy) with SSD cream was, however, higher than the results reported in other reports applying other topical agents: 7% with calendula [23], 0–2% with biafine [17, 24], and 0% with metamethasone [25]. These differences may be attributed to the different total dose delivered, chest wall versus breast irradiation, additional chemotherapy in all patients of our study, patients' characteristics, and finally the different efficacies and/or dosage of the agents which warrants comparative trials.

The severity of skin reactions during and following breast irradiation depends on a number of treatment- and patient-related factors. Treatment-related factors include the total dose delivered and fraction size, the volume of tissue irradiated, the surface area exposed, the type of radiation, and the addition of chemotherapy. Patient-related factors include physical characteristics (e.g., breast size, obesity), age, having problems with skin integrity, smoking, poor nutritional status, and also genomic constitution [4]. The results of our study supported the role of chest wall anatomy as a predictor of the severity of skin injury.

There are some limitations to our study. Because of the specific color and smell of the SSD cream, it was impossible to perform a real double-blind placebo-controlled study. Although the patients were instructed to clean the radiation area from the cream before starting the irradiation schedule of each week, the possibility of un-blindness of the clinical assessor still exists. Also, skin injury was assessed by standard criteria with an observer and it was helpful if we assessed what patients felt about the efficacy of the SSD cream by asking regarding satisfaction with the treatment, subjective symptoms like pain, and more importantly the quality of life. Evaluating the objective variables such as permeability barrier

function of the skin [26] and inflammatory responses would also enhance the validity of the results. We had a short post-radiation observation period of 1 week. We had to design such a relatively short-time evaluation scheme because it was impossible for most of our patients to undergo more frequent observations for practical reasons (such as long-distance travel). On the other hand, skin injuries gradually heal once radiotherapy is finished but, unfortunately, we did not follow patients to see if healing would be more rapid in the SSD group.

Conclusions

SSD cream is an effective, safe, inexpensive, and readily available topical agent that can be used for the prevention/treatment of acute radiation dermatitis, and we recommend it for these patients. Further trials on using SSD cream in other irradiated sites where risk factors may differ and also on comparing SSD cream with other topical agents are warranted. Future trials should focus not only on the preventive/therapeutic effects of the agents but also on the patients' quality of life.

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Conflicts of interest There is not any conflict of interest.

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