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Efficacy of non-adherent dressing versus gentian violet for treatment of radiation-induced moist desquamation wounds in patients with nasopharyngeal carcinoma

Key Messages

1. Although there were no significant differences between the two dressing groups in healing time, wound pain, or measures of distress, this study provides information about the clinical effects of different types of dressing on radiation wound healing. Practitioners can use these data for further research into dressing(s) able to achieve moist wound healing and overcome the problems of drainage and bolus effect without daily removal during radiation therapy.
2. This is the first study demonstrating the physical and psychological disturbances caused by radiation skin ulceration in a population of nasopharyngeal carcinoma patients treated with radical radiation therapy. These findings apply to patients with other types of head and neck cancers treated by radical radiation therapy. It represents a model for demonstrating how radiation skin complications affect psychological and social behaviour, an area in which there is little information.

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Introduction

Moist desquamation is a red, hot, painful, and moist skin reaction that can drain or crust. It is associated with exposure of the dermis and oozing of serum, and occurs when ionising radiation at a dose of greater than 3000 cGy kills the cells of the basal layer of the skin. With the increasing use of chemotherapy and radiation as combined treatment modalities, moist skin reactions are occurring with greater frequency. Chemotherapeutic agents can prolong wound healing by impairing fibroblast production and creating a more intense skin reaction if given before, during, or after radiation therapy.

There is controversy between institutions concerning care techniques for skin reactions. A variety of dressings have been used to manage radiation-induced desquamation wounds. Hydrocolloid dressings have been used to manage skin reactions to radiation.[1] Our 1998 study comparing gentian violet with hydrocolloid dressings found drawbacks with hydrocolloid dressings including melted gel, leaking, and pain and tissue trauma on dressing removal before each irradiation.[2]

Topical application of gentian violet has been used conventionally to treat radiation-induced wounds because of its antifungal and antiseptic effects. However, it dries the dermis and may interfere with wound healing. The tissue-damaging potency of the triphenylmethane group of dyes in crystal violet, including necrotic ulceration, has been demonstrated in animal studies on rats and rabbits.[3] The tissue-irritating effect of crystal violet ('gentian violet'), together with disadvantages such as masking, and staining of clothing, skin, and work areas, along with being visible on the patient's skin, has made its use controversial in radiotherapeutically induced moist wounds.

Until recently, much of the literature has promoted the use of non-adherent dressings for managing skin reactions to radiation. These dressings have a plastic film or other non-adherent materials on their contact surface to prevent them from sticking to the wound and causing trauma to newly re-epithelialised tissue. The plastic film can be perforated to allow the passage of wound exudate into the absorbent layer of the dressing. The application and removal of such dressings is not difficult. No studies examining radiation wounds and non-adherent dressings have been found in the literature, so their benefit in the management of radiation-induced wounds remains unclear. Theoretically use of such dressings may overcome the problems we have experienced with hydrocolloid dressings.

Objectives

This study aimed to compare the effectiveness of gentian violet and non-adherent dressings in the treatment of radiation-induced moist desquamation wounds by comparing the wound healing time, pain, mood, social isolation, appearance disturbance, sleep, neck mobility (movement) levels, and treatment cost between

the two dressing types.

Methods

This study was conducted from January 2001 to February 2003.

Study design

This was a prospective stratified randomised trial comparing the effectiveness of gentian violet and non-adherent dressings for treating radiation-induced moist desquamation wounds. Patients who were treated with radical radiotherapy for nasopharyngeal carcinoma and developed radiation-induced moist desquamation skin reactions were included in this study. The exclusion criteria were: (1) patients with previous radiotherapy to the head and neck region; (2) evidence of tumours on the skin; (3) patients diagnosed with clinical wound infections.

Eligible patients were approached in the oncology out-patient department of a public-funded hospital in Hong Kong. If patients met the eligibility criteria and agreed to participate, they were stratified according to two factors—receiving concomitant chemotherapy and wound size of greater than 30 cm^2—before being randomly assigned to one of the two dressing protocols.

Moist desquamation wounds were cleansed by gentle washing with 0.9% normal saline after each assessment visit. In the study group, a non-adherent dressing was applied to the wound after cleansing. For patients in the control group, gentian violet was applied topically to the wound after cleansing.

Baseline information about each participant was recorded before randomisation. Wound healing parameters including wound size, wound pain, and signs of infection were documented and re-evaluated every 2 days. Patients in both study groups were asked to complete Profile of Mood States (POMS) questionnaires and 'MSSA' forms including four single questions about mobility, sleep, social isolation, and aesthetic acceptance at the beginning of the study (time 1), and at the fifth visit (the median wound healing time, ie 11 days in Mak et al's study[2]) or upon completion of the treatment if the wound had not healed before the fifth visit (time 2), and 3 weeks after the wound had healed (time 3).

Sample size

Based on the results of our previous study[2] comparing gentian violet and an adherent (hydrocolloid) dressing, the median time to wound healing when using gentian violet is about 11 days. In order to achieve 90% power, with a one-sided 5% level test, and detect a 30% improvement in healing rate in the non-adherent dressing arm, it was estimated a total of 135 wound-healing events must be studied. An attrition rate of 7% was anticipated in this study, increasing the sample size to 146 subjects.

Study instruments

The study instruments included the following:

(1) Healing time—defined as time in days between recruitment and observation of complete re-epithelialisation and absence of moist desquamation and burning. For patients with multiple wounds, the worst wound would be considered the primary end-point. For patients, healing was defined as complete return of skin integrity to all wounds. Also, the wound perimeters were digitised using a software program that calculated the wound area within an image that was taken on the first visit.

(2) Incidence of clinical infection—assessed by observing the following: (a) erythema and/or oedema of the surrounding normal tissue; (b) increased drainage; (c) change in the nature of drainage from serous to purulent; (d) increased tenderness in and around the reaction site; and (e) systemic signs of infection including fever and leukocytosis. A routine wound swab for microbiological growth was taken at the beginning of the study and also when signs of infection developed.

(3) Wound pain—evaluated using Wong and Baker's[4] Faces Rating Scale, which consists of a 5-point scale with anchor words at each grade (grade 0=no pain and grade 5=very painful).

(4) Mood disturbance—assessed using the Chinese version of the 65-item POMS[5] that provides a composite score. Higher scores indicate greater mood disturbance.

(5) Neck mobility and sleep problems, social isolation, appearance disturbance—these were assessed by four head- and neck-radiation skin ulceration-specific questions using a 10-point Likert scale where higher scores indicate more distress. This was devised in the absence of any validated specific head and neck radiation skin ulceration questionnaire.

Results

Of the 146 patients recruited, three withdrew from the study group before completion due to transport problems or because they were too busy to return for wound assessment after finishing radiotherapy; five withdrew from the control group for similar reasons and two patients refused gentian violet because of discomfort and requested dressing materials to cover the wound.

The radiation port covers the craniofacial skin overlaying the nasopharynx, oropharynx, and posterior oral cavity, and all the skin of the neck on both sides. 6 MV photons were used, giving a dose of 200 cGy per fraction every day from Monday to Friday. Overall 33 fractions totalling 6600 cGy to the nasopharynx and upper neck, and 5400 cGy to the lower neck were given. In 85 patients a further boost dose of 2000 cGy in 10 fractions over 2 weeks was given to the nasopharynx and upper neck immediately following the basal course of radiation therapy. Fifty-one patients also received concurrent chemotherapy with weekly cisplatin.

Table 1. Clinical characteristics of study subjects by randomisation*

	Non-adherent dressing group (n=76)	Gentian violet group (n=70)
Sex		
Male	66 (87%)	58 (83%)
Female	10 (13%)	12 (17%)
Age (years)	54.09 ± 13.9	53.07 ± 11.31
Diabetes mellitus	7 (9%)	5 (7%)
Dermatitis	1 (1%)	1 (1%)
Known skin allergy	9 (12%)	15 (21%)
Body mass index (kg/m^2)	17.63 ± 2.6	18.18 ± 2.3
Initial wound size (cm^2)	10.51 ± 9.1	11.38 ± 19.9
Initial wound size		
≤10 cm^2	33 (43%)	22 (31%)
>10 cm^2	43 (57%)	48 (69%)
Concomitant chemotherapy	26 (34%)	25 (36%)
Dose of radiation received (cGy)	6012.8 ± 637	6190.7 ± 689
UICC† T stage		
T1 and T2	52 (68%)	53 (76%)
T3 and T4	24 (32%)	17 (24%)
UICC N stage		
N1 and N2	61 (80%)	62 (89%)
N3	15 (20%)	8 (11%)
UICC overall stage		
I and II	25 (33%)	35 (50%)
III and IV	51 (67%)	35 (50%)
Radiation boosting	47 (62%)	38 (54%)

* Values are shown as No. (%) or mean ± standard deviation
† UICC denotes International Union Against Cancer

Table 2. Univariate analysis of the predictors for prolonged time to wound healing

Variable	P value
Sex	0.0477
Male	
Female	
Initial wound size	0.0007
≤10 cm^2	
>10 cm^2	
Use of concurrent chemotherapy	0.006
No	
Yes	
Use of radiation boosting	0.0216
No	
Yes	
UICC* T stage	0.0271
T1 and T2	
T3 and T4	
UICC N stage	0.0006
N1 and N2	
N3	
UICC overall stage	<0.0001
I and II	
III and IV	

* UICC denotes International Union Against Cancer

Table 3. Multivariate analysis of the predictors for prolonged time to wound healing

Variable	Hazard ratio	95% confidence interval	P value
UICC* N stage	0.56	0.3-0.9	0.0281
Radiation therapy dose received at recruitment (Gy)	1.56	1.19-2.05	0.0011
Initial wound size >10 cm^2	1.74	1.2-2.5	0.0025
UICC overall stage	0.61	0.4-0.9	0.0030
Type of dressing treatment	1.16	0.8-1.6	0.39

* UICC denotes International Union Against Cancer

Table 4. Baseline mean scores for wound pain, distress, and mood measures at time 1

	Non-adherent dressing group (n=73)		Gentian violet group (n=69)	
	Mean	SD	Mean	SD
Wound pain	2.42	0.95	2.41	1.01
Neck mobility problem	6.00	2.03	5.91	1.60
Sleep problem	6.28	2.26	5.92	2.34
Social isolation	7.42	2.64	7.34	2.62
Appearance disturbance	6.90	2.28	7.91	11.41
Profile of Mood States				
Tension	15.69	9.03	16.43	10.06
Depression	23.00	16.07	23.10	17.86
Anger	17.26	12.11	18.40	14.81
Vigor	13.41	7.72	13.65	8.91
Fatigue	14.94	8.17	15.01	7.76
Confusion	11.35	6.84	11.91	7.88
Total mood score	68.57	46.92	71.2	52.6

The baseline clinical characteristics of the patients enrolled in the study are shown in Table 1. Both groups were similar. The healing time was analysed using a Cox regression analysis. An intention-to-treat principle was applied in the analysis. In those patients who violated the treatment protocol, the wound healing time was censored.

In the study group receiving non-adherent dressings, radiation-induced desquamation wounds healed in a median of 14 days (95% confidence interval [CI], 12-14 days), which was not significantly different (P=0.09) from the healing time in the control group receiving gentian violet (median, 14 days; 95% CI, 12-16 days). Nonetheless there was a trend toward shorter wound healing times in a subgroup of the study population whose wounds took longer to heal. There were no clinical wound infections in any of the participants and none developed cellulitis.

The variables found to be significantly associated with wound healing time in the univariate model are detailed in Table 2. To further confirm the findings of the univariate analyses, the aforementioned variables were subject to a multivariate analysis using the Cox regression model, which confirmed that an initial wound size of larger than 10 cm^2, a higher dose of radiation received at recruitment, the International Union Against Cancer overall stage and N stage were independent determinants of prolonged wound healing times, while the type of dressing was not a significant factor (P=0.39) [Table 3].

Scores measuring the impact of radiation-induced wounds on patients collected at the beginning of the study (time 1) are shown in Table 4. No differences were found between the two groups in levels of wound pain, disturbance

Table 5. Comparison of financial cost of non-adherent dressing versus gentian violet*

	Non-adherent dressing	Gentian violet
Dressing change frequency	Daily	Twice per day
Amount of dressing used per change	2 pieces	10 mL
Price of dressing	$3/piece ($10\times10$ cm^2)	$0.5/20 mL
Price of irrigation syringe	$5	$5
Price of saline	$8 per change	$8 per change
Price of tape	$0.8 per change	-
Cost per dressing change	$19.8	$13.5
Nursing time spent per dressing change	20 mins	5 mins
Cost of 1 nursing working hour	$120	$120
Nursing labour costs per change	$40	$10
Cost per change: labour + materials	$59.8	$23.5
Cost per healing†	$837.2	$329.0

* All costs are shown in HKD
† The two forms of dressing took a median of 14 days to heal wounds

of neck mobility, sleep, social interaction, appearance, and mood.

The mean scores for the worst levels of pain during treatment were 2.51 in the study group and 2.80 in the control group. There was a trend towards decreased subjective pain from the desquamated wound among patients in the group receiving non-adherent dressings but this did not reach statistical significance (P=0.07).

No statistically significant differences were detected between the two groups at the time of receiving the dressing intervention when wounds had not healed (time 2) and upon completion of wound healing (time 3) with respect to wound pain, neck mobility, sleep, social isolation, appearance disturbance, and mood disturbance.

Costs were measured by including the amount of follow-up, number of dressings, additional materials, and nursing time required (Table 5). There was a significant difference in the total cost per treatment arm. The total cost per healed wound using non-adherent dressings was $837.2, over twice as much as the $329.0 per healed wound in the group treated with gentian violet.

Discussion

This study shows that non-adherent dressings are as effective as gentian violet for shortening healing times in radiation-induced wounds, and for reducing the impact of those wounds on pain, mood states, social interaction, sleep, appearance, and neck movement. Nonetheless, the total cost of using non-adherent dressings to treat these wounds was higher than that of using gentian violet.

Wound dressings are considered beneficial because they protect the wound from external contamination and infection, and prevent further irritation or friction. Non-adherent dressings have not been found to be superior for healing the wound. Although having a non-adherent wound contact layer makes the dressing easy to remove, it also produces a rather dry environment that is not conducive to fibroblast migration and epithelial proliferation. Furthermore, when the wound is large and moist, the fluid might not be sufficiently absorbed and forms a sticky layer upon drying. This predisposes the wound to trauma, especially if the dressing needs to be removed frequently, as happens during a course of radiation therapy when the dressing is within the radiation port. This is consistent with our previous study into the use of hydrocolloid dressings on irradiated wounds, which showed no significant shortening of the wound healing time compared to gentian violet, while the wound pain score was higher,[2] despite the ability of hydrocolloids to facilitate rapid wound healing on the basis of the 'moist wound healing' principle.[1] The use of non-adherent dressings and hydrocolloid dressings shared a common problem in that both types of dressing require removal before each daily fraction of radiation therapy, which may cause more damage to the skin integrity because of their different levels of adherence.

Although this study found there was a trend towards lower pain scores in the non-adherent dressing group, the difference was not significant. This is likely to be due to trauma caused by the need for a repeated change of dressings after a sticky dry layer had formed.

The problem caused by the need for a daily change of dressing might be specific to radiation therapy. This is because the megavoltage photons used in therapeutic radiation have a 'skin-sparing' effect, in that the superficial millimeters of skin next to the air-skin interface receive a lower dose than the deeper tissue. The presence of a dressing over the wound would lead to loss of this sparing effect, as the skin surface is no longer next to the air, but embedded beneath the dressing. Thus the dressing must be removed during each radiation therapy treatment.

In this study, large wound size, a higher cumulative dose of radiation received at recruitment, and use of concurrent chemotherapy were significant determinants of prolonged wound healing. The implication is that the radiation-induced wounds should be managed as early as possible when they are small. Patients being treated with a radiation boost dose and/or chemotherapy represent an at-risk group who should be educated specifically about the likely radiation skin reaction and care and be monitored more closely.

In our patients, moist desquamation is usually noted along both sides of the neck and the supraclavicular fossa towards the end of the course of radiation therapy. The finding of increasing scores for disturbance in 'mood', 'mobility', 'sleep', 'social interaction', and 'appearance' from the time of the emergence of the wound to the time of

starting wound dressing, and a trend toward a decrease in those scores at the completion of wound healing, suggests that measures to shorten the duration of moist desquamation is likely to reduce the adverse impact on patients. However non-adherent dressings have not been proven superior to gentian violet dressing. It is also possible that, other radiation side-effects such as oral mucositis, odynophagia, and xerostomia may override the effect of the type of dressing on symptom scores.

Of the two types of dressing for radiation-induced wound treatment, gentian violet proved to be the most cost effective. The difference in cost could be accounted for by the increase in nursing time required to soak adherent dressings off the wound before the placement of non-adherent dressings after each irradiation.

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