Original Article
Middle East Journal of Cancer; July 2021; 12(3): 406-414

A Double-Blind Randomized Trial on the Effectiveness of Mometasone 0.1% Cream and Hydrocortisone 1% Cream on the Prevention of Acute Radiation Dermatitis in Breast Cancer Patients following Breast Conserving Surgery

Mahsa Kianinia*, MD, Mahnaz Roayaei*, MD, Hoda Mahdavi♦, MD, Simin Hemati*, MD**

*Department of Radiation Oncology, Omid Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
**Department of Radiation Oncology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran

Please cite this article as: Kianinia M, Roayaei M, Mahdavi H, Hemati S. A double-blind randomized trial on the effectiveness of mometasone 0.1% cream and hydrocortisone 1% cream on the prevention of acute radiation dermatitis in breast cancer patients following breast conserving surgery. Middle East J Cancer. 2021;12(3):406-14. doi: 10.30476/mejc.2021.83528.1173.

♦**Corresponding Author:**
Hoda Mahdavi, MD
Department of Radiation Oncology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran
Tel/Fax: +982182141000
Email: mahdavi.h@iums.ac.ir

Abstract

Background: Despite the high prevalence of acute radiation dermatitis (ARD) in breast radiation treatment, data about its prevention is inconsistent. We conducted the present research to investigate whether the use of topical corticosteroids with different potencies or moisturizing cream could prevent ARD.

Method: In this double-blind randomized trial, 120 patients, who had undergone breast conserving surgery for breast cancer, were randomly assigned to use Mometasone 0.1% cream or hydrocortisone 1% cream or moisturizing base cream from the first day of radiotherapy throughout the entire course. CTCAE v. 4 scale was utilized to score the grade of ARD. The outcomes were analysed with relevant statistical methods.

Results: 105 subjects were analysed. Mometasone delayed the incidence of grade 1 ARD in a week. However, no differences were observed among the groups concerning the incidence of the maximum ARD grade (χ^2 (6, N= 104)=8.12, *P*=0.2). Moreover, the timing of the maximum ARD was not significantly different among the groups (χ^2 (4, N =84) = 2.87, *P*=0.58).

Conclusion: This study demonstrated that the application of corticosteroid creams (hydrocortisone 1% or Mometasone 0.1%) does not result into a significant difference concerning the timing and incidence of ARD occurrence when compared with daily skin care and use of emollient.

Keywords: Breast cancer, Acute radiation dermatitis, Topical steroids

Received: October 03, 2019; Accepted: January 27, 2021

Introduction

Radiotherapy (RT) is believed to be an essential part of treatment of several types of cancers. Ionizing radiation, applied in this treatment modality, acts by producing free radicals. Normal tissues compensate the damage through repair mechanisms; consequently, RT is principally more lethal for cancerous cells. The skin, as the first organ that external beam radiation penetrates through, is affected even though it is often not the target for RT of the breast. At molecular level, permanent DNA brakeage of reproductive cells and release of pro-inflammatory cytokines, chemokines, tyrosine kinases, and adhesion molecules cause destruction. This is termed acute radiation dermatitis (ARD).[1,2] Roughly 85% of patients experience this side-effect.[1] Patient-related factors, as well as total delivered dose, RT fraction dose, and energy of the beam affect the intensity of ARD.[3] This side-effect is typically reversible, yet the irritation of skin may have a negative impact on the quality of life,[1] or trigger treatment interruptions.[4-9] The clinical presentations in this regard could range from mild erythema, formation of dry desquamation, to more severe moist desquamation with bulla, ulcers, and necrosis.[4,5] Grading systems, such as National Cancer Institute-CTCAE, provide an objective gross description of skin damage.[10] In attempt to prevent ARD, routine washing of the skin is a widely accepted standard of care.[1,2,11,12,13] A variety of dressings, gels, or ointments derived from hyaluronic acid, Aloe Vera, and sucralfate have been introduced; however, no substantial benefits have been yet obtained.[1, 14] Steroids, such as Hydrocortisone, Mometasone,[6,15,16] and Betamethasone[4,5] are of anti-inflammatory properties. Some clinical evidence support steroid utilization for prevention and delaying ARD,[9] and reducing discomfort and alleviating ARD severity. The majority of trials have used potent steroids,[1,16,17] whose long-term use have a small risk of skin atrophy, telangiectasia, or infection;[1,2,16] these limit the acceptance for prescribing them for several weeks of the RT course. There is no evidence confirming that any steroid compound is superior to the others, but a possible different skin reaction profile could be expected.[2] Water based moisturizing creams or emollients are not radioprotective and their bolus effect is minimal. Nevertheless, their alleviating properties could be ascribed to softening the non-viable tissue, bacteria shedding, and reduction of water loss from dry desquamated skin.[1,2, 9,18] Attributable to cytokine release in the pathophysiology of ARD damage, anti-inflammatory agents, both non-steroids[19] and steroids, have been widely employed and shown efficacy in preventing erythema and dry desquamation. The assumption of this study was based on the idea that the majority of patients treated with RT to the breast post BCS may not need specific therapy for ARD prevention. Firm washing instructions, beside bland moisturizers might be the least but most effective skin care. Steroids of different potency and an emollient were compared for objective dermatitis score utilizing CTCAE v.4 grading system. Thus, the studied groups comprised three groups of patients who were instructed about washing hygiene beside 1- daily Mometasone 0.1% as a high-medium potency topical corticosteroid, 2- daily hydrocortisone 1%, as a lower-midium potency topical corticosteroid, and 3- a moisturizing base cream as the control group. The groups were compared regarding ARD incidence and timing.

Methods and Materials

The trial followed a prospective, randomized, triple masked, controlled design with three parallel arms. The eligible patients were at least 18 years old with histologically confirmed localized breast cancer, who had received breast conserving surgery (BCS) and completed the appropriate systemic therapy if indicated between May 2017 and September 2017. They were eligible if they had no known skin eczema, psoriasis, connective tissue disorder, or previous radiation to the breast. The exclusion criteria included those developing a progressive disease or refusing continuation of the procedure. The participants were recruited with convenience sampling and enrolled after signing in an informed consent. Our subjects were randomized employing a random code by Random

Table 1. Patient characteristics

	Control n= 36	Mometasone n=38	Hydrocortisone n=31	Total n=105	Difference
Age (mean, range)	48.06 (28-80)	47.98 (29-66)	55.87 (36-81)	50.36 (28-81)	Sig*
Menopause					Sig
Pre-	13	10	1	24	
Post	23	28	30	81	
Breast ptosis					NS
Yes	24	23	26	73	
No	12	14	5	31	
Stage					NS
IA	10	10	5	25	
IIB	8	13	15	36	
IIB	9	5	3	17	
IIIA	4	8	5	17	
IIIC	1	0	0	1	
Unknown	4	2	3	9	
Pathology					NS
IDC	33	36	30	1	
ILC	2	1	0	99	
Mucinous	1	0	0	3	
Micropapillary	0	0	3	1	
Pathologic grade					NS
G1	7	2	4	13	
G2	16	16	16	48	
G3	8	12	6	26	
ER					NS
Positive	25	27	15	67	
Negative	5	6	7	18	
HER-2/neu					NS
Positive	5	10	5	20	
Negative	24	21	16	61	
Chemotherapy					NS
Yes	30	32	29	91	
No	6	6	2	14	
Radiotherapy field					NS
Breast	13	18	14	45	
Breast+ SC	23	20	17	60	
Bolus					NS
0	20	22	17	59	
5 mm	14	16	13	43	
10 mm	2	0	1	3	
Fractionation					NS
Standard	33	32	28	93	
Hypofractionation	3	6	3	12	

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, ER: Estrogen receptor, HER-2: human epidermal growth factor receptor 2, SC: supraclavicular. Level of significance $P < 0.05$

Allocation Software (Windows software, version 1.0, Saghaei, license BioMed Central Ltd.) into one of the three arms: 1- Mometasone 0.1% (Behvazan lab., Rasht, Iran), 2- hydrocortisone 1% (Emad lab., Saveh, Iran), and 3- moisturizing base cream (Dr. Shah-Talebi lab., Isfahan, Iran) with a 1:1:1 allocation ratio. At the end, the records for 105 patients were completed as illustrated in figure 1. The formulation of the moisturizing cream was deionized water, paraffin, stearic acid, propylene glycol, glycerine, Vaseline, acetyl alcohol, glycerol Monostearate triethanolamine,

bee wax, methyl paraben, and propyl paraben with no added essence. The cream textures and labelled containers were identical. The patients were instructed to apply a thin layer of the cream on a daily basis, to the irradiated area from the first day of RT until week 5. They had to wash their skin with tap water and a neutral baby shampoo every day prior to receiving their daily RT fraction. The patients were examined weekly for 5 weeks. Breast ptosis was also documented. The patients, physicians, research assistants who distributed and renewed creams and provided instructions to the patient, and researchers who graded ARD where not aware of the content of the containers.

Breast RT was conducted with opposed 6 MV photon tangential beams with or without nodal coverage, boost dose, or bolus as decided by the radiation oncologist. The whole breast RT plan was either standard fractionated: 50 Gy (2 Gy/fraction), or hypofractionated: 40 Gy (2.67Gy/fraction). The whole RT area was examined by the same researcher weekly and ARD was graded using CTCAE v. 4.[10] The highest observed grades in all the areas were documented at each visit. In case of development of grade 3 lesions, which needed additional treatment, the researcher would prescribe medication. Otherwise, no other topical products were allowed.

The primary and secondary endpoints were the maximum radiation dermatitis (RD) grade during RT and the time taken to reach the maximum ARD grade. All the analyses were employed for treatment purposes, with outcomes compared using the χ^2 test, Kruskal-Wallis Test and ANOVA. The plots were designed with MATLAB (v. 2015a, Mathworks co.). The present study was approved by the Ethics Committee of our institute under the approval code: IR.MUI.REC.1396.3.111.

Results

Table 1 represents the demographic data of 105 women involved in the analysis, which

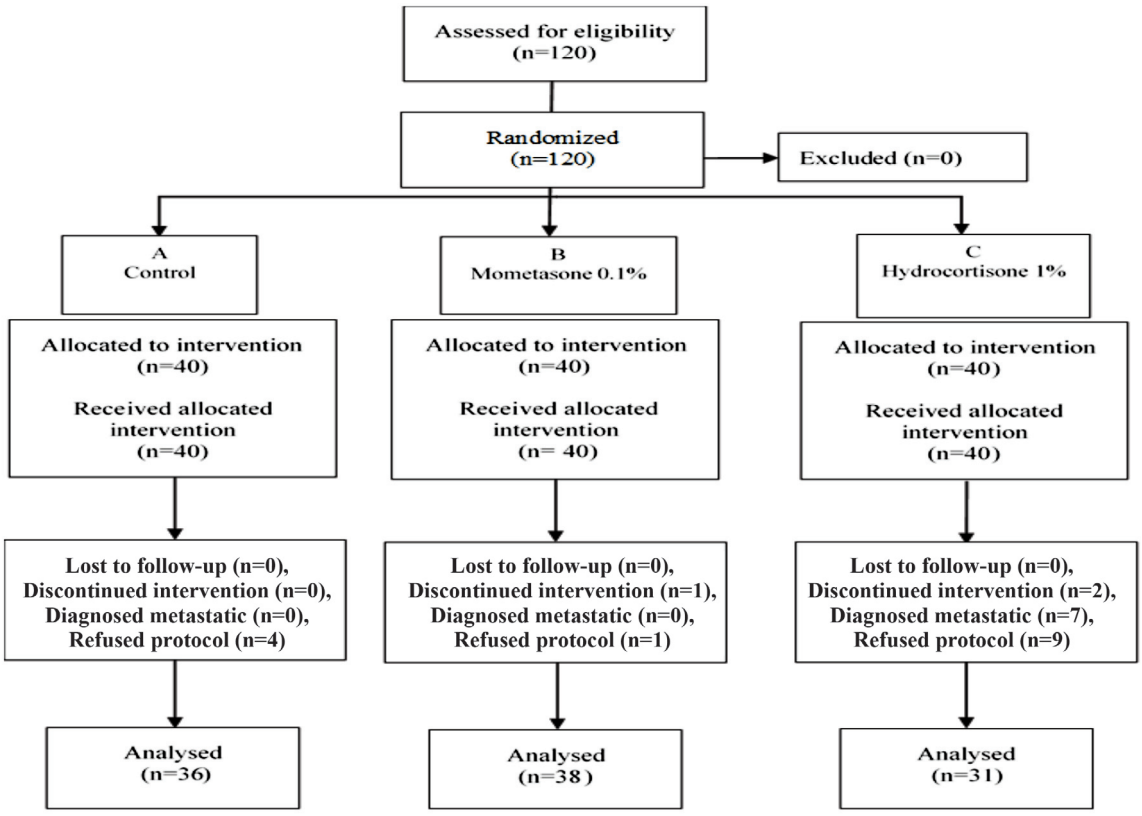

Figure 1. This figure illustrated CONSORT Flow Diagram of the trial.

indicates that age (F(2, 101) = 5.45, *P*= 0.006) and menopausal status (χ^2 (2 , N = 105) = 10.62, *P* = 0.005) were significantly different between the groups but the other factors were not. The results revealed that 84 patients (77.4%) experienced ARD. Figure 2 shows the mean ARD grade recorded weekly for each group. As it is shown on the plot, none of the patients experienced ARD at the end of week 1. The patients in the mometasone group had no ARD by week 2.

Treatment and patient related factors

The relations between the maximum ARD grade and breast ptosis, menopausal state, pathological or stage variables, and history of receiving chemotherapy were not significant. However, certain treatment factors, such as presentation of bolus and dose fractionation, were found to be correlated. The presentation of bolus was significantly associated with the maximum grade of ARD (χ^2 (3, N = 104) = 11.33, *P* = 0.010) (Figure 3). 50% of the patients who received hypo-fractionated RT did not experience ARD. In contrast, ARD was absent in only 16% of all the subjects who had received standard fractionated RT.

Maximum ARD grade

The maximum ARD grade is defined as the highest observed ARD grade during the RT course of each individual. This was grade 1 for 31 (29.5%), grade 2 for 42 (40%), and grade 3 for 10 (10.5%) individuals. No patients had grade 4 ARD. Table 2 depicts the incidence within the groups. The relation between types of cream application and the maximum ARD grade was not significant (χ^2 (6, N = 104) = 8.12, *P* = 0.2).

Timing of maximum ARD

The time to reach the maximum ARD was recorded for 84 patients; the rest did not experience ARD. Most patients (77.4%) reached the maximum ARD by week 5. However, 14.3% and 8.3% had the maximum ARD by weeks 4 and 3. The groups were not significantly different in this regard (χ^2 (4, N =84) = 2.87, *P* = 0.58). The treatment field (breast or breast+ supraclavicular lymph nodes) made a marginal significance with timing of the maximum ARD (χ^2 (2, N = 83) = 5.7, *P* = 0.057). Menopausal status, breast ptosis, or inclusion of bolus were not correlated with the time of the maximum ARD.

Comparison within weeks

Figure 4 shows the incidence of dermatitis grade per week for each group. According to the plot, at week 4, there was a higher proportion of observed grade 2 radiodermatitis in the control group as compared with the hydrocortisone or Mometasone group (14.8% vs. 11.1% vs. 4.2%). At week 5, there was a higher proportion of observed grade 3 radiodermatitis in the control group as compared with the hydrocortisone or Mometasone group (18.2% vs. 6.3% vs. 7.1%). Fisher's exact test statistics showed that there were no statistically significant associations between the groups and each ARD grade per week (*P* = 0.13, 0.93, 0.34, 0.37, for weeks 2 to 5). However, the mean ARD grades for Mometasone group were delayed and lowered in each week compared with the other groups (Figure 2). The increase in the mean dermatitis severity

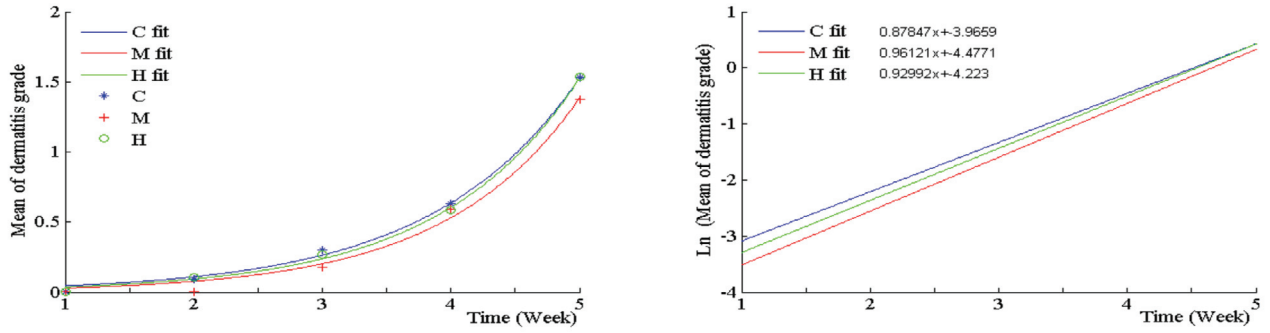

Figure 2. This shows the means of dermatitis grade recorded weekly for each group and trend-line in C= Control, M= Mometasone 0.1%, H= Hydrocortisone 1% groups.

Table 2. Incidence of Maximum CTCAE 4. grade of acute radiodermatitis within groups

Grade	Control N=36	Mometasone 0.1% N=38	Hydrocortisone 1% N=31
0	7	11	3
1	10	9	12
2	12	16	14
3	7	2	2

per week followed an exponential pattern. To visualize the severity changes, the best fitted functions of each group were computed and plotted. In the linear function of Mometasone group, an initial delay of dermatitis was almost compensated by a steeper slope.

Discussion

Our study demonstrated that throughout the RT course, the application of low-mid potency (hydrocortisone 1%) or a high-medium potency (Mometasone 0.1%) corticosteroid cream have no further advantages in reducing the maximum ARD grade compared to skin care and a moisturizing base cream formulation, albeit, topical Mometasone delayed the occurrence of ARD grade 1 (erythema or dry desquamation).

Our results are in line with the idea that emollients and moisturizers may be prescribed for reducing erythema and dry desquamation during RT.[13] However, our results did not replicate the results of a meta-analyses on nine randomised controlled trials on prevention and management of ARD with topical steroids in breast cancer patients.[17] Their results demonstrated that topical steroids reduced the incidence of moist desquamation by at least 5 times when compared with controls. Accordingly, topical steroids have been recommended for ARD prevention.[20] It should be noted that data in this report was diverse, as in only four trials, linear accelerators were used and a considerable number of subjects[4,15,16] received Cobalt-60 or superficial X-rays for breast RT (21%). These low energy treatments caused higher incidence and more severe ARD and since the skin is not targeted in breast RT except tumoral involvement, these are now obsolete methods of breast RT. Merely 38% of the subjects of the pooled data were treated with conventional fractionated RT and the rest with hypofractionated scheme. Instead, 88% of the subjects of our study received conventional fractionated RT and the rest were treated with hypofractionated RT, all with 6 MV photons. Considering different effects of each technique on skin dose, our different results may be justified. Remarkably, we believe

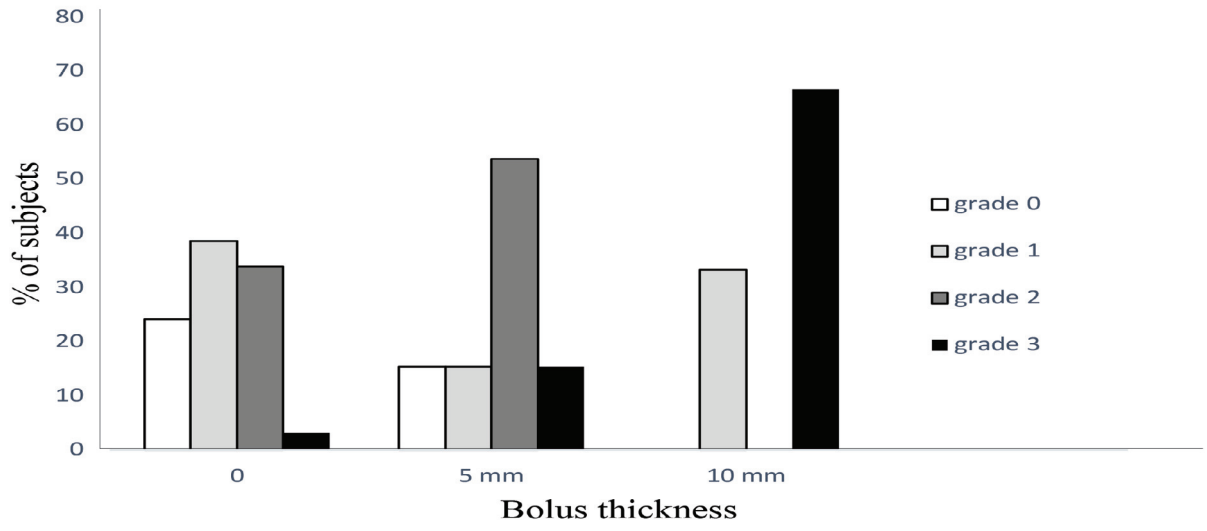

Figure 3. This figure shows the prevalence of the maximum grade of acute radiodermatitis and bolus thickness in the subjects.

that since basic instructions for skin care, cream formulations, ARD grading systems, and patient selection were different among trials, it is difficult to make derive definitive recommendations out of trials.

The type of the applied topical agents did not affect the timing of the maximum ARD in the patients with breast ptosis in our trial. Apparently, bolus affected ARD grade. In the only similar trial on pure BCS patients treated with conventional RT, the subjects presented a lower incidence of ARD by the potent topical mometasone 0.1% compared with Diprobase, which were measured based on a simplified clinical scale with spectrophotometer.[16] The scale with erythema per se regarding its intensity was equivalent to grade 1 in CTCAE. A visual analogue scale developed by the authors was also used. Such differences in the indicis used in these trials make it difficult to compare the results since none of the common scales have been validated for this purpose.[17] Another trial examined Betamethasone plus Essex or Essex or Canoderm cream in BCS or modified radical mastectomy (MRM) for the patients during conventional RT. A significant difference was observed in RTOG grades between the groups at week 4 and 5.[4] Our results for the same analysis CTCAE was not significant. On the contrary, a trial was launched on breast cancers following BCS and MRM who applied mometasone 0.1% or Dermobase emoliant during conventional RT. The groups were different concerning the subjective reports, for instance itching, but similar regarding the objective ARD measured with CTCAE 3.0 grading system.[15]

Our results illustrated that hypofractionated RT caused less ART as it has been reportedly demonstrated further skin protecting since ARD is proportional to total dose.[21] In terms of prevention of ARD in hypofractionated RT by steroids, this was examined comparing mometasone 0.1% to an emollient in breast cancer patients who had received MRM or BCS. A modified RTOG grading system, on top of an

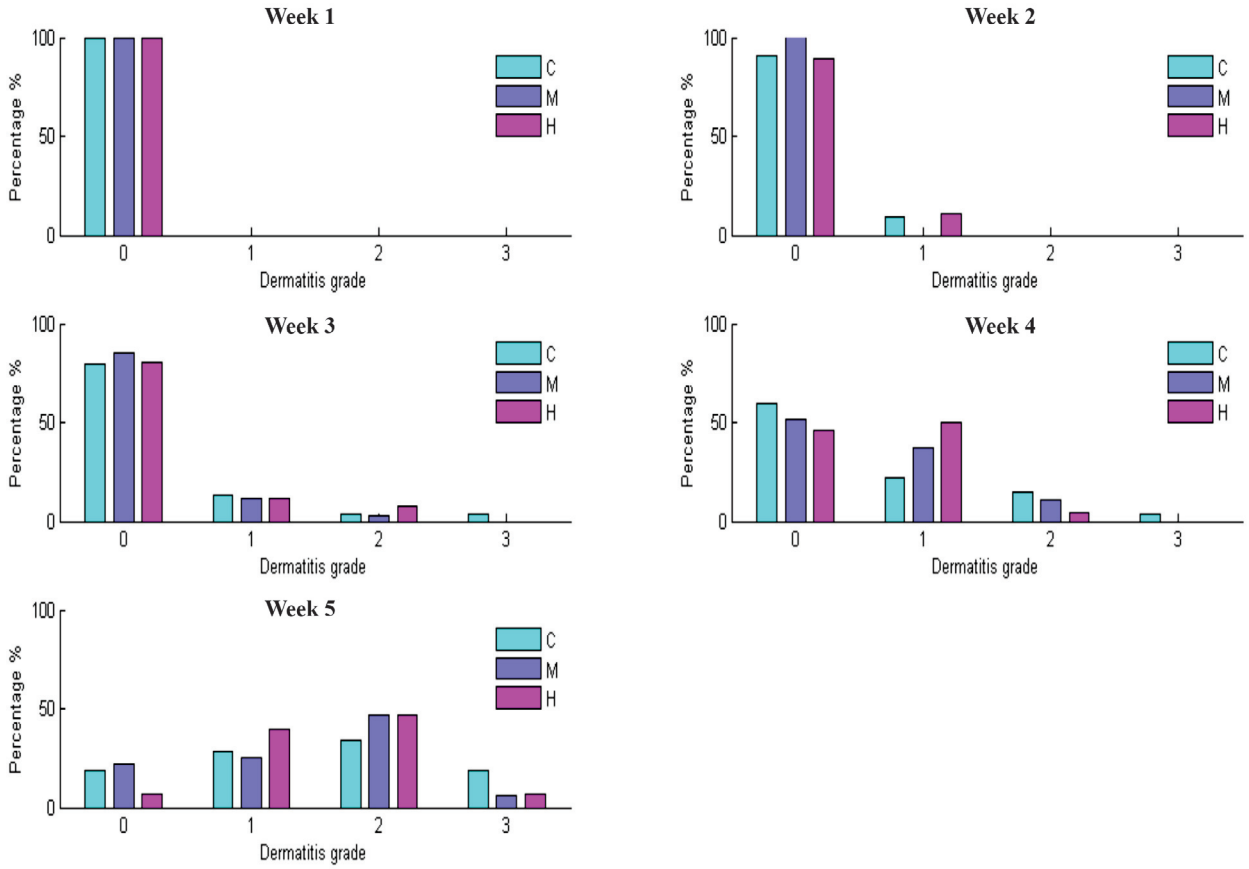

Figure 4. This figure documented the incidence of acute dermatitis grade per week for each treatment group.

erythema spectrophotometer, were used and indicated that mometasone 0.1% had a statistically significant effect on maximal ARD (odds of 2.38). The analysis of grades according to week interactions and time to reach the maximum ART were not statistically significant.[6] Another trial on betamethasone-17-valerate cream or Essex also showed that the preventive effect was significant regardless of fractionation schedule using RTOG grading system.[22] Our results did not support their findings.

Another finding opposed to the initial delay in the occurrence of grade 1 in the mometasone group; the maximum ARD grade was not different among the groups. Similarly, the number of trials[23-27] indicated an initial good response of ARD to steroids, which diminished after weeks and was followed by even more severe dermatitis. Some have suggested that this could be attributed to the use of low potency of steroid;[23] on the other hand, on a number of occasions, it has been regarded as a 'breakthrough phenomenon' with an unknown mechanism described with the use of potent topical steroids.[24,25] In fact, it has been suggested to be possibly related to contact dermatitis[16] or other reactions that affect skin barrier. The possibility of adverse effects of the continues use of steroids should be apprehended.

The results of this study could be generalized to the cases treated with modern RT, in which skin dose may be adjusted with the help of the Treatment Planning System. Further studies are required to focus on the quantification of early damage and dose-response diagrams once preventive measures are taken. Yet, clinical data still provide no clear consensus for the choice and potency of topical steroids.

The trial herein was not designed to identify objective data, such as the quality of life and other factors that help the selection of patients who are more likely to benefit from preventive medication, which was the limitation of the current work. For instance, we did not asses skin color types that might have affected the degree of damage. Furthermore, the evaluation of the groups after the sampling revealed that they were different concerning the mean age and menopausal status. These factors may have affected the results since they are linked to dry and irritable skin.

Conclusion

Ultimately, the results of this trial suggested that benefit of any topical steroid for ARD prevention may be minimal. Since skin dose yielded from RT technic is the main driver for ARD, further uniform data are required on breast conserved patients in order to assess the actual role of steroids in ARD prevention, when compared with washing instructions.

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