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Topical betamethasone for the prevention of acute radiation dermatitis in breast cancer patients

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ABSTRACT

Background: Acute radiation dermatitis is a very common side effect of radiation therapy in large numbers of cancers including breast cancer. Despite high prevalence rate of acute radiation dermatitis and also wet desquamation, a few trials on prophylaxis of this complication using topical treatment have been conducted. Despite effectiveness of topical corticosteroids in treatment of acute radiation dermatitis which are focused in the literature, yet there are some controversy about their usage in this regard. For this reason we attempted to investigate this subject via conducting a clinical trial.

Materials and Methods: This trial included 76 patients with pathologic diagnosis of breast cancer for whom radiotherapy has been planned. Patients were 27-70 years old. Patients with radical mastectomy received 5000 cGy within 5 weeks, and those with conservative surgery received 6000 cGy within 6 weeks divided in 200 centigray fractions. Patients were divided randomly into two groups, betamethasone and placebo, 38 patients in each group. In placebo group, 3 patients did not attend for weekly assessment. Additional one patient did not refer during follow-up period. Thus, they were excluded from the study. One group was given betamethasone 0.1% and other group was administered base of ointment as placebo.All patients consumed drug or placebo from the 1st day of treatment until one week after treatment completion as twice daily within tangential field. Patients were monitored for assessing dermatitis severity and its symptoms and also possible drug adverse effects one week after the therapy commenced and afterwards by one-week intervals as well as in an appointed day. Three weeks after termination of therapy, patients were also visited, and each examination provided information about dermatologic complications which were registered in the questionnaire.

Results: Mean times development of dermatitis in both betamethasone and placebo groups were 3.2500 and 2.2571 (weeks) respectively ($t=-3.898$, $p \leq 0.001$). Maximal dermatitis intensity during treatment in betamethasone group was 3.5% 0, 86.8% I, 7.9% II, 0% III, 0% IV and in base of ointment receiving group were 0 %, 60% , 37.1%, 2.9% and 0% ($P = 0.008$), respectively. Maximum severity of complaints stated by patients in terms of burning and pruritus had been lesser in betamethasone group ($P< 0.001$). No significant differences were observed between two groups in terms of pain intensity.

Conclusion: Betamethasone valerate ointment is statistically significantly more effective than base of ointment alone in reducing acute radiation dermatitis. *Iran. J. Radiat. Res.; 2003, 1(2): 105 – 111.*

Keywords **:** *Breast cancer, dermatitis, radiotherapy, corticosteroids.*

INTRODUCTION

Acute radiation dermatitis is a common complication of radiotherapy in various kinds of cancers including breast cancer. Due to using tangential field which delivers maximal dose to skin, majority of patients develop some degrees of acute dermatitis. Severe acute reactions such as blister and wet desquamation conteract with patient daily activities and necessitates discontinuation of therapy.

Topical corticosteroids have been shown to have an anti-inflammatory effect and are

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prescribed for radiation dermatitis. It has been determined that acute and chronic effects of radiation are accompanied by excessive production of eicosanoids (prostaglandins, prostacyclin, thromboxanes, and leukotrienes). Glucocorticoids are known to inhibit eicosanoid synthesis by interfering with phospholipase A_2, and nonsteroidal anti-inflammatory drugs (NSAIDs) prevent prostaglandin/thromboxane synthesis by inhibiting cyclooxygenase, (Mendelsohn *et al.* 2002). Several studies have shown that administration of glucocorticoid or NSAID groups attenuate, to a large extent, the effects of radiation in humans.

Simonen and colleagues(1998) examined the effects on erythema of 1% topical indomethacin and 1% topical hydrocortisone applied before and during radiotherapy. Differing intensities of reactions in the 2 treatment arms did not occur until the third week after starting treatment. At that time, patients treated with indomethacin spray developed more severe erythematous reactions until about 5 weeks after starting therapy. The researchers proposed that hydrocortisone applied at the time of radiation produces a lasting agitation of the inflammatory cell infiltrate and, as a result, beneficial effects of hydrocortisone can still be seen several weeks after application is discontinued.

In a more recent study, Bostrom *et al*. (2001) determined whether a potent corticosteroid cream, mometasone furoate (MMF), used as prophylaxis and treatment, could reduce the intensity of the erythema in acute radiation dermatitis. They randomized patients to receive either MMF plus emollient cream or emollient cream alone. The authors concluded that adding MMF to an emollient cream is statistically significantly more effective than emollient cream alone in reducing acute radiation dermatitis.

Schmuth and colleagues (2002) conducted a study to compare treatment with topical 0.1% methylprednisolone vs. 0.5% dexpanthenol in a cohort of patients undergoing fractionated radiation therapy for breast cancer. They provided evidence that prophylactic and ongoing use of topical therapy with either topical corticosteroid or a dexpanthenol-containing emollient ameliorates, but does not prevent radiation dermatitis. Their data suggest, but do not prove, a benefit of a topical corticosteroid versus a dexpanthenol-containing emollient.

Despite effectiveness of topical corticosteroids in treatment of acute radiation dermatitis which are focused in the literature, yet there are some controversy about their usage in this regard. A scant number of available trials provides little information in this respect. The aim of this study was to investigate the effect of betamethasone valerate ointment in prophylaxis of acute radiation dermatitis.

MATERIALS AND METHODS

This study was conducted as double blind randomized clinical trial. The interested population included patients suffering from breast cancer having referred to radiotherapy department of Imam Khomeini hospital, from August to December 2002, with radiation therapy considered in their therapy. A total of 76 patients were assigned into two groups, betamethasone and base of ointment, 38 patients in each group. In base of ointment group, 3 patients did not refer for weekly examination, and one additional patient also did not refer during follow-up period, and therefore were excluded from the study. All patients were treated using Cobalt machine (Theratron 780 C & E, Canada). The dose received by patients with radical mastectomy was 5000 cGy within 5 weeks, and for conservative surgery patients was 6000 cGy for 6 weeks divided in 200 centigray fractions.

Inclusion criteria were: histologic diagnosis of breast cancer, no skin involvement, no concurrent chemotherapy, lack of previous radiotherapy, no medical contraindication to betamethasone ointment, lack of ulcerative rash or non-healed scar at the site of therapy, no history of connective tissue disease and minimum dose of 50 gray.

One group was given betamethasone 0.1% and other group was administered base of ointment as placebo. The ointments which were of comparable consistency, were placed in identical-appearing 100-ml containers ,only was labeled with red or blue color signs. Written informed consent was obtained from all patients prior to enrolment. Patients were instructed to apply the assigned ointment to the tangential field twice daily from the initiation of radiation therapy, and to continue twice-daily topical treatment for a 1-week period after completion of radiation therapy. To lower bolus effect patients were advised not to consume drug at least 4 hours prior to each radiotherapy sessions. Meanwhile, they were recommended that avoid water and soap irrigation, consuming other oints and also tight cloth dressing. Patients were monitored for assessing dermatitis severity and its symptoms (burning, pruritus and pain) and also possible drug adverse effects one week after the therapy commenced and afterwards by one-week intervals.

Three weeks after treatment completion they were also visited. In each examination, grade of skin toxicity were registered objectively and according to RTOG standard grading (table 1) and severity of symptoms(burning,pruritus and pain) assesed using inquiry from patient as mild, moderate and severe. For testing assumptions, the T-test and $\chi 2$ were applied.

Table 1. Grade of Skin Toxicity with Radiation therapy alone

Grade	Description
0	No change over baseline
1	Follicular, faint, or dull erythema/epilation/dry desquamation/decreased sweating
2	Tender or bright erythema, patchy moist desquamation/moderate edema
3	Confluent, moist desquamation other than skin folds, pitting edema
4	Ulceration, hemorrhage, necrosis

Table 2. Maximal intensity of dermatitis during treatment in two groups

Treatment group / Dermatitis intensity	Placebo	Betamethasone
0	0	2 5.3%
1	21 60%	33 86.8%
2	13 37.1%	3 7.9%
3	1 2.9%	0
Total	35 100%	38 100%

$\chi 2=11.813$, P=0.008

RESULTS

Mean times development of dermatitis in both betamethasone and placebo groups were 3.2500 and 2.2571 (weeks) respectively (t=-3.898 , p≤ 0.001). After hypothesis test, equality of variances in both treatment groups considering P ≤ 0.001, it was observed that there was significant differences between both groups in terms of time of development of dermatitis. Consequently, the results show that time of emergence of dermatitis in treatment group using base of ointment was sooner than that of betamethasone treated group.

Also, during follow-up period, less percentage of patients in betamethasone group (26.3%) developed dermatitis compared to base of ointment group (73.5%) which indicates sooner improvement of this patients. Dermatitis intensity at the first week did not show significant difference between both groups but at weeks 2, 3, 4, and 5 as well as follow-up period a significant difference was observed between two groups in terms of dermatitis severity. The result obtained from test in case that maximal dermatitis intensity being considered showed that there is a significant difference between two groups by P <0.05 such that the percentage of patients with high intensity dermatitis was greater in base of ointment group than betamethasone group (tables 2, 3 and figure 1).

Weekly mean dermatitis grade was repeatedly lower in betamethasone group than placebo group in all five treatment weeks and also follow up (FU) period (figure 2).

At weeks 4 and 5 severity of symptoms of patients such as burning and pruritus did show significant difference between two groups by P < 0.05. such that the percentage of subjects of higher grade within betamethasone treatment group was less. No significant differences were observed between two groups in terms of pain intensity.

There is no correlation among variables of age, weight, menopause status, type of surgical operation, past history of chemotherapy, use of bolus and tamoxifen tablet as well as separation length and intensity of dermatitis. Furthermore, time of development of dermatitis is independent of above mentioned variables. During follow-up period one patient of each treatment group referred with grade 3 dermatitis and received supportive therapy.

Table 3. Maximal intensity of dermatitis during follow-up period in two groups

Treatment group / Dermatitis intensity	Placebo	Betamethasone
0	9 26.5%	28 73.7%
1	22 64.7%	9 23.7%
2	2 5.9%	0
3	1 2.9%	1 2.6%
Total	34 100%	38 100%

$\chi 2=17.039$, P=0.001

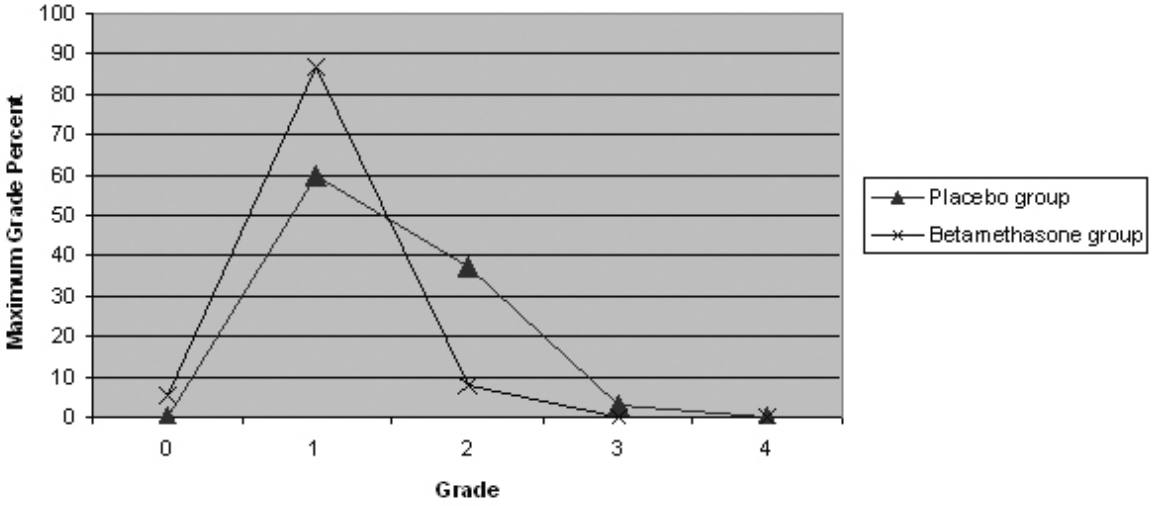

Figure 1. Maximum grade of dermatitis.

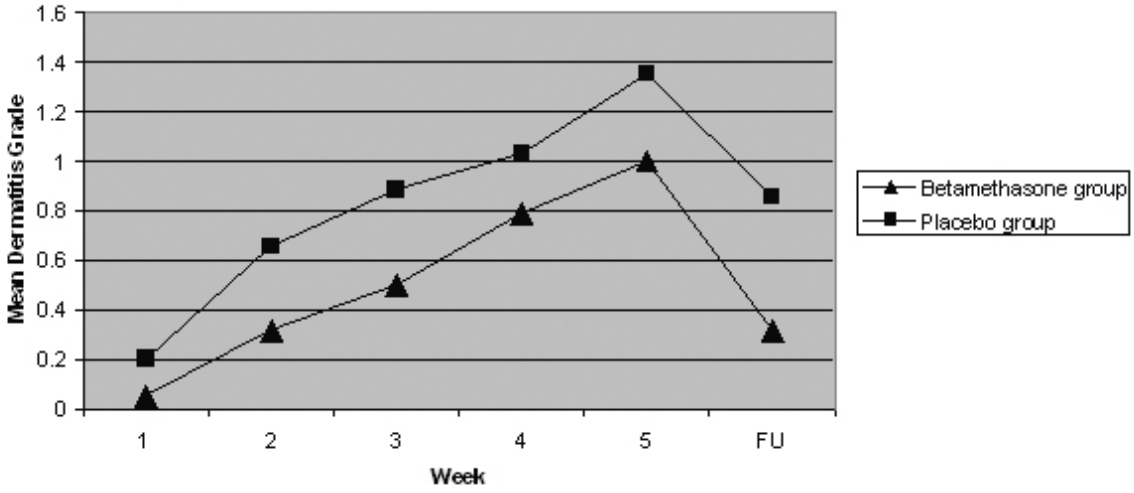

Figure 2. Weekly mean dermatitis grade

DISCUSSION

Despite high prevalence rate of acute radiation dermatitis and also wet desquamation, a few trials on prophylaxis of this complication using topical treatment have been conducted.

Effectiveness of topical corticosteroids therapy in acute radiation dermatitis has been focused in studies however only in 3 studies its positive effect has been demonstrated, (Bostrom *et al.* 2001, Bjo"rnberg *et al.* 1965 & 1967). In these 3 studies local steroid betamethasone and or a steroid with similar potency to

betamethasone were used. Our study is the 4th one in this respect in which positive effects of local steroid in the prevention of acute radiation dermatitis has been established. Lack of obtaining positive result in other studies can be due to several reasons. First, use of less potent steroids such as hydrocortisone, (Potera 1982) and second, in some studies the treatment was begun only when the acute radiation dermatitis became manifest and it had not been used as a prophylaxis. This is while the results of these 3 studies and our study support utilization of potent local steroid from the first day of therapy up to 1-3 weeks after completion of therapy as prophylaxis against acute radiation dermatitis.

In the present study it was observed that dermatitis severity in betamethasone treatment group was less than that of in base of ointment group. In betamethasone treated group majority of patients developed grade 0 and 1 but in base of ointment group mostly developed grade 1 and 2 which is nearly compatible with statistics provided in Bostrom's study that in which mometasone furoate cream has been used. Mean time of onset of dermatitis in betamehtasone treated group was later than base of ointment group (average one week). Maximal patients' symptoms of burning and pruritus, was observed in weeks 4 and 5 of treatment in that with consideration to maximal dermatitis grade development at above times, observation of this finding seems logic. Patients in the betamethasone group clearly tended to report less burning and itching, but in Bostrom's study in spite of less symptoms reported by patients in the steroid group, this difference was not significant. No infection was observed in patients within therapeutical field and discontinuation of therapy due to emergence of severe dermatitis was not required except one case in base of ointment group who was placed under supportive therapies and after improvement the treatment was continued.

Occurrence of one case of grade 3 dermatitis at the time of follow-up in betamethasone group, despite initial good effects seemed bizarre, nevertheless in literature such event has been reported as breakthrough phenomenon, (Bjo"rnberg *et al.* 1964) with a possible etiology of contact dermatitis in reactions to the use of local steroids.

In this study we demonstrated that betamethasone valerate ointment is more effective than base of ointment alone in the treatment of acute radiation dermatitis, and this difference is statistically significant. In this study base of ointment was utilized as placebo and dermatitis intensity in this group is nearly compatible with statistics delivered by RTOG in terms of severity of acute dermatitis by radiotherapy alone (grade 0,13%; I,52%; II, 32%; III, 2%; IV, 1%). But establishing this point necessitates another randomized trial in which base of ointment alone being compared.

The results from this study support the use of moderate to potent steroid ointments as prophylaxis against acute radiation dermatitis in radiotherapy field from the first day of radiation therapy until one week after its completion.

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