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Do topical corticosteroids improve the [skin] side effects of radiation in terms of radiation dermatitis for women undergoing radiation treatment for breast cancer?

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Do topical corticosteroids improve the [skin] side effects of radiation in terms of radiation dermatitis for women undergoing radiation treatment for breast cancer?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not topical corticosteroids prevent and/or reduce symptoms and severity of radiation dermatitis in breast cancer patients receiving radiation therapy to the chest wall.

Study Design: Review of three double blind randomized controlled clinical trials (RCTs) published in 2002, 2007, and 2011

Data Sources: Three peer-reviewed RCTs were found using PubMed. These studies compared topical corticosteroid use against various placebos in the treatment of radiation dermatitis

Outcomes Measured: Severity of radiation dermatitis as reported using quality of life questionnaires, Skindex scores, and Radiation Therapy Oncology Group (RTOG) scaling. Significant outcomes were evaluated through the use of p-values and t-tests.

Results: Schmuth et al (2002) found significant difference between the two treatment arms for embarrassment ($p<0.05$) and approached significance for dimensions of fear ($p=0.06$) and physical discomfort ($p=0.057$). Furthermore, while all dimensions worsened in the dexpanthenol treated group, only four of seven dimensions worsened in the corticosteroid group. In Miller et al (2011) itching, irritation, the persistence of symptoms, the recurrence of toxicity symptoms, and annoyance with dermatitis were all reduced by a statistically significant fraction in the treatment group compared with the placebo group in the Skindex-16. The total Skindex-16 score, however, did not reach statistical significance between the MMF arm and placebo arm with a $p=0.07$. In Omidvari et al (2007) all patients developed some degree of radiation dermatitis. However, patients receiving betamethasone had less severe acute radiation dermatitis than the petrolatum receiving or control groups throughout the course of the study; this difference was only significant by the end of the third week ($p=0.027$).

Conclusion: Conflicting results from these three RCTs demonstrates that the use of topical corticosteroids in the prevention and treatment of radiation dermatitis is inconclusive

Key Words: Corticosteroids, Radiation Dermatitis, Breast Cancer, Chest wall Irradiation

INTRODUCTION

With an increase in technology and screening, there is now better detection and treatment for breast cancer. While there is great benefit in the improved management of breast cancer, it is essential to consider the subsequent side effects of treatment and how best to manage those. Radiation therapy, for example is used in definitive, preoperative, and postoperative or palliative treatment in the management of breast cancer.[1] Because of the increase in radiation therapy there has also been an increase in cases of radiation dermatitis, an acute injury within hours to weeks after radiation exposure as a result of structural tissue damage, generation of short-lived free radicals, irreversible double stranded breaks in nuclear and mitochondrial DNA, and initiation of an inflammatory response in the epidermis and dermis.[2] The exact mechanism of radiation induced inflammation is not fully understood, but research to date suggests that fibroblasts are a key cell type responsible for the late or delayed effect of radiation.[2]

Care for this side effect is essential because without reduction in the cosmetic and uncomfortable disturbance of radiation dermatitis from therapy, patients often become non-compliant with appropriate breast cancer treatment.[1] Due to the variance in severity and response to skin treatments, there are no specific guidelines on the number of visits each year for radiation dermatitis. Regardless, with an increase in cases of radiation dermatitis (affecting about 87% of patients receiving radiation[1]), it is very fortunate that mid-level practitioners, like physician assistants, are capable of managing these effects of radiation.

In the treatment of any dermatitis, it is necessary to consider the treatment options to reduce discomfort, cosmetic disturbances, and recurrence. Unfortunately, there is currently no treatment of choice to benefit all patients with radiation dermatitis[1,3], making it necessary for practitioners to be aware of all pharmacologic as well as non-pharmacologic management

strategies for managing the dermatitis. Though there are several different recommendations for treatment, all studies imply the importance of maintaining appropriate hygiene and avoidance of obvious irritants. The affected skin, for example, should remain clean and dry after washing with lukewarm water, and mild, synthetic soaps. Patients must avoid skin irritants including sun exposure, perfumes and alcohol based lotions, and instead use unscented, lanolin-free, water based moisturizers. Loose fitting clothes will also benefit the patient in order to avoid friction injuries to the affected skin.[1,3,4,5]

After considering the number of simple recommendations for their radiation dermatitis, patients and practitioners must choose among the assortment of topicals used in the treatment of this conditions. Aloe vera, calendula, petrolatum-based emollients, trolamine-containing formulations, topical corticosteroids, and sucralfate cream are the most commonly suggested topicals[1]; no general agreement, however, exists concerning how to treat or prevent radiation dermatitis.[3] Though there are a number of options to choose from, this selective EBM review seeks to explore the potential benefits of using topical corticosteroids as the sole topical treatment for radiation dermatitis. Topical corticosteroids, if beneficial in the prevention and treatment of radiation induced dermatitis, are a good option as a topical treatment because they are both affordable, ranging from $27 to $42 (in the reviewed studies)[6,7,8], and have limited additional side effects.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not topical corticosteroids prevent and/or reduce symptoms and severity of radiation dermatitis in breast cancer patients receiving RT to the chest wall.

METHODS

Three double blind randomized controlled studies were used in this review. Each study followed a group of women who had previously had surgical treatment for breast cancer and were to undergo radiation therapy (RT). Over the course of their RT, topical corticosteroids were introduced into the experimental groups. The specific topical corticosteroid, dose, and application duration varied across the studies, as did the structure of each control group; the commonality, however, was the absence of corticosteroid cream application for the comparison control group. After the application of the creams to the irradiated skin for a specified duration, patients were asked to be assessed for or report the outcome of their treatment based on the severity of their radiation dermatitis.

Key words used in search included corticosteroids, radiation dermatitis, breast cancer, and chest wall irradiation. The chosen articles were all written in English and published in peer-reviewed journals between 2002 and 2011. Each was found through PubMed database, and selected based on its relevance to my initial clinical question and its ability to be correlated to the outcome in question. The inclusion criteria consisted of RCT's and a population of female breast cancer patients with previous surgical treatment and were receiving RT. Women receiving other therapies for their radiation dermatitis were excluded, as were women with a history of other skin conditions, or inflammatory breast carcinoma. In the analysis of each trial, p-values, t-tests, and/or Kruskal-Wallis tests were utilized to determine the summary of statistical significance of topical corticosteroid use.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Omidvari (2007)[1]	RCT	58	20-70	Female pts who underwent modified radical mastectomy and chemo for stage II or III and needed RT. Without hx of RT, DM or systemic CTD	Patients who were receiving concurrent chemotherapy and radiation or were on systemic corticosteroids	7	Betamethasone 0.1%
Schmuth (2002)[3]	RCT	31	18-80	Women receiving RT for breast cancer after breast conserving surgery	No prior history of radiation dermatitis or RT to same area; pts with skin conditions a/w barrier defect or those receiving systemic corticosteroids	2	Methylprednisolone 0.1%
Miller (2011)[4]	RCT	176	≥18	Invasive breast or ductal carcinoma in situ; continuous, definitive, or adjuvant external beam RT to whole breast as part of breast conservation therapy or to breast wall as part of postmastectomy RT	Inflammatory carcinoma, allergy to mometasone, imidazolidinyl urea, or formadelhyde; use of leukotriene inhibitors or OTC med with hydrocortisone/ corticosteroid prep; pregnant or breast feeding; bilateral breast carcinoma	10	Mometasone fuoate 0.1%

OUTCOMES MEASURED

Each breast cancer patient who successfully adhered to all experimental procedures, was asked to either complete a quality of life questionnaire/Skindex-score survey, or was evaluated with RTOG scaling to determine the results of topical corticosteroid use during and after RT.

These assessments successfully measured the impact of the RT on the skin in terms of severity, patient symptoms, and morbidity associated with the skin changes.

Schmuth et al (2002) assessed patients' quality of life (QOL) using a medical outcome study 36-item short form health survey as well as the Skindex survey. The former was developed to identify general physical and mental components of health related QOL with 36 items measuring eight general health dimensions.[3] The Skindex scoring system was slightly different, as it was developed to identify skin disease specific health related QOL rather than that for general health. This 61-item version included two physical (discomfort and limitations) and three major psychosocial (cognitive, social, and emotional) dimensions as they related to QOL in regards to skin disease.[3] Scores for both assessments of QOL were standardized to 100, with the higher scores indicating a better outcome.

In Miller et al's study (2011), patient reported outcomes were measured using the Skindex-16 and the skin toxicity assessment. The skin toxicity assessment tool is a skin-specific instrument that consisted of a provider assessment as well as patient reported discomfort. The patient completed QOL assessment consisted of six questions, with responses ranging from 0 (poor QOL) to 10 (best QOL).

Rather than assessing acute radiation dermatitis with QOL surveys like the previously explained studies, Omidvari et al. utilized RTOG acute radiation morbidity scoring criteria for the skin. With each visit throughout the study, patient's irradiated skin was scored grades 0-4 based on the level of dermatitis experienced by the patient. Grade 0 referred to no skin changes over baseline, or no radiation dermatitis. Grades 1-4 represented skin changes ranging from erythema, dry desquamation, and decreased sweating to ulceration, hemorrhage, and necrosis. In terms of patient outcome and perspective, grade 1 was considered less bothersome than the

obvious pain experienced by patients with grade 4 radiation dermatitis.[1] Thus, the higher the grade assigned to the patient, the worse radiation dermatitis was to be experienced by the patient.

RESULTS

Three double blind RCT's compared the severity of radiation dermatitis in female, breast cancer patients receiving standardized RT after surgical treatment with topical corticosteroid treatment as compared to other topical therapies for the skin condition. Miller et al (2011) used patients receiving the non-steroidal topical cream as the control group while the other two studies had a control group of individuals using no topical treatment. Omidvari et al (2007) and Schmuth et al (2002), thus had three groups of individuals participating in the study; those receiving topical corticosteroids, a non-steroidal cream, and a group without topical cream treatment. The inclusion and exclusion criteria of all three studies were relatively similar, with small differences primarily seen in exclusion criteria (Table 1).[1,3,4] Women receiving concurrent chemotherapy and radiation were excluded from the studies because there is an additive response between combined chemo and RT, leading to an increase in severity of radiation dermatitis.[9]

Data from all trials were reported as continuous data and could not be converted into a dichotomous format; therefore, calculations evaluating tolerability, adverse events, and treatment effects could not be computed. Patients in the studies received written information and consented to participate in each trial prior to randomization. Because the women were free to withdraw, each study lost a few participants over the course of the treatment for reasons that were not shared. The losses, however, were minimal, ranging from 0-2 patients from a given group.[1,3,4]

In Schmuth et al (2002), a preliminary cohort of 15 patients who did not receive topical therapy served as a control group. After obtaining the baseline data from the initial control

cohort, a subsequent cohort of patients was recruited and randomized to one of the two groups in a double blind fashion; one group receiving 0.5% dexpanthenol and the other the interventional treatment in question, 0.1% methylprednisolone. The study population was selected from consecutive patients attending the Department of Radiation Therapy in Innsbruck. Twenty three patients were randomized into one of the two groups applying a specific type of cream. Two patients withdrew from the methylprednisolone group due to either inadequate adherence to treatment (n=1) or patients' request (n=1). At the completion of the study, there were 11 patients using the topical dexpanthenol and 10 patients using the methylprednisolone. The severity of each patients' radiation dermatitis was monitored weekly throughout the study; with six weeks of fractionated RT and two weeks of follow-up after its completion.[3]

Clinical and functional parameters with questionnaire based QOL assessment of patient's own experience of their disease and response to therapy was performed using the SF-36 and Skindex QOL assessments. Of the 21 patients who completed the study, only 16 and 17 patients for the Skindex and SF-36 questionnaires, respectively, were usable, yielding final response rates of 76% and 81%, respectively. An unpaired t-test was first used to calculate differences in QOL scores between the treatment arms. Post-treatment QOL scores were then compared with the pretreatment baseline scores by the paired t-test; a p value of <0.05 was considered significant. In both the SF-36 and Skindex inventories, scores largely deteriorated from pretreatment to post treatment, reflecting appearance of radiation dermatitis in all subjects. Severity of change, however, differed between those treated with corticosteroids versus dexpanthenol. While all dimensions worsened in the dexpanthenol treated group, only four of seven dimensions worsened in the corticosteroid group, indicating that topical corticosteroids may in part reverse negative impact of radiation dermatitis. The difference between the two treatment groups was

significant for the dimension of embarrassment and approached significance for the dimensions of fear and physical discomfort.[3]

Table 2: Difference in post-treatment v. pretreatment QOL scores for 0.1% Methylprednisolone v. 0.5% Dexpanthenol

	P values
Embarrassment	<0.05 (value not given)
Fear	0.06
Physical discomfort	0.057

Miller et al (2011) recruited 176 patients between September and December 2007, with a follow up period of two weeks after RT completion. Of the 176 patients 90 were randomly assigned to the treatment group applying 0.1% mometasone fuorate and 86 were randomly assigned to the control group with the application of a placebo cream. After randomization, 5 patients in the MMF arm and 2 patients in the placebo arm declined participation, for 169 eligible patients. Data was missing for 3 patients, leaving 166 patients eligible for evaluation. The secondary endpoints of patient reported skin toxicity (outcome measures using Skindex-16 and skin toxicity assessment tool) and QOL were analyzed by comparing the mean responses between the study arms using the Kruskal-Wallis test. Itching, irritation, the persistence of symptoms, the recurrence of toxicity symptoms, and annoyance with dermatitis were all reduced by a statistically significant fraction in the treatment group compared with the placebo group in the Skindex-16. The total Skindex-16 score, however, did not reach statistical significance between the MMF arm and placebo arm with a $p=0.07$. The patients in the MMF arm also reported less discomfort and burning, less itching, and less redness using the Skin Toxicity Assessment tool and symptom experience diary.[4]

Table 3: Patient-reported maximum Skindex-16, Skin Toxicity Assessment Tool, and Symptom Experience Diary toxicity scores

	Maximum Skindex-16 score		
Toxicity Characteristic	MMF (n=83)	Placebo (n=83)	p value
Itching	2.3	3.1	0.008
Irritation	2.6	3.4	0.01
Persistence/recurrence of sx	2.3	3.0	0.02
Annoyance of sx	1.2	1.8	0.04
Total Skindex-16 score	1.4	1.7	0.07
	Skin Toxicity Assessment score		
Discomfort or burning	1.5	2.1	0.02
Itching	1.5	2.2	0.002
	Symptom Experience Diary score		
Redness	5.1	6.8	0.003

*****Lower score indicated less toxicity

In Omidvari et al (2007), eligible patients were female patients who previously underwent modified radical mastectomy for pathologically proved breast cancer and needed treatment with RT. During a three month period, 58 eligible patients were randomly assigned by a computer based system to receive petrolatum, bethamethasone 0.1%, or none. Of the 58, seven patients failed to complete the study course or were excluded because of declining to participate, new onset DM (part of exclusion criteria), or prolonged radiation course due to other causes, leaving 51 statistically evaluable cases at the end of the study. Of these 19 were in the betamethasone group, 17 in the petrolatum group, and 15 in the control arm.[1]

The severity of the patients' radiation dermatitis was determined using RTOG acute radiation morbidity scoring criteria for skin as described earlier in the review. The betamethasone acute radiation dermatitis (ARD) scoring was lower throughout the study. The data showed that though patients applying topical corticosteroid did have ARD after RT, the severity of the condition was lower and with a delayed onset when compared to the other two arms of the study. Significant difference, however, was only found at the end of the third week, only 26.3% of the betamethasone group with Grade I dermatitis compared with 64.7% and

66.7% in the emollient and control arms respectively; these results were considered statistically significant with a p-value of 0.027 (statistical significance achieved when $p<0.05$). Furthermore with this data, the numbers needed to treat can be calculated with an NNT=2 patients. At the conclusion of the topical treatment, all petrolatum-receiving patients developed Grade II or higher ARD. At the same time, all patients had some degree of ARD but betamethasone receiving patients had lower mean dermatitis grade than the other two arms. These results, however did not reach significance but approached it with $p=0.055$.[1]

DISCUSSION

Using three double blind RCT's this systematic review assessed the effects of topical corticosteroids in the prevention and treatment of radiation dermatitis. Each article selected female breast cancer patients who were undergoing radiation therapy post-surgical treatment for their cancer and assessed the severity of radiation dermatitis that resulted from radiation to the skin. The validity and blinding of each RCT was without error, however the sample sizes were relatively small despite the low drop-out rate. Furthermore, quality of life was the main assessment of patient outcomes in this study, but many others do exist.

Since their introduction to dermatologic therapy in 1952, topical corticosteroids have become widely available and are very useful in treating numerous skin conditions. When use as directed, this topical therapy is safe and very effective. Inappropriate or overuse, however, can lead to several topical and systemic side effects that practitioners must be mindful of when prescribing the topical medication. All topical corticosteroids, for example, have been shown to cause some degree of skin atrophy. Topical corticosteroids are contraindicated as primary treatment of bacterial infections because they are known to mask an infection by their vasoconstrictive and anti-inflammatory properties, making diagnosis of infections more difficult.

Other relative contraindications include Candidal, dermatophyte, and herpetic infections.[10] Thus, despite their broad availability, efficacy, relative low cost, ease of application, and lack of black of box warnings, practitioners must be mindful of the risks associated with topical corticosteroids.

CONCLUSION

The use of topical corticosteroids has shown inconclusive results in the prevention and treatment of radiation dermatitis in breast cancer patients undergoing radiation therapy to the chest wall. Though the data is statistically inconclusive, these studies support the notion that topical corticosteroids do in fact provide some relief to patients experiencing radiation dermatitis. Both Miller et al (2011) and Schmuth et al (2002) provided evidence a decrease in the decline of QOL with the use of topical corticosteroids as compared to the control. Likewise, Omidvari et al's (2007) results demonstrated a delay in radiation dermatitis and an overall lower grade radiation dermatitis score for those using the betamethasone in comparison to the group.

The use of topical corticosteroids in all studies relied on patient compliance and honest report of application. Furthermore, the correct amount of the cream may not have been equal for all patients throughout the study, possibly altering the true benefits/harms of using the steroid creams. In the future, reliability could be improved by clinician administration of the cream in order to standardize and control the proper use of the topical treatment. The known anti-inflammatory effect of corticosteroids on the irradiated skin warrants further investigation. Continuing research should continue to compare different treatments for the skin condition to come to a consensus on how best to treat radiation dermatitis. Research should also consider the duration of experiencing radiation dermatitis after completing radiation therapy.

References

1. Omidvari S, Saboori H, Mohammadianpanah M, et al. Topical betamethasone for prevention of radiation dermatitis. *Indian J Dermatol Venereol Leprol*. 2007;73(3):209.
2. Julie L Ryan, PhD, MPH, Marilyn Ling M. Radiation dermatitis. UpToDate Web site.http://www.uptodate.com/contents/radiation-dermatitis. Published November 13, 2013. Updated 2013. Accessed 10/05, 2014.
3. Schmuth M, Wimmer MA, Hofer S, et al. Topical corticosteroid therapy for acute radiation dermatitis: A prospective, randomized, double-blind study. *Br J Dermatol*. 2002;146(6):983-991.
4. Miller RC, Schwartz DJ, Sloan JA, et al. Mometasone furoate effect on acute skin toxicity in breast cancer patients receiving radiotherapy: A phase III double-blind, randomized trial from the north central cancer treatment group N06C4. *Int J Radiat Oncol Biol Phys*. 2011;79(5):1460-1466. doi: 10.1016/j.ijrobp.2010.01.031; 10.1016/j.ijrobp.2010.01.031.
5. Hymes S, Strom E, Fife C. Radiation dermatitis: Clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol*. 2006;54(1):28-46.
6. Mometasone (topical). Lexicomp Web site.http://online.lexi.com.ezproxy.pcom.edu:2048/lco/action/doc/retrieve/docid/patch_f/1799125. Updated 2014. Accessed 10/05, 2014.
7. Betamethasone (topical). Lexicomp Web site. http://online.lexi.com.ezproxy.pcom.edu:2048/lco/action/doc/retrieve/docid/patch_f/5004842. Updated 2014. Accessed 10/05, 2014.
8. Methylprednisolone. Lexicomp Web site. http://online.lexi.com.ezproxy.pcom.edu:2048/lco/action/doc/retrieve/docid/patch_f/7282. Updated 2014. Accessed 10/05, 2014.
9. Archambeau JO, Pezner R, Wasserman T. Pathophysiology of irradiated skin and breast. *International Journal of Radiation Oncology* Biology* Physics*. 1995;31(5):1171-1185.
10. Cornell RC. Contraindications for Using Topical Steroids. *Western Journal of Medicine* 1987;147(4):459-460.