DOUBLE-BLINDED, RANDOMIZED, CONTROLLED TRIAL TO STUDY THE EFFECT OF OMNILUX LIGHT-EMITTING DIODE ON WOUND HEALING FOLLOWING LOWER EXTREMITY SURGICAL WOUNDS LEFT TO HEAL BY SECOND INTENTION

Amendment #1: 12/10/12

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I. INTRODUCTION

The first published data that the LED (Light Emitting Diode) light may be beneficial during wound healing occurred during the 18th century by Fubini and colleagues. Their early work on subcellular organelles was confirmed nearly 100 years later by Tina Karu demonstrating that 633 nm light targeted cytochrome c in the mitochondrial electron transport chain.[1] Much recent research on LED has occurred largely as a result of NASA's program to develop a light source to grow plants on space shuttles. This recent research has focused on how the LED works on biological tissue and its applications to medicine.

Similar to the 633 nm light emitted by the LED, red light from the HeNe 633 nm laser has been shown to induce fibroblast monosheet formation faster with better alignment when compared to non-irradiated controls.[2] The LED, when used in the 830 nm range, stimulates macrophages and neutrophils to perform chemotactic, phagocytic functions more quickly. It also increases fibroblast release of fibroblast growth factor by nearly 30 times.[3-5] Perhaps most intriguingly, 633 nm and 830 nm LED light has been shown to stimulate keratinocytes to release a large amount of cytokines, and migrate into the dermis to aid in the dermal wound healing process.[6] These photoactivated keratinocytes improve the cellularity and epidermal organization especially in the stratum corneum.7

The 830/633 nm LED has been used to improve wound healing after an Er:YAG/CO2 ablative laser system treatment.[8] The experimental group received the 830/630 nm LED following ablative laser therapy while the control group received only the 630 nm LED after ablative laser treatment. The mean healing time for the experimental group was 6 weeks versus 13 weeks for the control group. Similarly, another study measured healing time after upper blepharoplasty and found healing time to be reduced one-half to one third in the 830/633 nm group.[9] Another study using the LED (830/633 nm) treatment after Er:YAG laser ablation of deep plantar warts reduced the healing time by nearly half and reduced post-operative pain by 10% involving 121 subjects.[10] Lower extremity ulcers have also been shown to be benefitted in terms of healing times by the 830 nm LED in a pilot study.[11]

Wounds on the lower extremity heal more slowly than wounds on the head and neck and can remain deep red or violaceous for six months to one year.[12] The decision to allow lower extremity wounds to heal by second intention is guided by a difficulty in using primary closure in many lower extremity wounds because of excess wound tension and limited tissue mobility. Decreased tissue laxity creates increased wound tension and an increased likelihood for wound dehiscence. By using second intention as a method for surgical defect management the physician

need not worry about dehiscence and retained suture material serving as a nidus for infection. Wound management is simple, requiring only a bandage and daily care that can be done at home by the patient, family, or visiting nurse. A major limitation of allowing surgical defects on the lower extremity to heal by second intention is the long healing time that can often take months. For this reason, modalities that can hasten this process are in demand.

II. OBJECTIVE

The goal of the study is to evaluate the efficacy of the light-emitting diode in the treatment of lower extremity surgical wounds left to heal by secondary intention by way of a double-blinded randomized, controlled study.

III. STUDY PLAN

Patients will be recruited from patients at the University of Miami Miller School of Medicine Mohs/Laser Unit. On the day of surgery and wound defect creation (day 0), patients will be informed of the study, and given the option of participating. If he or she decides to participate, the patient will be randomized into one of two groups in blocks of two by coin flip. The patient will remain blinded to the outcome of randomization. The experimental group will receive treatment with the light emitting diode (LED) for one session lasting 20 minutes of exposure at an intensity of 105 mW/cm2 for a total of 126 J/cm2 over the wound site. The LED emits light at wavelengths of 633 nm and 830 nm at fluences of 126 and 66 J/cm2. This study will only utilize the 633 nm wavelength. The control group will receive sham light treatment for 20 minutes with standard of care for second intention healing and no LED treatment. In this case, a sham light treatment refers to regular light (not LED) exposure for 20 minutes. The sham light comes from the same device as the treatment light (Omnilux machine) however, this light has no anticipated effects on wound healing and is used simply to reduce the amount of bias that sometimes complicates the results of these studies. There is no added risk or benefit for the patients in the control group exposed to the sham light.

On day 0 the patients will be informed of the study and randomized into one of two groups by coin flip to either the experimental or control group. The patients will be blinded to which group they have been randomized too. Group 1 is the control group, which will receive sham light treatment and standard of care for lower extremity wounds. Group 2 represents the experimental group, which will receive LED treatment plus standard of care. The experimental group will receive treatment with the light emitting diode (LED) at 633 nm at one session lasting 20 minutes of exposure at an intensity of 105 mW/cm2 for a total of 126 J/cm2 over the wound defect, one week after wound creation (+/- 3 days). The control group will receive no LED treatment, however they will be exposed to a sham light for the duration of 20 minutes as well as receive standard of care for their lower extremity wound. Treatment will occur at one-week intervals (+/- 3 days) for a total

of 4 treatments for both the experimental and control/sham groups. The wounds will be created as a result of Mohs micrographic surgery or surgical excision, and left to heal by secondary intention. An Aranz silhouette camera will be used with a measurement stick on the picture. Changes from the baseline wound (including length and width) will be measured along with wound depth. These two parameters will be compared at the 1 week, 2 week 3 week, and 4-week treatment (or sham treatment) visits. After the 4th and final treatment with the LED or sham light, the patients will be followed at 1-week intervals (+/- 3 days) until the wound has closed or for a maximum of 3 months, whichever occurs first. Once the wound has closed, patients will be evaluated a final time, 1 week after wound closure to ensure that complete wound healing has indeed occurred. After this final wound evaluation, the patient's commitment required for this study will end and regular follow-up with dermatology will resume outside the scope of this study.

The clinical photographs taken before and after either LED or sham light treatment at each study visit will be evaluated by blinded assessor(s) who are board-certified dermatologist(s).

IV. SUBJECT POPULATION

A. Number of Subjects

We plan to prospectively enroll 40 patients in this study.

B. Inclusion Criteria

Surgical defect on the lower extremity left to heal by secondary intention. There is no minimum size for the wound. Women of child-bearing potential must be using medically-accepted contraceptive measures in order to participate in the study. Patients must be able to complete all study-related visits as scheduled. Maximum size of the wound is 5cm x 5cm.

C. Exclusion Criteria

Any history of porphyria, photosensitive cutaneous eruptions, diabetes mellitus, history of venous insufficiency, or known history of peripheral arterial disease as defined by an ABI < 0.8, any ointments or creams containing known photosensitizers such as coumarins or porphyrins should be discontinued for 2 weeks prior, any systemic or topical retinoids, especially isotretinoin, in the past 6 months, current pregnancy or lactating, any patient with a history of metastatic cancer. Individuals under the age of 18 years will also be excluded from the study.

V. STUDY PROCEDURES

Those patients who have a surgical defect on the lower extremity that will be left to heal by secondary intention and are willing to participate in the study will be consented and enrolled in the study.

The following information will be recorded in a prospective fashion: Patient's age, gender, race/ethnicity, type of skin cancer removed, clinical size of lesion (mm) and size of resulting defect following surgery. It will also be recorded to what group, treatment with LED and standard wound care versus sham light treatment and standard wound care with no LED. Clinical photos of the lesion will also be taken.

The experimental group will receive treatment with the light emitting diode (LED) for 20 minutes of exposure at an intensity of 105 mW/cm2 for a total of 126 J/cm2, over the wound site. The LED emits light at wavelengths of 633 nm and 830 nm at fluences of 126 and 66 J/cm2. This study will only utilize the 633 nm wavelength. The control group will receive sham light treatment for 20 minutes duration and standard of care for second intention healing without the LED treatment. This includes maintenance of a clean and moist wound environment. Patients will keep the wound covered with an occlusive bandage and will perform daily dressing changes. Daily gentle cleansing with soap and water and the application of antibacterial ointment as needed for wound hydration will be the recommended standard of care for both treatment and control groups.

VI. ADVERSE EVENTS

The patients enrolled in the study will be treated with the standard of care for lower extremity wounds following surgery. There are no potential economic/financial, legal, psychological, social or other risks to which research participants may be exposed as a result of their participation in this research. Minor physical risks such as bleeding and infection are involved with the standard of care procedure. If a wound infection occurs the patient will be started on appropriate antibiotic therapy.

VII. STATISTICAL CONSIDERATIONS

This will depend on whether we want to measure a change between the experimental and control group at particular time intervals and between groups (ANCOVA) OR do we just want to measure the difference between the control and experimental groups at particular time periods (t test). If we just do a t test, then we will not be able to make intragroup comparisons, but it will be very easy to analyze, yet still determine if the experimental group accelerates wound healing in comparison to the control group. In addition, we should probably run an unpaired t test at baseline to make sure no statistically significant difference exists in wound

size between the experimental and control groups, otherwise it could confound our results one way or the other.

VIII. DATA HANDLING

The records for the study will be kept in a locked room with access limited to approved study personnel. The records will be kept at the Sylvester Cancer Center Mohs Unit under supervision of Dr. Keyvan Nouri. Access to this computer will be password restricted to authorized study personnel only.

IX. SUBECT REIMBURSEMENT AND COSTS

Patients involved in this study will receive no financial or other reimbursement. Participants will have no costs associated with this study.

X. REFERENCES

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