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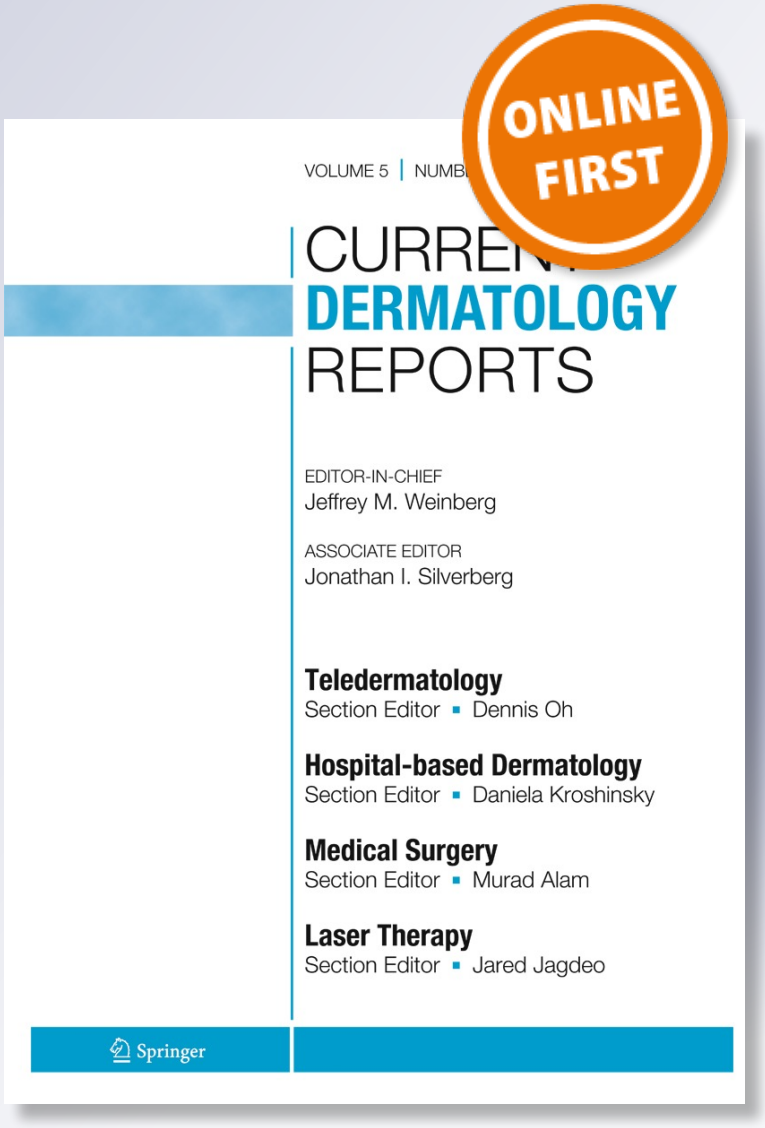

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LASER THERAPY (J JAGDEO, SECTION EDITOR)

Accelerating Ablative Fractional Resurfacing Wound Healing Recovery by Photobiomodulation

Daniel Barolet[1,2]

Abstract Ablative cosmetic procedures are almost inevitably followed by an acute healing phase resulting in discomfort, erythema, edema, and crusting. Since patients are constantly asking for no downtime procedures, a considerable challenge to health care providers has resulted. Recently, photobiomodulation (PBM) with light-emitting diodes has attracted attention in wound healing management via its anti-inflammatory effects and increase in skin collagen production. PBM has been shown to promote wound healing processes both in vitro and in vivo at the epidermal and dermal levels in the skin. The combined favorable anti-inflammatory and collagen metabolism effects enhance collagenesis and elastinogenesis. A growing body of clinical evidence is showing that PBM, using 600–1000 nm light wavelengths, as soon as possible post-procedure and thereafter, successfully accelerates the acute healing phase via faster wound healing so as to reduce patient downtime. This article reviews that evidence and shows that PBM applied pre- and post-ablative fractional resurfacing treatment minimizes postoperative downtime enhancing patient satisfaction. It will hopefully become part of our rapidly expanding treatment armamentarium in order to ultimately improve patient care.

Keywords LED · Light-emitting diodes · Photobiomodulation · Low level light therapy · LLLT · Ablative fractional resurfacing · Erbium: YAG laser · Photoprevention · Complimentary treatment · Wound healing · Wound recovery · Rejuvenation · Rhytids · Wrinkles · Erythema · Edema

This article is part of the Topical Collection on *Laser Therapy*

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Introduction

Various rejuvenation modalities have been used to reverse the cutaneous signs of extrinsic and intrinsic aging. The most effective treatment methods remain ablative so as to induce a controlled skin injury followed by wound healing to promote new collagen formation and dermal matrix remodeling leading to textural improvements. Such treatment modalities include dermabrasion, chemical peels, and ablative laser resurfacing with carbon dioxide (CO_2) or erbium: yttrium-aluminum-garnet (Er:YAG) lasers or a combination of these wavelengths [1]. These procedures require intensive post-treatment care with short-term undesirable after effects including intense erythema, swelling, pain, bleeding, and oozing [2]. Although ablative fractional resurfacing (AFR) has become the ablative treatment of choice to reduce the risk of hypopigmentation and scarring, it still engenders an acute post-treatment wound lasting for more than a week [3]. Patient dissatisfaction with the prolonged downtime and the clinician's desire for faster recuperation time lead to the development of complimentary treatment methods to reduce downtime. Photobiomodulation (PBM) has been known for years to promote wound healing processes, especially by the use of more convenient light-emitting diodes (LED) covering a much larger treatment surface area than comparable lasers [4]. In this split-face study, we measure the effects of using PBM pre/post-AFR (Er:YAG laser at 2940 nm) facial laser treatment.

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Background and Objectives

The purpose of this study was to evaluate, in a real life scenario, the benefits of combining LED therapy with AFR laser treatments in order to reduce the healing and recuperation period ("downtime"). PBM, a non-thermal, non-coherent visible, or infrared (IR) light, could be very useful for patients considering an ablative laser treatment that typically would result in a downtime of several days. Partially ablative laser treatments such as fractional resurfacing would benefit significantly from this LED wound healing promoter if patients could see their downtime reduced significantly [5].

This pilot study provides a preliminary indication of the wound healing enhancement properties of a 660/850 nm pulsed/CW (continuous wave) LED light source applied pre/post-2940 nm (Er:YAG) laser treatment in accelerating treatment after effects and recuperation time as a result.

Material and Methods

Subjects

Fourteen (14) female volunteers with a mean age of 54 (39–70) with bilateral photodamaged and aged skin were recruited from the investigator's clinical population or through approved advertisement. The subjects were randomly assigned to one of four (4) groups (Table 1).

Inclusion criteria:

- Subjects aged between 40 and 70 years old
- Facial wrinkles/photodamaged skin according to Fitzpatrick classification, class II–III, within phototypes I through III.

Exclusion criteria:

- Subjects under 40 and older than 70 years of age.
- Current use of the following medications: cortisone (prednisone), anticoagulant therapy, and drugs known to cause photosensitivity reactions. In addition, during the 6 months preceding the study, subjects are required not to have taken accutane (isotretinoin).

Table 1 Fitzpatrick skin phototypes I to III were ramdomly assigned in four treatment groups

Fitzpatrick phototype	A	B.1	B.2	B.3
I	0	1	1	0
II	2	3	0	3
III	1	0	3	0

- Use of corticosteroids on the face within 2 weeks of first treatment.
- Use of topical tretinoin for at least 1 month prior to enrolment.
- Tanned skin around wrinkle site.
- Topical medicated treatment at the treatment site for the duration of the study.
- Known diseases:

  A. Skin: vitiligo, psoriasis, severe eczema, and poor skin healing.
  B. Chronic or acute: active infection, immunosuppression, coagulation problem, peripheral arterial disease, hematologic abnormalities, vasculitis, and history of epilepsy.
- Pregnancy.
- Alcohol or drug abuse before and during the study.
- Participation in another study which may interfere with the results of this trial during the 4 weeks preceding this study.

Pretreatment Evaluations

- Informed consent.
- Detailed history.
- Exclusion/inclusion criteria.
- Subject randomization.
- Pretreatment with LumiPhase-R (660 nm) for groups B.1 and B.2.
- Digital photography.

Ablative Fractional Resurfacing Treatment

The Lux 2940 Er:YAG laser (Palomar, Boston USA) fractional resurfacing treatment protocol was used, according to the manufacturer's recommended treatment guidelines.

Prior to the first treatment, a test spot(s) was conducted to confirm the safety of the treatment parameters in each subject. The location of test spots was on the neck or body site with similar skin texture and color, preferably in close proximity to the treatment area. After the test spots were administered, skin response (e.g., erythema, bleeding) was recorded using a subjective grading scale. Once the safety of the selected parameters had been confirmed, treatment began.

Prior to treatment, the areas were gently cleansed with mild soap and water and wiped clean with an alcohol wipe. Any visible hair was shaved before cleansing. Photographs were taken pretreatment and immediately posttreatment. Treatment sites included the periorbital, perioral or other facial area,

neck, chest, or other body site as deemed appropriate by the investigator (mainly periorbital or full face).

Pain tolerance at each treatment site was assessed using a 10-point numerical rating scale for pain intensity. The patient self-rated their level from 0 (no pain) to 10 (most extreme pain imaginable). If discomfort during treatment became unacceptable (typically pain ratings > 6), the treatment was either limited to a lower parameter range or topical and/or intradermal anesthetic was administered before continuation to higher treatment parameters. Immediately post-treatment, clinical assessment of skin response was recorded.

Anesthesia

The use of pretreatment topical anesthesia, such as EMLA® or Maxilene 5 (ElaMax®), was optional and at the discretion of the investigator. During treatments, subjects could be given a local intradermal injection of 1–2 % lidocaine with 1:100,000 epinephrine for areas treated with more aggressive energy settings.

Subjects were instructed on post-treatment care of the treatment area including the use of sun protection and sun avoidance.

Lumiphase-R/IR Treatment (Group A)

The PBM LED treatment involved the application of 660 nm (±10 nm) red light delivered in a sequential pulsing mode like a morse code (D50: duty cycle 50 %) with an irradiance of 50 mW/cm^2 (fluence 4 J/cm^2) and a treatment duration of 160 seconds followed by CW (continuous wave) infrared at 850 nm (±10 nm) for 10 minutes with a total fluence of 18 J/cm^2 (irradiance 30 mW/cm^2) using a LumiPhase-R/IR* device (OpusMed, Montreal, Canada). The spot size was 20 × 23 cm. No cooling method was used.

Lumiphase-R *Compact* for Home Use (Groups B.1 and B.2)

The PBM LED treatment involved the application of 660 nm (±10 nm) red light delivered in a sequential pulsing mode (D50) with an irradiance of 50 mW/cm^2 (fluence 4 J/cm^2) and a treatment duration of 160 s using the LumiPhase-R Compact* device (Opusmed, Montreal, Canada). The spot size was 10 × 6 cm. No cooling method was used.

Group A ($n = 3$): Subjects received LED treatments in the office immediately after as well as 1, 2, 3, and 4 days post-2940 procedure. One half of the face was treated and the other half was not.

Group B.1 ($n = 4$): Subjects received LED treatments in the office pre-2940 procedure and performed at-home LED treatments once daily pre- (starting 2 days before) and post-2940 procedure for 30 days (at home), or until redness was resolved. Both sides of the face were treated with LEDs.

Group B.2 ($n = 4$): Subjects received LED treatments in the office pre-2940 procedure and performed at-home LED treatments once daily pre- (starting 2 days before) and post-2940 procedure for 30 days (at home), or until redness was resolved. One half of the face was treated with LEDs and the other half was not.

Group B.3 ($n = 3$): Control group. Subjects receiving no LED treatments post-2940 procedure.

All groups received bilateral 2940 laser treatments.

*Lumiphase devices used (R/IR & Compact) in the study were provided by Opusmed inc. (Montreal, Canada), and were available in Canada and USA when the study was performed. LED parameters including sequential pulsing modes were chosen based on former studies [6, 7].

Immediately after treatment, subjects were asked to rate the pain on a scale of 1 to 10. The treatment and control areas were photographed. Objective measurements were performed with a dermaspectrometer (Erythema index) after every photograph on days 0, 1, and 7. Subjects were instructed on post-treatment care of the treatment area including the use of sun protection and sun avoidance.

Follow-up Visits

The subjects returned to the clinic for follow-up visits 1, 4, 7, 14 days and 1 and 3 months after treatment. At the last follow-up visit, subjects were given the option to receive LED treatments of the LED untreated side. The treatment area and control sides were photographed. Objective measurements were performed with a dermaspectrometer (Erythema index) after every photograph on days 0, 1, and 7. Subjects were instructed on posttreatment care of the treatment area including the use of sun protection and sun avoidance.

Study Endpoints

Subject Satisfaction Questionnaire

Subjects were also asked to evaluate their overall satisfaction at the post-treatment visits. They were asked to rate the treatment procedure (length, frequency, and comfort) using the following scale:

1 = not satisfied

2 = little satisfaction
3 = somewhat satisfied
4 = satisfied
5 = very satisfied

Subjects were asked to rate the likelihood of undergoing this entire procedure again or recommending it to others using the following scale:

1 = never
2 = little likelihood
3 = some likelihood
4 = likely
5 = definitely

Subjects were asked to rate the overall improvement in the appearance of the treated area using the following scale:

1 = no improvement
2 = little improvement
3 = some improvement
4 = significant improvement
5 = complete improvement

Side Effects Scale

Subjects were asked to rate their side effects on a severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) for pain, erythema, swelling, bleeding, running, dryness/tightness, peeling, scabs, and brownish-skin on days 1, 2, 3, 4, 5, 6, 7, and 14 as well as on months 1 and 3.

Clinical Assessment of Digital Photographs and PRIMOS

Close-up digital photographs of treated and untreated sides, eyes closed, were taken using Canon EOS 40D pre and post on days 1, 4, 7, 14, and months 1 and 3. A PRIMOS 3-D micro-topography measurement was also performed pre and at month 3. Emphasis was placed on keeping the ambient lighting and camera angles exactly the same for each scheduled photograph during the study. Three blinded medical evaluators were instructed to indicate, for each randomly presented photograph, the severity level for the following signs: erythema, edema, scaling/crusting, bronzing, textural changes, hyperpigmentation, and hypopigmentation using the following scale: 0 = none, 1 = mild, 2 = moderate, 3 = moderately severe, and 4 = severe. They were also instructed to evaluate the level of improvement in rhytids from the baseline photograph (pretreatment) using the following scale: 0 = none, 1 = mild, 2 = moderate, 3 = good, and 4 = excellent and provide a wrinkling classification score (I, II, or III) and sub score (1–9) using the Fitzpatrick scale for degree of wrinkling and elastosis [8].

Dermaspectrometer Readings

Objective measurements (erythema index) were performed with a dermaspectrometer (Cortex Technology, Hadshund, Denmark) after every photograph on days 0, 1, and 7.

Statistical Analysis

For every measurement (erythema, edema, etc.) data were analyzed using type III sum of squares statistical analysis with $p < 0.05$ as our level of significance.

Results

Subject Satisfaction Questionnaire

The mean satisfaction score was of 4.7, suggesting that, overall, subjects were satisfied to very satisfied with the procedure. One third of patients reported significant improvement on the treated side while 90 % of subjects stated that they would "definitely" undergo this entire procedure again or recommend it to others.

Side Effects Scale Rated by Patients

Data were collected comparing left to right side of the face photographic (negative values suggesting improvement) percent difference in side effects as a function of time and group. Differences in severity ratings were observed for pain, erythema, swelling, bleeding, running, dryness/tightness, peeling, scabs, and brownish skin at all time points.

Clinical Assessment of Digital Photographs by Blinded Observers

Overall, following blinded observer evaluation, the left to right side of the face percent change showed that LED treatments reduced the clinical signs (essentially: erythema—Fig. 1 and edema—Fig. 2) mainly in the first few days (D4 to D14) for groups A and B.2 (erythema $p < 0.05$, edema $p < 0.05$). A typical reduction in erythema and edema is shown in Fig. 3 for three patients from group B.2. As expected, no important differences were observed for groups B.1 and B.3, as these groups received the same treatment regimen on both sides of the face.

Rhytid Improvement

As expected, rhytids were maximally improved at M3 on both sides for all groups; improvement ranging from 32–62 % (PRIMOS Ra and Rz measurements). However, no significant advantage was shown on LED-treated sides either from

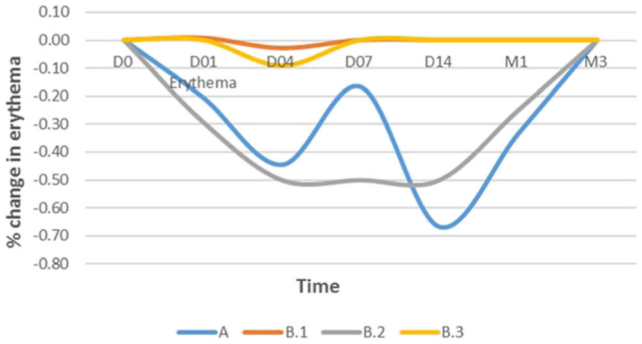

Fig. 1 *Left* to *right* side of the face percent change in erythema severity as a function of days and groups

blinded observer evaluation or by objective PRIMOS micro-topographic measurements.

Dermaspectrometer Readings

Objective measurements of erythema (erythema index) were performed with a dermaspectrometer on days 0, 1, and 7. Results showed a reduction in erythema at both day 1 and day 7 with the greatest reduction observed at day 1 for group B.2 (-15 %, $p < 0.05$). At day 7, only groups A and B.2 demonstrated a decrease in erythema index on the LED-treated side ($p < 0.05$) (Fig. 4).

Discussion

Over the last few years, PBM has been demonstrated to be a promising therapeutic modality for a wide range of dermatological and cosmetic applications. These include photorejuvenation, acne, photoprevention, vitiligo, herpes virus, psoriasis, scars, the treatment of alopecia (hair loss), cellulite, and undesirable fat deposits [9]. More recently, the use of PBM has been described to accelerate wound healing recovery (essentially to reduce erythema) after some cosmetic procedures [5, 10–12].

Gupta et al. showed that wavelength is a key parameter in promoting the healing of dermal abrasions [13]. Indeed, the

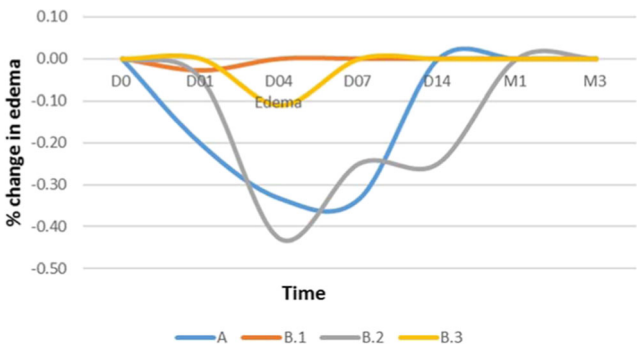

Fig. 2 *Left* to *right* side of the face percent change in edema severity as a function of days and groups

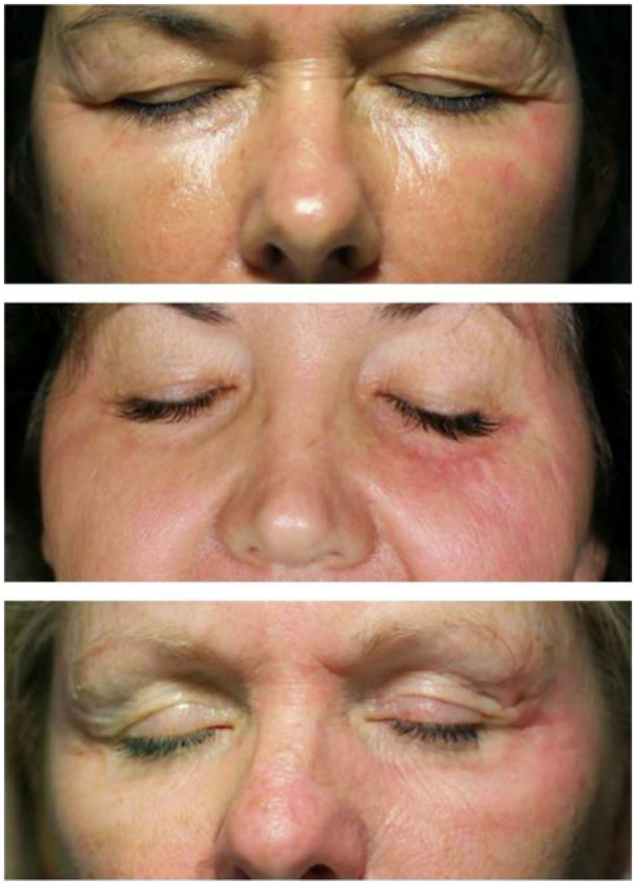

Fig. 3 Digital photographs of three patients in group B.2 at day 4 post-AFR treatment. The LED-treated side (*right side*) shows a significant reduction in erythema and edema

635 and 810 nm wavelengths were found to be the most effective compared to the 730 and 980 nm ones. Also, it has been shown that two combined wavelengths may enhance PBM tissue regenerative response or may be antagonize each other [14••]. Also, pulsing provides additional upregulation of collagen production in wound healing processes compared to CW mode [6, 7].

Conversely, Bay et al. reported no erythema reduction ($n = 20$) after using PBM ($\lambda = 830/590$ nm combination) post-AFR on normal (non-lesional) upper back skin [15]. However, despite the use of a questionable wavelength

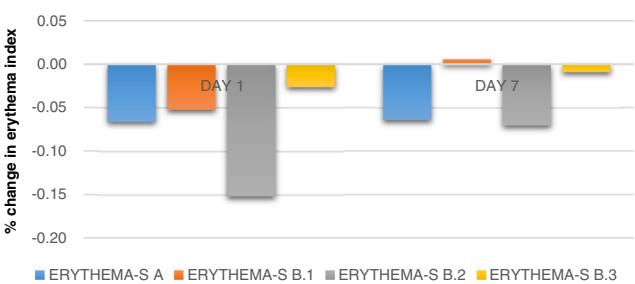

Fig. 4 *Left* to *right* side of the face dermaspectrometer measurements at days 1 and 7

combination, skin reflectance objective measurement was performed only once at day 4.

In the present study, we are clearly showing that there is a significant benefit using PBM at 660 nm alone (or combined with 850 nm as in group A) from an LED light source which emits light in either pulsed and/or continuous wave (CW) modes, applied post-AFR (2940 nm Er:YAG) laser procedure to accelerate ablative treatment sequelae and, as a result, recuperation time. Above all, we found that erythema and edema were significantly reduced in the first week post-AFR, according to blinded observer evaluation (digital photography). Furthermore, blinded observer assessment correlated with objective erythema measurements (dermaspectrometer) at days 1 and 7 post-AFR.

The most remarkable results were obtained in group B.2 [unilateral at-home pulsed 660 nm PBM pre-(2 days)/post-(30 days) AFR] which showed much faster recuperation in the first week on the LED-treated side. Since group A [unilateral in-office pulsed 660 nm/850 nm PBM post-(4 days) AFR] did not respond as much as group B.2, one may assume that starting PBM pre-(2 days) AFR preconditions the skin, providing additional beneficial effects in the form of greater erythema and edema reduction in the first week as compared to the situation when it is applied only after AFR. This preconditioning of the skin is the photoprevention effect [16, 17, 18•]. To our knowledge, it is the first study reporting such a beneficial effect on AFR wound healing recovery.

Nevertheless, no additive or synergistic effects were found on rhytid improvement at 3 months on the LED-treated side compared to AFR alone. As a matter of fact, bilateral rhytid improvement ranging from 32–62 % (PRIMOS Ra and Rz measurements) was micro-topographically measured at 3 months as expected in all groups. Correspondingly, rhytid improvement did not show superior improvement on the LED-treated side at 1 and 3 months when evaluated by blinded observers.

Overall, patients were satisfied to very satisfied with the procedure with a mean satisfaction score of 4.7. More than one third of patients reported significant improvement (less erythema and edema especially groups A and B.2) on the LED-treated side while 90 % of subjects stated that they would definitely undergo the entire procedure again or even recommend it to others. As for side effects rated by patients, differences in severity ratings were observed for pain, erythema, swelling, bleeding, running, dryness/tightness, peeling, scabs, and brownish skin at all time points as expected. All in all, patients experienced a typical post-AFR wound healing process with the exception of faster healing (less downtime) on the LED-treated side, in the first week.

Although this pilot study involved only a small number of patients ($n = 14$), these preliminary data open the way for further research to better understand the underlying mechanisms of wound healing post-ablative procedures. We should also pay more attention to the potential use, in our daily practice, of PBM to precondition the skin prior to a traumatic event like AFR.

The clinical use of thermal energy-based devices inducing post-treatment wounds is expanding around the world particularly for cosmetic indications. However, patients are more than ever asking for no downtime procedures. PBM may well become an excellent complimentary treatment modality to hasten downtime in the first week, avoiding unnecessary days off at work. It energizes wound healing like the space shuttle's solid rocket boosters enable and assist in its liftoff. As such, the main acute healing event in the skin is lifted off to another level by PBM. The cellular and molecular mechanisms of action of PBM have become reasonably well-understood in recent years [9]. The two principal chromophores are cytochrome c oxidase (CCO) in the mitochondrial respiratory chain and TRPV (transient receptor potential vanilloid) ion channels [17]. Photon absorption leads to dissociation of inhibitory nitric oxide from CCO leading to increased enzyme activity and raised ATP production and a burst of reactive oxygen species (ROS). The extra ATP produced can activate the Na+/K+ ATPase pump. Another type of calcium ion channel, the TRPV, is activated by both visible and infrared light. Calcium signaling is a very important pathway in multiple cell types. Mitochondrial ROS show a triphasic dose-response with two distinct peaks. The nature of ROS is such that it may act as a beneficial signaling molecule at low concentrations and a harmful cytotoxic agent at high concentrations [19]. Changing the redox state of the mitochondrial membrane activates the formation of the transcription factor NF-kB. NF-kB is transported into the nucleus, which causes the expression of more than 150 genes; many of which are involved in wound healing processes and defense mechanisms against cell stress [13]. A better understanding of the mechanism of action will direct clinicians in their treatment approach.

Conclusion

This 14 patient pilot study showed that you can avoid a few days of downtime using PBM post-AFR, especially in reducing erythema and edema in the first week. Surprisingly, there seems to be an additional advantage using PBM not only after but also before AFR to precondition the skin before the skin injury happens. Such a new complimentary treatment approach is very promising since it minimizes the social impact of AFR-induced downtime. Obviously, further studies are needed to validate the use of this complimentary treatment modality and improve treatment parameters to shorten post-AFR wound healing. PBM could even become the silver lining of every laser practice to shorten downtime after all thermal energy-based procedures. It will hopefully become part of

our rapidly expanding treatment armamentarium in order to ultimately improve patient care.

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Compliance with Ethical Standards

Conflict of Interest Dr. Daniel Barolet delares patented technology related to photobiomodulation using sequential pulsing modes.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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