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Pilot study to investigate the toxicity of Aloe vera gel in the management of radiation induced skin reactions for post-operative primary breast cancer

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Abstract

The purpose of this Phase 2 Breast Skin Care Pilot Study was to compare the acute skin reaction in patients undergoing radiation therapy for early breast cancer who use Aloe vera gel on the irradiated skin, with the acute skin reaction in patients from our earlier study who followed a normal skin care routine. Two secondary objectives were to assess patient compliance with the use of Aloe vera gel and the ease of using two skin toxicity scoring tools.

A total of 109 patients undergoing radiotherapy following surgery for breast cancer between October 1997 and February 1998 consented to participate in this study. Each patient applied the Aloe vera gel three times daily to the irradiated area during radiation treatment. Skin reactions were assessed objectively on a weekly basis during radiation using the Radiation Therapy Oncology Group (RTOG) and the Acute Skin Reaction Index (ASRI) skin scoring tools and subjectively by patients. All patients were followed for up to 3 weeks following treatment.

The use of Aloe vera gel did not increase the acute skin reactions due to irradiation when compared with the two arms of the previous Phase 1 Breast Skin Care Study. This pilot study demonstrated that patients could safely use Aloe vera gel while undergoing radiation therapy treatments. All patients complied uniformly with the instructions of using the gel during the study. The ASRI skin scoring tool was easier to use and more sensitive in displaying differences in skin reactions in comparison to the RTOG scale.

Keywords

Radiation therapy; breast cancer; acute radiation skin reaction; Aloe vera gel

INTRODUCTION

Post-operative radiation therapy is the accepted standard treatment for the majority of women who have undergone surgery for primary breast cancer. In the past, patients undergoing radiation therapy to the breast experienced acute skin reactions ranging from mild erythema to moist desquamation. With the advent of megavoltage therapy and its skin sparing capability, radiation induced skin reactions are now less pronounced in severity and frequency.[1]

Many breast cancer patients undergo cytotoxic chemotherapy at the same time as radiation therapy, therefore they experience a synergistic action of both treatment modalities that may result in increased skin toxicity.[2] The management of skin care during radiation therapy varies among different clinics.[3] Historically, prior to 1995, the guidelines for skin care at the Princess Margaret Hospital (PMH), Toronto, were: to not wash; to keep the skin dry and; to use baby powder or cornstarch in the treatment area.[1,4] The application of any skin products was thought to contribute to a dose buildup or 'bolus effect'. Heavy metals or alcohol in skin products was thought to increase skin reactions from radiation therapy.

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In 1994 a Phase 1 Breast Skin Care Study was conducted at PMH by Meegan and Haycocks.[5] This clinical study, which compared the acute skin reactions of two different skin care regimens during breast irradiation (any skin care products versus a policy of no soap or deodorant in the irradiated area), found no difference in the acute skin reactions between the two regimens. Thus, patients at this institution are now advised to continue with their normal skin care routine using lotion, deodorant and soap.

Aloe vera gel is relatively inexpensive, readily available and has been widely used to treat many skin conditions including skin burns.[6] It has been documented that Aloe vera gel has anti-inflammatory, antibacterial, antiviral and wound healing properties.[7] This suggested further research in the role of Aloe vera gel in the management of radiation-induced skin reactions.[5,8]

The primary objective of this non-randomized, controlled Phase 2 Breast Skin Care Study was to compare the acute skin reaction in patients undergoing radiation therapy for early breast cancer who use Aloe vera on the irradiated skin with the acute skin reaction in patients from our earlier study who followed a normal or traditional skin care routine. The secondary objectives were to examine patients' compliance and to investigate the ease of using two skin toxicity scoring tools: Radiation Therapy Oncology Group (RTOG) and the internal Acute Skin Reaction Index (ASRI).[5,9]

ALOE VERA: HISTORY AND PHARMACOLOGY

Aloe vera, classified as Aloe Barbadensis, belongs to the lily family and grows in tropical and subtropical climates. The plant does not grow in dry deserts or rain forest regions.[10,11] Historically, Aloe vera has been used for many centuries because of its different healing and cathartic abilities.[6,12–14] The medicinal use of the plant has been mentioned in 1750 B.C. Mesopotamian clay tablets. Egyptian books from 550 B.C. advise it for skin infections. Greek physicians from 74 A.D. mention the skin healing abilities of the plant.[6] Up to the present day the plant has been popular in many different cultures and is used in non-traditional medicine.

Modern research on the activity of Aloe vera gel started after the publication of a paper in 1935 by Collins and Collins entitled 'Roentgen dermatitis treated with whole leaf Aloe vera'.[15] This paper describes a case of a woman who received a depilatory X-ray dose to her scalp. She developed itching, burning and pain that persisted up to 8 months. A skin graft was planned, however the patient was treated temporarily with the application of the gelatinous part of fresh Aloe vera to her scalp. Within 1 day, the itching and burning disappeared, and the dermatitis was healed within 5 weeks.

In 1937, Crewe reported effective treatment of palmar eczema, thermal burns, and intra oral ulcers that developed after intra oral radium treatment. By the late 1930's, in the United States, it was reported that the demand for fresh Aloe vera leaves was so great that there were problems supplying them.[10]

Studies conducted by Rowe in 1941 demonstrated the beneficial healing effects of fresh Aloe pulp on radiation-induced skin ulcers in rats.[16] A 1953 study conducted on rabbits with beta irradiation-induced ulcers concluded that Aloe vera juice in aquafor was more effective than whole leaf aloe.[17] By 1980, Rowe et al. criticized reports of the use of Aloe vera in humans, citing the lack of control groups and individual case histories in these studies.[10]

A clinical study was conducted in 1997 on 27 patients with partial thickness burns. Each patient's wound was divided into two equal size parts; the distal part was treated with Aloe vera gel and the proximal part with vaseline gauze. The mean healing time of the area treated with Aloe vera gel was 11.89 days versus a mean of 18.18 days with vaseline gauze.[18] Robson stated that a 70% concentration of Aloe vera could be therapeutically beneficial in a burn wound.[7]

To date, the only Phase 3 study to determine the effectiveness of Aloe vera gel as a prophylactic agent for radiation induced dermatitis was inconclusive.[8] Williams (1993) noted that 'once radiation dermatitis develops, agents such as steroid cream, Aloe vera gel, vitamin E cream, or lanolin are frequently utilized, despite definitive proof that they are helpful'.[8] Despite the lack of supportive

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data, Aloe vera gel is still recommended in clinics that participated in this study.

Davis et al. (1991) noted that Aloe vera hydrates and softens the skin as oils do, covering the skin in an occlusive manner to prevent loss of water, which is necessary for wound healing.[19] In an extensive review of Aloe vera properties, Grindlay and Reynolds (1985) concluded, 'Aloe vera cannot be dismissed out of hand, since there is sufficient indication that some people benefit from its use. The "scientific" evidence for its rejection is almost counteracted by the "scientific" evidence for its beneficial properties'.[10]

Adverse reactions to Aloe vera gel are rare, however cases of contact dermatitis have been reported.[20–22] Spoerke has suggested that the gel be scraped off the Aloe vera leaf because the outside leaf contains latex which, when applied externally, may exert a cathartic effect.[23] The gel, which has the viscosity of water and is almost colourless, is obtained by stripping away the outer covering of the leaf. The mucilaginous pulp is then stabilized and processed for different commercial purposes. The gel contains approximately 99% water and about 0.5% organic and inorganic components such as glucose, protein, cholesterol, triglycerides, salicylic acid, sodium, potassium, magnesium, chloride, calcium and inorganic phosphorus. There are traces of vitamins (C, E) and metals (zinc, copper).[6,7,10] No single mechanism of action of Aloe vera has been described. Leung writes that the polysaccharide base and various components work synergistically.[24] This observation is confirmed by Davis et al.[19] and other sources.[13,25]

Anti-bacterial and antiviral properties of Aloe vera gel have been reported with as low concentrations as 60%.[7] Davis suggests that polysaccharide mannose-6-phosphate present in Aloe stimulates the activation of fibroblasts, thereby affecting the wound healing process.[14] Anti-prostaglandins within Aloe vera have an anti-inflammatory function, causing vasoconstriction which reduces swelling and inflammation. Magnesium lactate, present in Aloe vera gel prevents the formation of histamine, which is considered to induce itching in the skin.[26] Another pharmacologically active component of Aloe is a protease inhibitor influencing the action of the agent responsible for pain where inflammation is present. The analgesic effect is thought to be due to the reaction of an aspirin-like compound and a high content of magnesium (Mg) ions. Lignin present in Aloe vera allows it to penetrate through the skin.[14]

MATERIALS AND METHODS

Materials

In this study, three different commercial products of Aloe vera gel were used from 3 different North American manufacturers, so as not to endorse one particular product. 'Aloex' and 'Jamieson' Aloe vera gels were donated by the companies while 'Lily of the Desert' gel was purchased for the study. Twenty-two patients used Aloex Aloe vera gel during the study, 25 patients used Jamieson and 59 patients used Lily of the Dessert. All products had an approximate concentration of 99.5% pure Aloe vera.

Dosimetric investigations

Prior to using the products clinically, dosimetric investigations were carried out to determine if the topical application of Aloe vera gel created a bolus effect on the skin thus enhancing skin reactions. We determined the evaporation rate of Aloe vera gel, the long-term build-up effect of each application of the gel and the increase in skin dose immediately after each application. The tests were performed on a 10x10cm surface of hybond paper with mylar backing to represent the skin surface. Mylar backing kept the evaporation in one direction. Before the experiment the thickness of an average application of the gel was established.

All three types of Aloe vera gel were tested for their evaporation rates. Weight measurements were taken every 5 minutes for the first hour to establish the evaporation rate. Within 35 minutes 34% of the Jamieson Aloe vera gel remained and 37% of Lily of the Desert Aloe vera gel. Aloex Aloe vera gel evaporated at slower rate than other gels, 65% of Aloex gel was left after 35 minutes (Fig. 1). However, after 1 hour all gels had similar evaporation rates.

Jamieson Aloe vera gel represented the median evaporation rate of all 3 gels therefore it was used for long-term build-up effect. Approximately 1g of the gel was spread on the paper 3 times a day for 5 days. The weight of the paper with the remaining residue was measured before each application. On day 5 after the last application of the gel, the paper

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was washed and dried. The test indicated that after 1g of Aloe vera application approximately 0.015g of solids are retained (~1.5%).

Skin surface radiation dose was measured on a dual energy (6MV/18MV) linear accelerator using a Capintec ion chamber (end window type # 35614) and a Keithely electrometer. Again a 10x10cm surface was used. The test indicated that there was a linear correlation between the thickness of the gel applied and the dose increase. It was calculated that 10mg/cm^2 which gave 0.1mm of the gel, increases the surface dose at 18MV by 2% and at 6MV by 4% (Fig. 2). After 1 hour the dose increase is ~0.4% on 6MV, which is a measurable dose but clinically negligible. This test demonstrated that the gel should be applied at least 1 hour before treatment or after the treatment in order to prevent the increase in skin dose. No dosimetric tests were done on Cobalt 60 since few patients have tangential breast treatments on these units.

Patient population

Patients eligible to enter the study had undergone either a lumpectomy with an axillary node dissection or a modified radical mastectomy for biopsy proven breast cancer. Patients received either 4000cGy in 16 fractions over 4 weeks to the breast or chest wall with a boost to the tumor cavity of 1250cGy in 5 fractions over 1 week, or 5000cGy in 25 fractions over 5 weeks to the breast or chest wall and regional nodes (supraclavicular and axillary nodes). Treatments were prescribed using photons from a 6MV linear accelerator or a 1.25MV^{60} Co Theratron unit. Patients were ineligible if there was a skin condition requiring medical intervention, a known allergy to Aloe vera gel or a pre-radiation treatment Eastern Cooperative Oncology Group (ECOG) performance status greater than 2 (Table 1).[27]

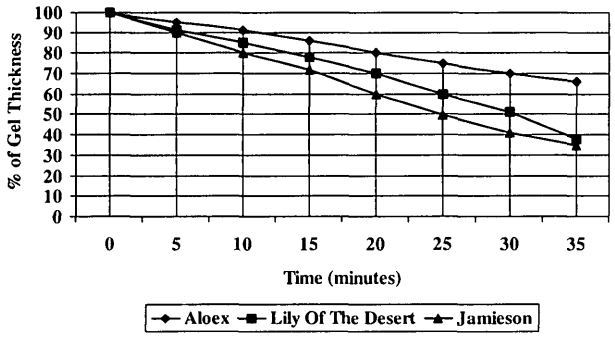

Figure 1 Evaporation rates of Aloe vera gels

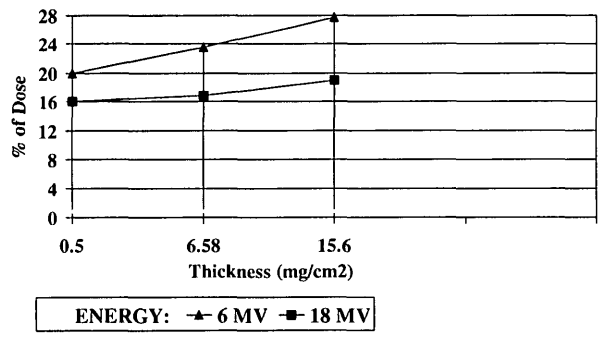

Figure 2 Dose increase after application of Aloe vera gel

METHODS

Patients were recruited to participate in the study at the time of their first radiation therapy planning visit. A verbal explanation and an information sheet describing Aloe vera was given to each patient. Prior to entry into the study, each patient gave informed consent. This study was approved by the Clinical Trials Committee at Princess Margaret Hospital and by the Human Subjects Experimentation Committee at the University of Toronto.

On the first day of treatment patients received one of three types of Aloe vera gel with written instructions on its use. Patients were asked to apply the Aloe vera gel 3 times daily to the entire treatment area starting from day 1 of the treatment throughout the course of radiation. No other skin products were permitted such as deodorants or emollients; however, washing with gentle soap and water was permitted. Patients were instructed not to apply the gel within 1 hour before each treatment. Hydrocortisone cream could only be used on very small areas of the breast and applied at different times than the Aloe vera gel. If moist desquamation occurred the gel was discontinued in that area and saline solution soaks were recommended. Study participants were instructed to

Table 1. ECOG Performance Status

0	Fully active
1	Restricted in physical strenuous activities
2	Ambulatory, capable of self care, up more than 50% of waking hours
3	Limited self-care, immobile for more than 50% of waking hours
4	Completely disabled, no self care

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wear natural fibers, such as cotton, next to the skin and to air the treatment area.

Within the first week of treatment a questionnaire was completed by patients to determine other adjuvant treatments, prescription and non-prescription medications, skin types, skin colour and other medical conditions. Whilst on treatment, weekly objective skin scoring was conducted by a designated trained radiation therapist on each of the treatment units. The scoring was conducted under the same lighting conditions on days 1, 5, 10, 15, 20, and 25 of treatment. Two separate scales were used to grade the skin reactions:

1. The Radiation Therapy Oncology Group (RTOG) scale.[9]
2. The Acute Skin Reaction Index (ASRI) scale (Appendix 1). The ASRI scale is a revised version of the RTOG scale developed by Meegan and Haycocks for the Phase 1 Breast Skin Care Study.[5]

Weekly during treatment, patients were asked to determine the level of discomfort, interference with normal activities and the use of analgesics for skin reactions (Appendix 1). Approximately 3 weeks after the completion of treatment, a follow-up phone call was made by the radiation therapist. The same three subjective questions were asked along with questions enquiring about their experience using the gel.

At the conclusion of the study the skin reactions of the Aloe vera group (Group C) were directly compared to the 2 groups of patients from the Phase 1 Breast Skin Care Study using the mean RTOG and ASRI scores. Group A, from the Phase 1 study, included 92 patients who followed traditional skin care advice using baby powder or cornstarch, and washing with water only. Group B consisted of 64 patients from the Phase 1 study, who continued their normal skin care routine using lotion, deodorant and soap. All 3 groups included patients with the same treatment techniques and doses, identical scoring tools were used and data was collected during a similar time of the year. The T-test was used to compare the mean RTOG and mean ASRI scores among the 3 groups of patients.[28]

RESULTS

Between October 1997 and February 1998 a total of 109 women were entered into the study. Two patients discontinued using the Aloe vera gel at the request of the attending Radiation Oncologist because of early, severe skin reactions suggestive of an allergic reaction and 1 patient was prescribed Hydrocortisone cream to the entire breast making them ineligible. All eligible patients complied uniformly with instructions to use the gel 3 times daily. The use of Aloe vera gel following treatment was optional and 80% of patients confirmed using the gel after the treatment was completed.

Using the RTOG skin reaction scale, the mean skin reaction scores were 0.55 (range 0–3), 0.62 (range 0–3) and 0.64 (range 0–3) for the Aloe vera, normal skin care and traditional skin care groups respectively (Fig. 3). This difference was not statistically significant when comparing Group A to Group C and Group B to Group C with $p>0.05$. The ASRI mean acute skin reaction scores were 0.82 (range 0–10), 1.37 (range 0–11) and 1.25 (range 0–10) for the Aloe vera, normal skin care, and traditional skin care groups respectively. The difference between the Aloe vera group versus the normal and the traditional skin care groups was significant at the 5% level, $p<0.05$ using the ASRI scale (Fig. 4).

The mean skin reaction scores were very similar for each of the three different Aloe vera products, suggesting there was little difference between them (Fig. 5). The mean RTOG, ASRI skin toxicity scores and the mean patients' subjective discomfort scores during treatment are illustrated in Figure 6. As expected, with time a cumulative effect of radiation is shown through the skin reaction severity. The ASRI scale is more responsive to skin changes over time as seen in the increasing difference between the two curves. Also, as anticipated, the peak reaction during treatment occurred in week five with a mean RTOG score of 1.4 and a mean ASRI score of 3.2.

Skin colour was subjectively rated on the questionnaire. It is interesting to note that patients who classified their skin as dark had the highest mean RTOG and ASRI scores. The mean RTOG reaction scores were, fair 0.56, medium 0.53 and dark 0.69. The ASRI mean scores showed a greater variation between the groups with values of 0.86 for fair skin, 0.82 for medium and 1.11 for dark skin.

Forty-four of 109 patients (42%) indicated that they were taking Tamoxifen, and 27 patients (25%)

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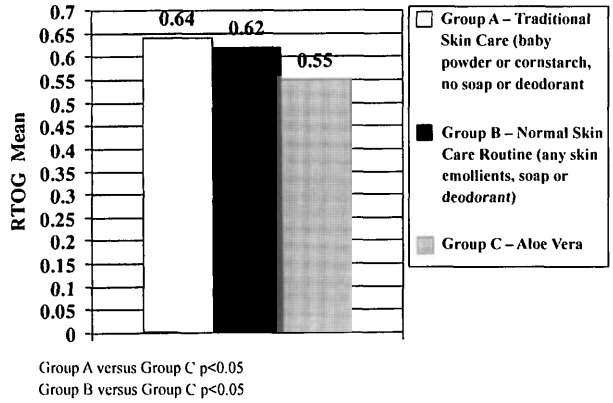

Figure 3 Mean RTOG skin score by group

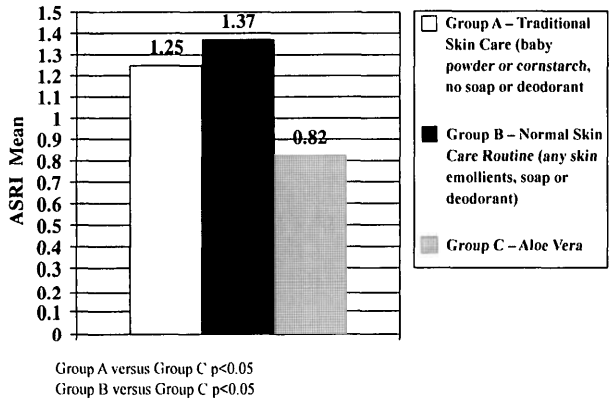

Figure 4 Mean ASRI skin score by group

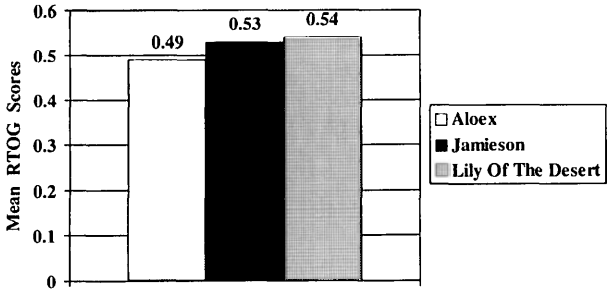

Figure 5 Mean RTOG scores for the three types of products used

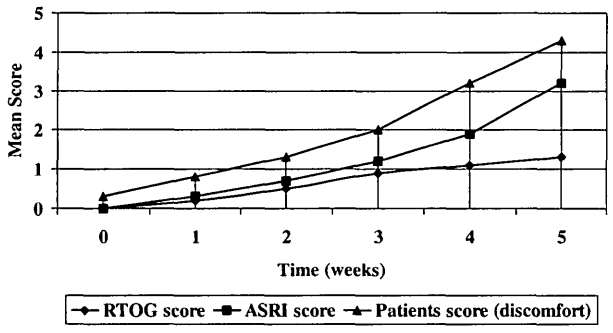

Figure 6 Reaction scores over time

were undergoing concurrent cytotoxic chemotherapy. The chemotherapy group had similar mean skin reaction scores as the rest of the patients.

CONCLUSION

The results of this pilot study demonstrated that patients undergoing radiation therapy for breast cancer could safely use Aloe vera gel during treatment. Aloe vera gel has not produced toxic skin reactions in our cohort of 109 patients. Aloe vera gel significantly reduces the acute skin reactions due to irradiation when using our internal ASRI scale. There was no sign of improvement nor increased toxicity noted with the use of the RTOG acute skin toxicity grading system.

Both the ASRI and the RTOG scales exhibit a change in score consistent with clinical experience. The ASRI scale seems to be more sensitive to small changes in skin reactions as demonstrated by the increase in the difference between the two mean scores during the course of treatment. The feedback from radiation therapists using the scales indicated that the ASRI scale was more specific and practical to use when compared to the RTOG scale. These results demonstrate that patient discomfort increases with time and this should be incorporated into current assessment scales for skin toxicity.

All patients received a telephone interview 3 weeks after the completion of treatment. Patients remarked on the ease of application of the gel and the cooling and soothing effect it had on the skin. Such cosmetic factors largely affect patient compliance and the success of the study. The majority of patients voluntarily continued using the gel after treatment, suggesting that most patients felt it helped their skin discomfort. Women participating in the study remarked on the benefit from taking care of their skin during the treatment. Basic quality of life questions revealed patients felt more in control of the management of their skin reaction when applying the Aloe vera gel from the beginning of the treatment. They exhibited positive attitudes toward the study and were generally satisfied with the products used.

This study supports the topical use of Aloe vera gel during radiation therapy for breast cancer. This

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research resulted in a revision of the skin care policy for breast cancer patients at PMH. Aloe vera gel is now advised in addition to normal skin care practice.

Recommendations for further studies are to develop a randomized double-blinded study to assess the effect of Aloe vera gel versus other skin products. Further investigations could be done on skin type and skin tone with their respect to skin reactions. Research is required to clarify the role of other topical agents, such as vitamin E, that claim to have similar skin healing properties as Aloe vera gel.

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Appendix 1. Grading system

1) **RTOG scale** (Radiation Therapy Oncology Group)

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 than skin folds, pitting edema
Grade 4	Ulceration, hemorrhage, necrosis

2) **ASRI scale** (Acute Skin Reaction Index)

Erythema	0 = none 1 = pink 2 = bright 3 = deep	**Dry desquamation**	0 = none 1 = flaking 2 = scaling 3 = itching
Patchy moist desquamation	0 = none 1 = < 2 cm 2 = 2 cm patch 3 = > 2 cm patch	**Moist desquamation**	0 = none 1 = skin fold 2 = non skin fold

3) **Patient score**

Level of discomfort	0 (low)	1	2	3	4	5	6	7	8	9	10 (high)
Interference with Normal activities	0 (low)	1	2	3	4	5	6	7	8	9	10 (high)

Use of analgesics for skin reactions
0 = none
1 = non prescription pain medication when needed
2 = non prescription pain medication regularly
3 = prescription pain medication

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