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SKIN TREATMENT WITH BEPANTHEN CREAM VERSUS NO CREAM DURING RADIOTHERAPY

A randomized controlled trial

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In several radiotherapy departments, dexpanthenol cream (Bepanthen 'Roche') has been used extensively to ameliorate acute radiotherapy skin reactions. The evidence base for this practice is obscure as no randomized trials have been performed. In the present clinical prospective study of 86 patients we have compared Bepanthen cream with no topical ointment at all. The cream was applied on randomly selected parts of treatment fields in laryngeal and breast cancer patients, and so each patient acted as his own control. Seven patients were withdrawn from analysis. Scoring of skin reactions in 16 laryngeal and 63 breast cancer patients was performed without knowledge of which area that had been given cream or not. Endpoints were a modified skin reaction grading according to EORTC/RTOG, and itching/pain in treated fields. The study did not indicate any clinically important benefits of using Bepanthen cream for ameliorating radiogenic skin reactions under the conditions applied.

An early sign of radiation injury to the skin is erythema, increasing during the first period of a radiotherapy course. A target cell has not been identified for erythema, which must be assumed to be related to subcutaneous and vascular tissues (1). Later during the course of radiotherapy, the epidermis may show signs of dryness, followed by a dry desquamation, and eventually by a moist desquamation. The denudation is assumed to result from continuous loss of mature cells from the surface and with a lack of reproduction of new cells from the basal layer. Itching and severe pain may evolve. If the radiation is discontinued, the skin reaction will last for 1–2 weeks and then gradually normalize (1, 2).

The development and severity of the skin reaction depends primarily on radiobiological factors, such as total dose, fractionation schedules, area of irradiated skin, and beam quality (3, 4). However, tradition and experience have in general dominated the clinical judgement and the care of these patients, and not always scientific facts. In our radiotherapy department, dexpanthenol cream (Bepanthen 'Roche') has been used extensively to ameliorate acute radiotherapy skin reactions. This is a recognized indication for Bepanthen, otherwise used mainly for treatment and prevention of skin sunburns (5). Fatty ointments in general have, however, traditionally been avoided in treatment of such skin reactions. We thus wished to make a prospective study in which we compared Bepanthen cream with no topical ointment at all. Patients with glottic laryngeal cancer (T1-2 N0 M0) and breast cancer patients were chosen for this study as two suitable patient groups for testing skin reactions. In the laryngeal cancers the irradiated area is small, but is treated with a large dose. In breast cancers, a large chest wall area is treated with a medium dose.

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Material and Methods

The present study included a total of 86 patients. Informed consents were obtained from the patients who should be suitable for follow-up and expected to be able to

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cooperate. Patient ineligibility criteria were skin diseases directly affecting irradiated fields, and allergic and/or other systemic skin diseases, even if not directly affecting irradiated areas. Skin type (6) was registered. Withdrawal criteria were change of radiotherapy, inability to cooperate, allergic or otherwise negative reaction to the ointment, or a general patient wish to withdraw.

The breast cancer patients were previously treated surgically either with mastectomy or with breast conserving surgery. All stages were eligible.The laryngeal T1-2 cases were subjected to definite radiotherapy alone. Patients were included consecutively during the study period and with no age limit specified. Of the 86 patients, 7 were withdrawn from the study, 4 due to non-compliance (mental state, change of radiotherapy, lost during follow-up, missing data, etc.) and 3 because of untoward/allergic reactions during the treatment with Bepanthen. Of the 79 patients included in the analysis, 63 were breast cancer patients. These patients aged from 31 to 78 years (median age 55). The 16 laryngeal cancer patients included aged from 51 to 85 years (median age 69). At visit 6 responses were registered for 78 patients (1 of the 79 with missing data at this visit). Twenty-one of the breast cancer patients received CMF adjuvant chemotherapy (low-dose) during the radiotherapy course. Previous chemotherapy was recorded in a few patients but they were all the same considered acceptable for inclusion.

Each patient served as his/her own control. Patients with laryngeal cancer treated one side field with Bepanthen, and the opposite field with no cream, randomized for side. Only the patient knew which side was treated, and was instructed not to inform the evaluating physician. Breast cancer patients treated one-half of the target area with Bepanthen and not the other part. The target area was divided horisontally through the centre of the radiation field. The cream application areas, whether lower or upper, were randomly selected per patient. Also for this group only the patient knew which area/side was treated with the ointment, and was instructed not to inform the evaluating physician.

The laryngeal cancer patients were treated with two opposed 6 × 6 cm standardized wedge fields. Both fields were treated 5 days a week with a midplane dose of 2 Gy per fraction up to a total dose of 70 Gy. A linear accelerator with 5 MV was used. For the breast cancer patients the radiotherapy was given by different techniques with two tangential, opposed wedge ^{60}Co fields to the breast and/or chest wall with or without bolus (depending on assumed risk of skin involvement and covering both parts of the treatment field), or with an electron beam to the chest wall. The electron energy was around 9 MeV (without bolus) in order to cover the tissues down to costal level. All fields were treated daily, and the patients received 2 Gy per fraction 5 times a week up to a total dose of 50 Gy. A 5 MV linear accelerator or telecobalt unit was used for tangential fields, and 6–12 MeV for the electron beam, depending on thickness of the target volume.

Bepanthen treatment was started from day 1 of radiotherapy, twice a day. A registration form was supplied with information about the study and instructions about care for the radiation field. Assessment of skin reactions was done weekly during treatment and two weeks after completed radiotherapy, and performed blindly by the physician. Furthermore, the patient was evaluated 6–8 weeks after finished radiation therapy. The appearance of treated skin was graded according to an expansion of the EORTC/RTOG acute skin reaction scoring system (7) and grade of their symptoms of itching and/or pain in both treatment fields (Table 1). Absorbance measurements of the cream in the UV spectrum was performed as for sunscreen creams at the Norwegian Radiation Protection Authority.

Erythema grade was chosen as the primary efficacy variable, and it was decided to include approximately 80 patients in the trial. The estimation of this number was originally based on an assumption of normally distributed data. Preliminary data indicated a mean grade of 2, and a standard deviation of 0.5. With a two-sided significance level of 5%, the power to detect a 20% difference between treatment and control would be >99%. Since the observations are actually categorized, we have later estimated power with a variety of methods to ensure that the risk of type II error is not too high.

It is difficult to make valid assumptions about a clinically relevant difference on a multinomial scale, and we therefore chose to merge categories and estimate power on a dichotomous scale. The actual power of the analyses performed with four or five categories will then be at least as high as estimated. Based on clinical experience, we assumed the success rate (defined as erythema grade 0 or 1) of using Bepanthen cream to be about 25%. The difference in success rates between using cream or not should be at least 20% to be of clinical interest. Assuming that 40% of the patients score differently with and without cream, and with a two-sided significance level of 5%, the power to detect this difference is with the power analysis program N estimated at 85% (8). If fewer patients score differently, the power will increase. Similar estimates can be made for the secondary variables.

Table 1

Grading of erythema, desquamation and clinical symptoms of itching and pain

Grade	Erythema	Desquamation	Itching/pain
0	None	None	None
1	Mild	Dryness	Mild
2	Moderate	Moderate flaking	Moderate
3	Severe	Severe flaking	Severe
4		Patchy moist desq.	

Both the primary and the secondary efficacy variables were analysed using Wilcoxon's signed rank-test. Logistic regression was used to examine the effect of possible prognostic factors.

Results

The skin reaction is reported according to the defined visits to the physician, spaced by one week, instead of weeks after start of treatment, since the patients did not start their treatment on the same weekday. For both cancer types the skin reactions seem most severe at visit No. 6, which was therefore chosen as a reference time point for evaluation. Visit No. 6 corresponds to the termination after 70 Gy in laryngeal cancer patients, and to 2 weeks after termination of 50 Gy for mammary cancer patients. The time courses of the skin reactions in the untreated areas are shown in Figs. 1 and 2. Fig. 1 shows the percentage of mammary cancer patients with different reaction parameters, and Fig. 2 correspondingly in laryngeal cancer patients. As we found no evident difference between the time courses in the two cancer types, the results have been pooled in the following.

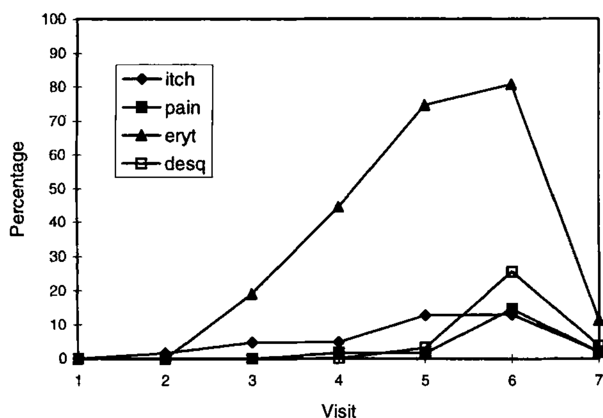

Fig. 1. Time course of percentage of breast cancer patients with different skin reaction in radiation field not treated with ointment. Data on itching grade 2–3 (itch), pain grade 2–3 (pain), erythema grade 2–3 (eryt), and desquamation grade 3–4 (desq) at each visit respectively. Most severe reactions at visit No. 6.

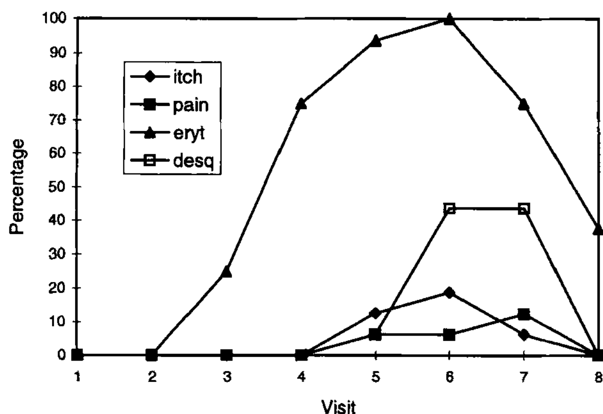

Fig. 2. Time course of percentage of laryngeal cancer patients with different skin reaction in radiation field not treated with ointment. Data on itching grade 2–3 (itch), pain grade 2–3 (pain), erythema grade 2–3 (eryt), and desquamation grade 3–4 (desq) at each visit respectively. Most severe reactions at visit No. 6.

Table 2 shows a cross-table of erythema grade. It consists of paired responses from each patient, and numbers along the diagonal represent patients with no difference between treated and untreated area. Numbers in the lower left represent patients who perform better on treatment, whereas numbers in the upper right represent patients with

Table 2

Number of patients within each erythema category at visit No. 6. The numbers along the diagonal show patients with no difference in erythema grade between the ointment treated and untreated area

Untreated area grade	Treated area grade			Total
	1	2	3	
1	10	2	0	12
2	3	20	4	27
3	0	3	36	39
Total	13	25	40	78

Table 3

Number of patients within each desquamation category at visit No. 6. The numbers along the diagonal show patients with no difference in desquamation grade between the ointment treated and untreated area

Untreated area grade	Treated area grade					Total
	0	1	2	3	4	
0	9	1	0	0	0	10
1	2	15	0	0	0	17
2	2	7	11	2	0	22
3	0	0	6	8	5	19
4	0	1	0	0	9	10
Total	13	24	17	10	14	78

Table 4

Number of patients within each itching category at visit No. 6. The numbers along the diagonal show patients with no difference in itching grade between the ointment treated and untreated area

Untreated area grade	Treated area grade				Total
	0	1	2	3	
0	35	8	2	0	45
1	9	12	1	0	22
2	2	5	3	0	10
3	0	0	0	1	1
Total	46	25	6	1	78

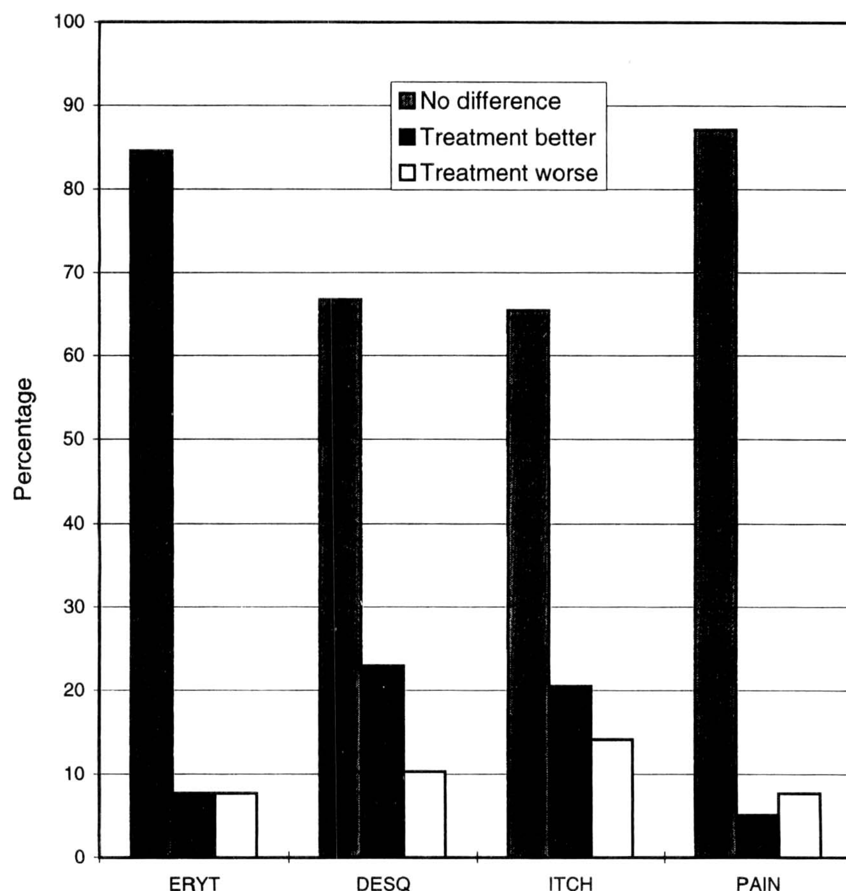

Fig. 3. Percentage of patients with no difference between treated and untreated area, and the percentage with a positive and a negative difference at visit No. 6 for each type of skin reaction. Point estimates (and 95% CI) for difference between 'treatment better' and 'treatment worse': Erythema 0.0 (−0.09, 0.09), Desquamation 0.13 (0.01, 0.25), Itching 0.06 (−0.07, 0.19), Pain −0.03 (−0.11, 0.05).

a more severe reaction on treatment. There is no difference between treatment and control ($p = 1.00$, Wilcoxon's signed rank-test, adjusted for ties). Table 3 shows the number of patients in each possible pair of desquamation categories. Here there is a significant difference between treatment and control ($p = 0.027$). If only transitions to category 3 or 4 are considered important, no significant difference is found ($p = 0.83$). Tables 4 and 5 respectively show the number of patients in each itching and pain category. No significant differences exist ($p = 0.43$ and $p = 0.56$ respectively).

Table 5

Number of patients within each pain category at visit No. 6. The numbers along the diagonal show patients with no difference in pain grade between the ointment treated and untreated area

Untreated area grade	Treated area grade				Total
	0	1	2	3	
0	58	3	1	0	62
1	3	1	1	1	6
2	0	0	9	0	9
3	1	0	0	0	1
Total	62	4	11	1	78

Fig. 3 summarizes the information from Tables 2–5. Here, the percentage of patients with no difference between treated and untreated area, and the percentage with a positive or negative difference at visit No. 6 are shown for each type of skin reaction. The percentage of patients with a difference is small, and there seems to be no clinically relevant difference between the percentage of patients who perform better with or without treatment.

Logistic regression analyses were performed to examine the effect of concomitant chemotherapy (yes/no), skin type (fair to black), gender and age, and upper versus lower area (mammary cancer patients). The dependent variable was either erythema (grade 0–1 vs. 2–3) or desquamation (grade 0–2 vs. 3–4) in the untreated area. No significant effect of any of the variables was found, neither as regards erythema, nor desquamation. There was no significant absorbance by the cream of wavelengths in the sun spectrum (>290 nm).

Discussion

The question of how to manage skin reaction during radiation therapy is of great importance. Generally early effects are considered to correlate poorly with risk of late serious sequelae (3, 9), but some interdependence of the reactions can be shown (10). The acute effects are, however, a problem of their own to the patients who need care, ameliorative treatment and support. Different types of topical ointments (wax, paraffin, aloe, almond, olive and herb oils) or corticosteroids have been used, generally with lack of convincing effects. Maiche et al. (11) found no major differences in skin reactions between areas treated with chamomille cream and almond ointment. Campbell & Illingworth (7) demonstrated a reduction of acute skin reactions when patients were allowed to wash irradiated fields with soap, a practice usually discouraged in most institutions.

The present study is a consecutive, prospective randomized study, and because all patients were their own controls, the study design should therefore ensure tracing of any major effects of the cream ointment, beneficial or negative. The actual dose to the skin probably differs widely in this series; 70 Gy to the larynx corresponds to c. 50 Gy in the skin, and in the breast cancer cases probably down to 30–40 Gy due to the skin dose sparing effect of the high voltage radiation. From other clinics, skin doses down to 20–25 Gy has been reported in connection with target dose of 50 Gy (12). If skin was considered part of the target volume due to risk of infiltration, bolus was used, raising the skin dose to the target dose level. The dose interval in this material should therefore make it fairly representative for radiotherapy in general.

The active ingredient of Bepanthen cream is dexpanthenol, the alcohol derivative of pantothenic acid. Dexpanthenol has the same action as panthothenic acid, to which it is converted in the body when taken orally. The alcohol nevertheless has the advantage of better absorption when topically applied. Pantothenic acid is a component of coenzyme A, which in the form of acetylcoenzyme A plays a central role in metabolism. Panthothenic acid is indispensable for normal skin integrity, deficiencies lead to dermatitis, and extra supply may be thought to promote epithelial formation and regeneration (13). Kristensen (14) compared Bepanthen (Roche) with Azulon (Homburg) powder but did not find any difference with regard to the skin erythema reaction. Bepanthen has a low fat content, especially the cream formulation. Nevertheless one cannot exclude that possible side-effects may be due to the fat. Moreover, there have been a few—yet not confirmed—reports of possible allergic reactions associated with the use of Bepanthen.

The skin reactions in this series followed the general patterns described in many reviews. The pooling of both cancer diagnoses in the evaluation may be criticized. However, it is a common observation that the time trend in the reactions is more determined by cell kinetics than total radiation dose, and maximal reactions in this material was also scored at about the same point of time. Even in accelerated treatments of laryngeal cancers, maximal reactions are recorded 6–7 weeks after start of treatment, which is long after the radiotherapy (15). Observations on skin erythema are also difficult to evaluate due to uncertainty even in so-called objective measurements of reflectance (16). Skin reactions are probably influenced by poorly understood complex regulatory processes potentially subject to therapeutic interference (1).

Skin type was earlier thought to influence ionizing radiation dermatitis in the same way as ultraviolet radiation, with more marked reactions in fair blue-eyed blondes or 'red-heads' (17–19). Radiotherapy patients are generally discouraged to sunbathing, because combination effects are also assumed. We did not find any significant sunscreen absorption by the ointment, and the claimed positive effects in prevention and treatment of sunburns (20, 21) cannot be explained by specific UV-absorption. If any positive effect can be traced in sunburn treatment, it must probably be based in some cell kinetic or DNA repair effect, giving hope also for a possibility of real pharmacologic actions even in radiodermatitis. We did, however, not see any influence of skin type in the radiotherapy field dermatitis, in accordance with more recent communications (1, 22, 23). Nor did we find any statistically significant differences between upper and lower part of the breast/chest wall fields, although we had some impression of increased reactions around the axillary fold. Older observations describe regional variations in skin reations, at least regarding erythema, with decreasing responses in the order axilla, mammary line just below the areola, and lowest for sternum (17). Skin over bone structures was considered less sensitive due to difference in vascularization, and recent reports may further substantiate this (10), but even regional variations within parasternal fields have been reported (24). Nor did use of cytostatics seem to influence the reactions, as has been described e.g. for Actinomycin D (23) and 5-fluorouracil (25). Our material might be too small to allow detection of a possible influence of these factors.

The radiogenic skin reactions were in general not influenced by Bepanthen treatment (Fig. 3). Although there was a statistically significant positive effect of cream treatment on desquamation (Table 3), this was mainly active for low-grade lesions. Several significance tests have been performed, and it is perhaps not surprising that one significant difference was found. If we had corrected for multiple tests, the reduction in desquamation grade would not have appeared significant. Moreover, the net positive clinical effect of reduction in skin dryness and/or moderate flaking by treatment is not considered as important as the slight increase in frequency of severe flaking and/or desquama-

tion in the treated areas. Further analysis of the data in Table 2 on the clinically most interesting transitions to grade 3 or 4 shows no significant effect of ointment. Any indifferent cream or ointment may appear beneficial for minor reactions. In addition, 3 patients in this series had to withdraw from the study due to side-effects of the ointment. Such side-effects must be kept in mind in comparison with any statistically significant benefit of the cream.

To conclude, this prospective study did not indicate any clinically important beneficial effects of using Bepanthen cream for ameliorating radiogenic skin reactions under the conditions applied. Side-effects have been noted, although other reasons than use of Bepanthen cannot be excluded. The study does not support the use of Bepanthen for treatment or prevention of severe radiation dermatitis, and the traditional use in our department will be discontinued.

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