Title

A randomized, controlled, double-blind study of light emitting diode photomodulation for the prevention of radiation dermatitis in patients with breast cancer.

Journal

Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.], 36(12)

ISSN

1076-0512

Authors

Fife, Douglas
Rayhan, David J
Behnam, Shahdad
et al.

Publication Date

2010-12-01

DOI

10.1111/j.1524-4725.2010.01801.x

A Randomized, Controlled, Double-Blind Study of Light Emitting Diode Photomodulation for the Prevention of Radiation Dermatitis in Patients with Breast Cancer

Douglas Fife, MD,* David J. Rayhan, MD,† Shahdad Behnam, MD,* Arisa Ortiz, MD,* Laila Elkeeb, MD,* Lisa Aquino, MD,‡ D. Eduardo Roa, PhD,§ Nilam Ramsinghani, MD,§ Jeffrey Kuo, MD,§ Robert Newcomb, PhD,¶ Christopher B. Zachary, MBBS, FRCP,* and Kristen M. Kelly, MD*

BACKGROUND AND OBJECTIVES Radiation dermatitis occurs in a majority of patients with breast cancer who receive radiation therapy (RT), causes significant pain, and may necessitate treatment delay. Light emitting diode (LED) photomodulation has been reported to minimize radiation dermatitis. This study sought to further evaluate the efficacy of LED photomodulation in lessening radiation dermatitis.

MATERIALS & METHODS After surgery, patients with breast cancer received LED photomodulation or sham treatments in conjunction with three-dimensional conformal RT. Reactions were evaluated using standardized photographs graded according to National Cancer Institute criteria.

RESULTS In the LED treatment group ($n = 18$), no patients had grade 0 reactions, six (33.3%) had grade 1 reactions, 12 (66.7%) had grade 2 reactions, and none had a grade 3 reaction. In the sham treatment group ($n = 15$), one (6.6%) patient had a grade 0 reaction, four (26.7%) had grade 1 reactions, 9 (60.0%) had grade 2 reactions, and one (6.7%) had a grade 3 reaction. Two (11.1%) patients in the LED treatment group and one (6.7%) in the control group had to interrupt treatment. Differences between groups were not statistically significant.

CONCLUSION LED photomodulation did not reduce the incidence of radiation-induced skin reactions or interruptions in therapy.

Funding was provided for this study through the Cutting Edge Research Grant, sponsored by the American Society for Dermatologic Surgery. The GentleWaves LED Select units were loaned for this study by Light BioScience

Background

Radiation therapy (RT) is a mainstay of treatment for breast cancer used in conjunction with chemotherapy after lumpectomy or mastectomy. A common side effect of RT is radiation dermatitis, which occurs in an estimated 75% to 87% of patients with breast cancer receiving RT.[1] Severe radiation dermatitis can be desquamative, cause significant pain, and require cessation of treatment while the skin heals, leading to prolonged treatment times and suboptimal results. Multiple modalities have been used to reduce or prevent radiation dermatitis, including petrolatum, Aquaphor (Beirsdorf Inc, Wilton, CT), Biafine, (Ortho Dermatologics, Skillman, NJ) topical corticosteroids, hydrogel dressings, antioxidants, and aloe, but none have clearly shown consistent efficacy.[2]

Light emitting diode (LED) photomodulation is a process by which specific sequences of low-energy light are used to regulate or manipulate cell activity without a thermal effect. LED photomodulation

*Department of Dermatology, †School of Medicine, ‡Department of Medicine, §Department of Radiation Oncology, and ¶Center for Statistical Consulting, Department of Statistics, University of California at Irvine, Irvine, California

ISSN: 1076-0512 • Dermatol Surg 2010;36:1921–1927 • DOI: 10.1111/j.1524-4725.2010.01801.x

has been successfully used to reverse the effects of skin photoaging.[3,4] In vitro studies have demonstrated that LED accelerates wound healing, increases procollagen synthesis, downregulates inflammatory mediators, and decreases dermal matrix metalloproteinase (collagenase) expression in cultured fibroblasts exposed to acute ultraviolet light injury.[3–7]

The proposed underlying mechanism for the activation of patient responses to LED photomodulation is believed to be light absorption by cytochrome molecules, specifically cytochrome oxidase within the mitochondrial membrane. These cytochromes absorb wavelengths of light from 562 to 600 nm. Light absorption causes conformational changes in mitochondrial cytochrome antenna molecules. Proton translocation from these changes ultimately leads to conversion of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). Additionally, receptor-like mechanisms appear to result in modulation of gene expression and up- or downregulation of a wide range of cell-signaling pathway actions.[8]

LED photomodulation has been proposed as a method to reduce suffering associated with RT, improve cosmetic outcome of skin in radiation fields, and eliminate breaks in radiation treatments that may be required as a result of severe radiation dermatitis. A recent retrospective study of 47 subjects by DeLand and colleagues[9] demonstrated that administering LED photomodulation after each radiation treatment for breast cancer significantly decreased radiation dermatitis in a majority of patients treated. Grade 1, 2, and 3 reactions were seen in 60%, 5%, and 0% in the LED group, compared with 14%, 64%, and 21% in the control group, respectively. Only 5% of patients in the LED group had to interrupt treatment, compared with 68% of the control group. Our study attempted to replicate the data of DeLand and colleagues in a prospective, randomized, double-blind, controlled study.

Objective

The purpose of this study was to determine the efficacy of GentleWaves LED photomodulation device (Light BioScience, LLC, Virginia Beach, VA) in preventing or lessening radiation dermatitis in patients with breast cancer receiving RT. The primary outcome measure was radiation dermatitis grades measured at week 5 of RT in conjunction with LED photomodulation. Secondary outcome measures were interruptions of RT due to severe skin reactions and patient satisfaction.

Materials and Methods

Study Design

This single-center, double-blind, randomized, prospective study compared the skin reactions of patients who received LED photomodulation before and after each RT session with those of control patients who received sham treatments before and after each RT session. The institutional review board of the University of California at Irvine approved the study.

Patients

The Department of Radiation Oncology at the University of California, Irvine Medical Center (Orange, CA) referred patients for study participation. All patients provided written informed consent before study enrollment, and the study conformed to the guidelines of the 1975 Declaration of Helsinki. To be eligible, patients had to be aged 18 and older and have clinically diagnosed breast cancer that would be treated with RT. All patients had undergone a prior lumpectomy or mastectomy. Patients who were pregnant or lactating were excluded from the study. Patients were assigned randomly to the treatment or control group.

Radiation Therapy

Patients in the treatment and control groups received a complete course of RT for breast cancer. Radiation treatments were given according to the standard

practice for breast cancer at our center (5 treatments per week for a total of 25 or 28 treatments, plus an additional 5 to 7 "boost" or additional treatments to the cancer site, for a total of 45 to 50.4 Gy to intact breast or chest wall and 60.4 to 61.2 Gy to the mastectomy scar or lumpectomy cavity). Radiation treatments were given using megavoltage photon beams with a source to axis distance of 100 cm, as is standard practice for breast cancer. Bolus, a tissue-equivalent material, was used in postmastectomy patients to treat the chest wall. To document actual skin doses, Harshaw-Bicron thermoluminscent dosimetry (TLD) monitors were placed at specific sites on the breast periodically to assess possible differences in radiation doses at the level of the skin between patients or between different locations in the same patient.

Figure 1. Light-emitting diode photomodulation device (Light BioScience, LLC, Virginia Beach, VA).

LED Treatments

Patients in the treatment group received LED treatments immediately before and after each radiation session. Each LED treatment was administered using the GentleWaves Select 590-nm high-energy LED array (Figure 1) with the panel being placed within 2 cm of the patient's skin. Each treatment lasted 35 seconds, using the same specific sequence of pulses used by DeLand and colleagues and in other studies, in which the pulses are 250 ms on and 100 ms off for 100 pulses.[9,10] Upon completion of the RT course, seven additional daily treatments were given over the next 2 weeks with the goal of preventing the delayed reaction seen in RT. Patients in the control group had sham treatments, in which the machine was placed on the skin at the same times in the same manner for the same duration of 35 seconds, but the button was not pressed to deliver the light. Patients in both groups had towels or eyeshields placed over their eyes to blind them as to whether the LED device was administering light treatments. All patients in the study were given Aquaphor to apply three to four times a day during the entire duration of the study.

Reaction Evaluation

Skin reactions were monitored at baseline, weekly during ongoing RT, at the completion of RT, and 2 and 6 weeks after the completion of RT. A dermatologist blinded to study group (KMK) graded standardized photographs of the week 5 visit according to the National Cancer Institute (NCI) 5-point scale for grading skin reactions (Figure 2).

Grading Scale

0	1	2	3	4
None	Faint erythema or dry desquamation	Moderate to brisk erythema or patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Confluent moist desquamation, ≥10 cm diameter, not confined to skin folds; pitting edema	Skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion

Figure 2. National Cancer Institute terminology criteria for adverse skin events.

All interruptions of RT were recorded. Patients in both groups were also given a questionnaire weekly and at the end of the entire treatment course. The questionnaire asked patients to assess the convenience, discomfort, and overall satisfaction with their treatment, as well as their assessment of the cosmetic appearance of the skin on a 6-point (0–5) scale.

Statistical Analysis

The primary outcome measure of the study was the grade of skin reaction at week 5 from photographs graded by a blinded dermatologist. Skin reaction grades of 0 and 1 are considered a mild reaction, and grades of 2, 3, and 4 are considered more severe. The proportions of reactions were compared for significant differences between the groups for favorable (grade 0 and 1) or unfavorable (grade 2–4) reactions using chi-square and Fisher exact tests. Statistical analysis was conducted using SAS software (SAS Institute, Inc., Cary, NC).

Results

No adverse events were observed with LED treatment, and all patients completed the study. Results are summarized in Table 1. Of the 18 patients treated with LED, none had grade 0 reactions, six (33.3%) had a grade 1 reaction, 12 (66.6%) had a grade 2 reaction, and none had a grade 3 or higher reaction (Figure 3). Two (11.1%) patients receiving LED treatment had temporary interruption in treatment secondary to skin breakdown.

Of the 15 patients who received sham treatments, one (6.6%) had a grade 0 reaction, four (26.7%) had a grade 1 reaction, nine (60.0%) had a grade 2 reaction, one (6.6%) had a grade 3 reaction, and none had reactions higher than grade 3 (Figures 4 and 5). One patient in the sham treatment group had a temporary interruption in treatment secondary to skin breakdown.

Skin reaction grades were not significantly lower ($p > .05$) in the LED treatment group than in the sham treatment group (chi-square and Fisher exact). All patients in the treatment and sham groups who experienced an interruption in treatment completed their RT course.

There was no significant difference in discomfort, pain, convenience, or satisfaction with treatment between the two groups based on results of the 6-point scale patient questionnaires ($p > .05$).

The mean TLD measurements from the inframammary fold were 178.7 cGy for the LED treatment group and 185.3 cGy for the control group. These

TABLE 1. Patient Grades, Treatment Interruptions, and Groups

Patient	*Skin Grade*	*Interrupted Treatment*	*Group*
1	1	No	LED
2	2	No	LED
3	2	No	Control
4	2	No	LED
5	2	No	Control
6	2	No	Control
7	2	Yes	LED
8	1	No	LED
9	1	No	Control
10	2	No	LED
11	1	No	Control
12	2	No	Control
13	2	No	LED
14	2	No	LED
15	2	No	LED
16	2	No	Control
17	1	Yes	Control
18	2	Yes	LED
19	2	No	LED
20	2	No	LED
21	1	No	LED
22	3	Yes	Control
23	1	No	Control
24	1	No	LED
25	2	No	Control
26	2	No	Control
27	2	No	LED
28	0	No	Control
29	1	No	LED
30	2	No	Control
31	1	No	LED
32	2	No	Control
33	2	No	LED

LED = light-emitting diode.

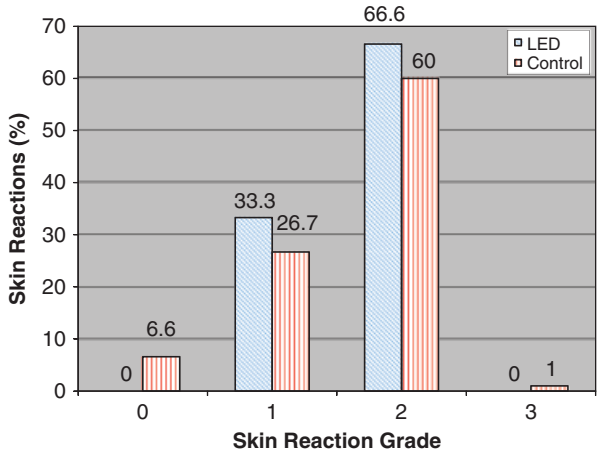

Figure 3. Skin reaction grades of patients in the light-emitting diode and sham treatment groups.

values were not significantly different between the two groups.

One study patient received RT for bilateral breast cancer and received LED to the right breast and sham treatments to the left breast, which made this patient a self-control. Both breasts developed equal grade 2 skin reactions.

Discussion

Our findings did not demonstrate a lower incidence or degree of radiation dermatitis when RT was administered in conjunction with LED. The statistical analysis did not reveal a lower incidence or degree of radiation dermatitis or a reduction in interruption of RT when RT was administered in conjunction with LED photomodulation.

The aforementioned findings, which are contrary to those shown by DeLand and colleagues, may be attributed to a variety of factors.[9] A blinded dermatologist conducted all evaluations of skin reactions in our study at one time based on standardized photographs; a nurse performed evaluations weekly in DeLand and colleagues' study. In our study, subjects were treated before and after each radiation treatment, instead of only after each radiation treatment, as in the study by DeLand and colleagues. Because LED and infrared exposure before ultraviolet exposure has been shown to limit cellular damage and clinical sunburn,[11,12] we thought that adding an LED treatment before each RT session might further enhance the effect of LED in preventing radiation dermatitis. It is also possible that a larger study could have greater power to detect small differences in skin reactions between groups.

The severity of skin reactions induced by RT is related to multiple factors influenced by treatment and patient characteristics (e.g., breast size, age, and genetics).[13,14] Patient characteristics may have

TABLE 2. Details of Radiation Therapy

Study Characteristics	*DeLand et al.*[9]	*Fife et al.*
Radiation modality	Intensity-modulated radiation therapy	Three-dimensional conformal radiation therapy
Photon beam energy	4–10 MV to whole breast	6 MV to whole breast
Electron beam energy	9–20 MeV to boosted volume	6–15 MeV to boosted volume
Source to axis distance	100 cm (standard setup)	100 cm
Treatment fraction (fx)	28 fx (1.8–50.4 Gy)	25 fx (1.8–45 Gy); 28 fx (1.8–50.4 Gy)
Boost fraction (fx)	5–10 fx (2.52 and 1.8 Gy/fx, respectively)	5–7 fx (2 Gy/fx)
Dose to whole breast or chest wall	50.4 Gy	45–50.4 Gy
Dose to tumor bed or mastectomy scar (boost)	63.0–68.4 Gy	59–60.4 Gy
Confirmed using thermoluminscent dosimetry measurements	No	Yes

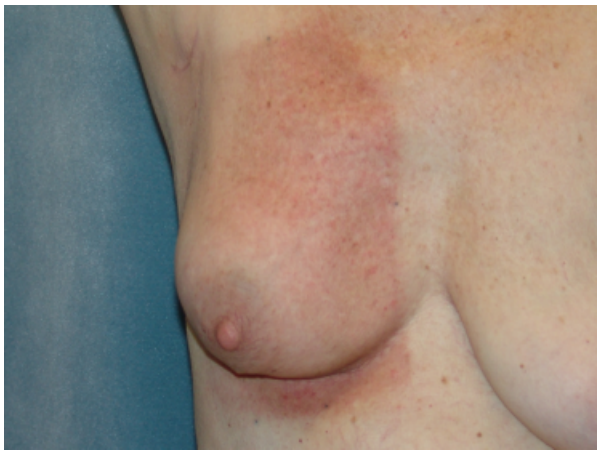

Figure 4. Grade 2 skin reaction.

differed in the patient populations of these studies. The differences between our study and the study by DeLand and colleagues are listed in Table 2. We used the three-dimensional conformal modality of RT, while Deland and colleagues used the intensity-modulated RT modality, which is known to produce less skin toxicity. Three-dimensional conformal remains the most commonly used modality, but interest is growing in the use of intensity-modulated RT for breast cancer in the radiation oncology community because of reports of lower skin dose toxicity and less tissue reaction than with three-dimensional conformal.[15–18]

In our study, severe reactions of grade 3 or higher were seen in only one patient in the control group and no patients in the treatment group. Overall, this is much lower than the number of grade 3 reactions that DeLand and colleagues recorded (6 of 28 patients in their control group). This could be because of subjective differences between evaluators in interpreting the NCI grading criteria. It is also possible that improvement caused by LED can be detected only when higher doses of radiation are used, such as in total chest wall radiation or in RT of head and neck cancers.

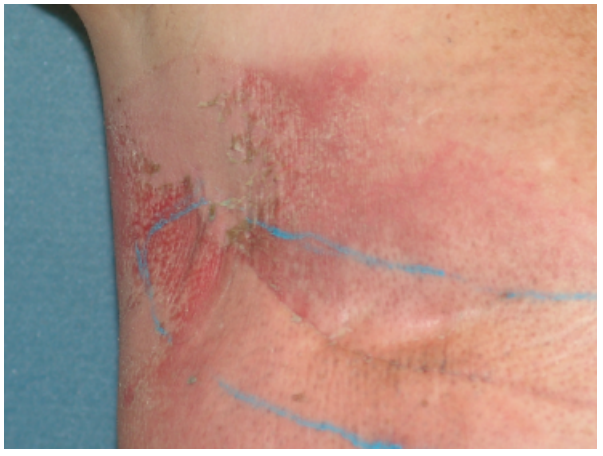

Figure 5. Grade 3 skin reaction.

In the study patient who received bilateral RT, the reaction was not less severe in the LED-treated breast. This finding, although in only one individual, strengthens the conclusion that LED treatment in conjunction with RT may not reduce the severity of skin reactions; additionally, it suggests that the effectiveness of LED treatment may depend on multiple factors related to the characteristics of the patient and the treatment.

In addition, the mean TLD measurements for inframammary radiation dose was higher in the control group. With these higher dosages, it would be expected that there would be a higher average reaction grade in the control group than in the LED treatment group, but the opposite was seen. This further calls into question the effectiveness of LED photomodulation for the prevention of radiation dermatitis.

There are no reports of any adverse effects related to LED treatment administered with RT. In our subjects, LED treatment in conjunction with RT did not increase discomfort or pain but also did not decrease overall convenience or satisfaction with treatment. We conclude that LED treatment is of no harm to patients undergoing RT for breast cancer, but the efficacy of LED photomodulation for prevention of radiation dermatitis requires further study.

References

1. Fisher J, Scott C, Stevens R, et al. Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast

irradiation: radiation therapy oncology group (RTOG) 97-13. Int J Radiat Oncol Biol Phys 2000;48:1307–10.

2. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. J Am Acad Dermatol 2006;54:28–46.
3. Weiss RA, McDaniel DH, Geronemus RG, Weiss MA. Clinical trial of a novel non-thermal LED array for reversal of photoaging: clinical, histologic, and surface profilometric results. Lasers Surg Med 2005;36:85–91.
4. Weiss RA, Weiss MA, Geronemus RG, McDaniel DH. A novel non-thermal non-ablative full panel LED photomodulation device for reversal of photoaging: digital microscopic and clinical results in various skin types. J Drugs Dermatol 2004;3: 605–10.
5. Geronemus R, McDaniel DH, Weiss R, Weiss M. LED photomodulation "reverses" acute UV induced matrix enzyme expression. Abstract 77. American Society for Laser Medicine and Surgery Abstracts. April, 2006
6. McDaniel DH, Geronemus RG, Weiss M, Weiss RA. LED photomodulation accelerates wound healing of acute skin injury. Abstract 107. American Society for Laser Medicine and Surgery Abstracts. April, 2006
7. McDaniel DH, Weiss RA, Geronemus R, et al. Light-tissue interactions 1: photothermolysis vs photomodulation laboratory findings. Lasers Surg Med 2002;14:25.
8. Weiss RA, McDaniel DH, Geronemus RG, et al. Clinical experience with light-emitting diode (LED) photomodulation. Dermatol Surg 2005;31(9 Pt 2):1199–205.
9. DeLand MM, Weiss RA, McDaniel DH, Geronemus RG. Treatment of radiation-induced dermatitis with light-emitting diode (LED) photomodulation. Lasers Surg Med 2007;39: 164–8.
10. McDaniel DH, Newman J, Geronemus R, et al. Non-ablative non-thermal LED photomodulation – a multicenter clinical photoaging trial. Lasers Surg Med 2003;15:22.
11. Barolet D, Boucher A. LED photoprevention: reduced MED response following multiple LED exposures. Lasers Surg Med 2008;40:106–12.
12. Frank S, Menezes S, Lebreton-De Coster C, et al. Infrared radiation induces the p53 signaling pathway: Role in infrared prevention of ultraviolet B toxicity. Exp Dermatol 2006; 15:130–137.
13. Harper JL, Franklin LE, Jenrette JM, Aguero EG. Skin toxicity during breast irradiation: pathophysiology and management. South Med J 2004;97:989–93.
14. Iannuzzi CM, Atencio DP, Green S, et al. ATM mutations in female breast cancer patients predict for an increase in radiation-induced late effects. Int J Radiat Oncol Biol Phys 2002;52: 606–13.
15. Harsolia A, Kestin L, Grills I, et al. Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. Int J Radiat Oncol Biol Phys 2007;68:1375–80.
16. Donovan E, Bleakley N., Breast Technology Group et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 2007;82:254–64.
17. Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 2008;26: 2085–92.
18. Haffty BG, Buchholz TA, McCormick B. Should intensity-modulated radiation therapy be the standard of care in the conservatively managed breast cancer patient? J Clin Oncol 2008;26:2072–4.

Address correspondence and reprint requests to: Kristen M. Kelly, MD, 1002 Health Sciences Road East, Irvine, CA 92612, or e-mail: kmkelly@uci.edu