Lasers in Medical Science (2019) 34:343–351
https://doi.org/10.1007/s10103-018-2599-1

ORIGINAL ARTICLE

Local and systemic effects of low-level light therapy with light-emitting diodes to improve erythema after fractional ablative skin resurfacing: a controlled study

Rungsima Wanitphakdeedecha[1] · Thanawan Iamphonrat[1] · Weeranut Phothong[1] · Sasima Eimpunth[1] · Woraphong Manuskiatti[1]

Received: 10 May 2018 / Accepted: 19 July 2018 / Published online: 3 August 2018

Abstract

Therapy with light-emitting diodes (LED) has been associated with the reduction of erythema and accelerated wound healing. LED phototherapy has been used in various clinical practices including post-laser wound healing enhancement. Fractional laser resurfacing is one of the popular dermatological procedures; however, the duration and degree of downtime may limit daily life activity and studies on the effect of LED low-level light therapy (LED-LLLT) on post-ablative laser wound care are still limited. To evaluate local and systemic effects of LED-LLLT on post-ablative laser erythema and wound healing acceleration after fractional ablative laser resurfacing. The study was divided into two arms. First, a prospective split-face randomized controlled and single-blinded study involved 17 patients (split-face group) to determine the local and systemic effect of LED-LLLT. Patients with acne scars or rhytides were treated with a single session of fractional CO_2 laser followed by 830/590 nm LED-LLLT on one side of their faces. The duration of post-laser erythema, the erythema index, and transepidermal water loss were collected at baseline, and compared with 7-daily follow-up visits posttreatment for the non LED- and LED-treated sides. The second controlled arm of the study was performed on an additional 19 subjects (CO_2 group). The patients received a single fractional CO_2 laser treatment without any LED-LLLT with the same follow-up protocol. All measurements were compared with the results from the patients from the split-face group. In the split-face group, the duration of erythema post laser was equal (7.4 ± 2.8 days). No significant reduction in the erythema index and transepidermal water loss was seen in the LED-treated vs the non-treated side (p values = 0.99 and 0.78 respectively). For the second part of the study that compared the results between the split-face group and the control CO_2 only group, the duration of the post-laser erythema was comparable (p value = 0.32). However, the percentage difference of the erythema index from baseline in the split-face group was significantly lower than the CO_2 group on days 1, 4, 5, and 7 post-laser treatment (p value = 0.03 on days 1, 4, 5, and 0.04 on day 7) and the LED-treated side provided the lowest percentage difference of the erythema index followed by the non LED-treated side compared with the control CO_2 only group. 830/590 nm LED-LLLT may provide both local and systemic effects on the degree of post-ablative laser erythema in human skin, however, appropriate protocol settings should be considered to achieve a significant clinical outcome.

Keywords Light-emitting diodes · LED · Wound healing · Post-laser erythema · Systemic effect of LED

Introduction

Light-emitting diodes or LEDs have been applied in low-level light therapy (LED-LLLT) which can cause photoactivation of the target cells without heat or tissue damage. LED-LLLT can reduce pain and inflammation, augment tissue repair, promote regeneration of different tissues and nerves, and prevent tissue damage via various mechanisms occurring after photoactivation [1, 2]. Eight hundred thirty nanometers of LED-LLLT is in the near-infrared spectrum which can stimulate wound healing by modulating fibroblast proliferation and attachment, as well as collagen synthesis [3]. The clinical outcomes from the relevant literature showed that near-infrared spectrum LED-LLLT can speed up the healing process of both acute and chronic ulcers such as herpes zoster wounds, and diabetic and vasculogenic ulcers [3–5]. Moreover, 830 nm LED can accelerate fibroblast

✉ Rungsima Wanitphakdeedecha
rungsima.wan@mahidol.ac.th

[1] Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Pran-nok Road, Bangkok 10700, Thailand

transformation, mast cell degranulation, as well as enhance the chemotactic and phagocytic activity of leucocytes and macrophages; therefore, it may provide a positive effect on skin rejuvenation [6]. Five hundred ninety nanometers of LED-LLLT is in the visible yellow spectrum. The rapid ATP production in mitochondria of cultured fibroblasts after 590 nm LED-LLLT has been observed and the clinical outcomes showed global improvement in facial texture, fine lines, background erythema, and pigmentation [7]. Pretreatment with 590 nm LED has been proposed to precondition the epidermis and enhance dermal tissue interaction when followed by 830-nm LED treatment. Until now, LED-LLLT has been used in various clinical practices such as to accelerate wound healing after surgical procedures, radiation therapy and infection, pain attenuation, skin rejuvenation, and acne treatment [3, 6, 8–12]. In addition, there was a study on 830/590 nm LED in an animal model which demonstrated that identical fractional laser burns on the dorsa of rats which then received LED-LLLT on their abdominal area showed significantly better wound healing than the control group which did not receive LED. The authors proposed that their findings showed LED-LLLT may provide an indirect or systemic effect on unirradiated areas [13]. However, there have not been any definitive clinical investigations on the systemic effect in human subjects.

The fractional ablative laser has become a popular method for nonsurgical skin rejuvenation. Even though the results are less effective than those seen in conventional ablative laser resurfacing, significant improvement in rhytides, atrophic scars, and laxity of the skin have been evidenced after one or two treatments with a diminished degree of post-laser erythema, duration of downtime, and incidence of post inflammatory hyperpigmentation. The 10,600-nm wavelength CO_2 laser is one of the fractional laser systems which achieves a deep-dermal coagulation effect. The recent data from our institute showed that complete re-epithelialization after fractional CO_2 laser took 3–6 days [14]; however mild erythema following the separation of the crusts could last up to 2 weeks (data not shown). The duration and degree of downtime following fractional laser may limit daily life activity.

We, therefore hypothesized that the 830/590 nm LED-LLLT may have a synergistic effect in speeding up wound healing, thus reducing the intensity and duration of post-laser erythema after fractional ablative laser resurfacing. To evaluate this, we designed the present study to assess the local and systemic effect of LED-LLLT on fractional laser-treated human skin compared with completely LED-untreated but laser-treated skin.

Subjects and methods

Patients

This study was approved by the Siriraj Institutional Review Board. After informed consent was obtained, healthy subjects with atrophic acne scars or rhytides aged 18–60 years were enrolled. The exclusion criteria consisted of patients with preexisting skin conditions and photosensitive dermatoses, current smokers, and those who were allergic to topical anesthetic cream, pregnant, or lactating.

Study protocol

This study was divided into two arms to evaluate the local effect and systemic effect of LED-LLLT vs a completely non LED-treated group. In the first arm, we designed a prospective split-face randomized control and single-blinded study (split-face group) to determine the local effect of LED-LLLT vs the systemic effect. Seventeen healthy subjects received a single treatment of lower face rejuvenation with a fractional CO_2 laser (10 mJ and average of 5% skin surface coverage). The treatment areas were cleansed using a mild cleanser, then lidocaine 2.5%, and prilocaine 2.5% cream (a eutectic mixture of local anesthetic, Rascer®) was applied under occlusion for an hour before treatment. We did not use any epidermal cooling device or ice pack during or after treatment. Immediately after laser treatment, one side of the face randomly selected by a block randomization method was treated with an 830/590 nm LED-based phototherapy system (HEALITE II™, Lutronic Corporation, Goyang, South Korea). The other side was masked off with an opaque black material. The LED parameters were an energy density of 60 J/cm^2 at intensity level three (80 mW/cm^2). Each treatment took approximately 13 min (1 min preemptive 590 nm energy on its own followed by approximately 12 min of 830/590 nm LED-LLLT).

As a control against the systemic effect of LED-LLLT, we performed the second arm of this study with fractional CO_2 laser treatment of both cheeks of an additional 19 patients at the same parameters as in the split-face group, but without any post-laser LED treatment (CO_2 group). The data from both cheeks were pooled, then compared with data from patients in the split-face group. The protocol is illustrated in Fig. 1.

All patients were advised to follow the standard post-ablative laser wound care recommendations for their entire faces after finishing this treatment protocol: this consisted of cleansing the treated sites gently with tap water and application of petrolatum ointment four times daily for 1 week. No prophylactic antibiotics or antivirals were given to any patient. Subjects were instructed to avoid exfoliants, to not excoriate healing lesions, to avoid sun exposure, and to wear a broad-

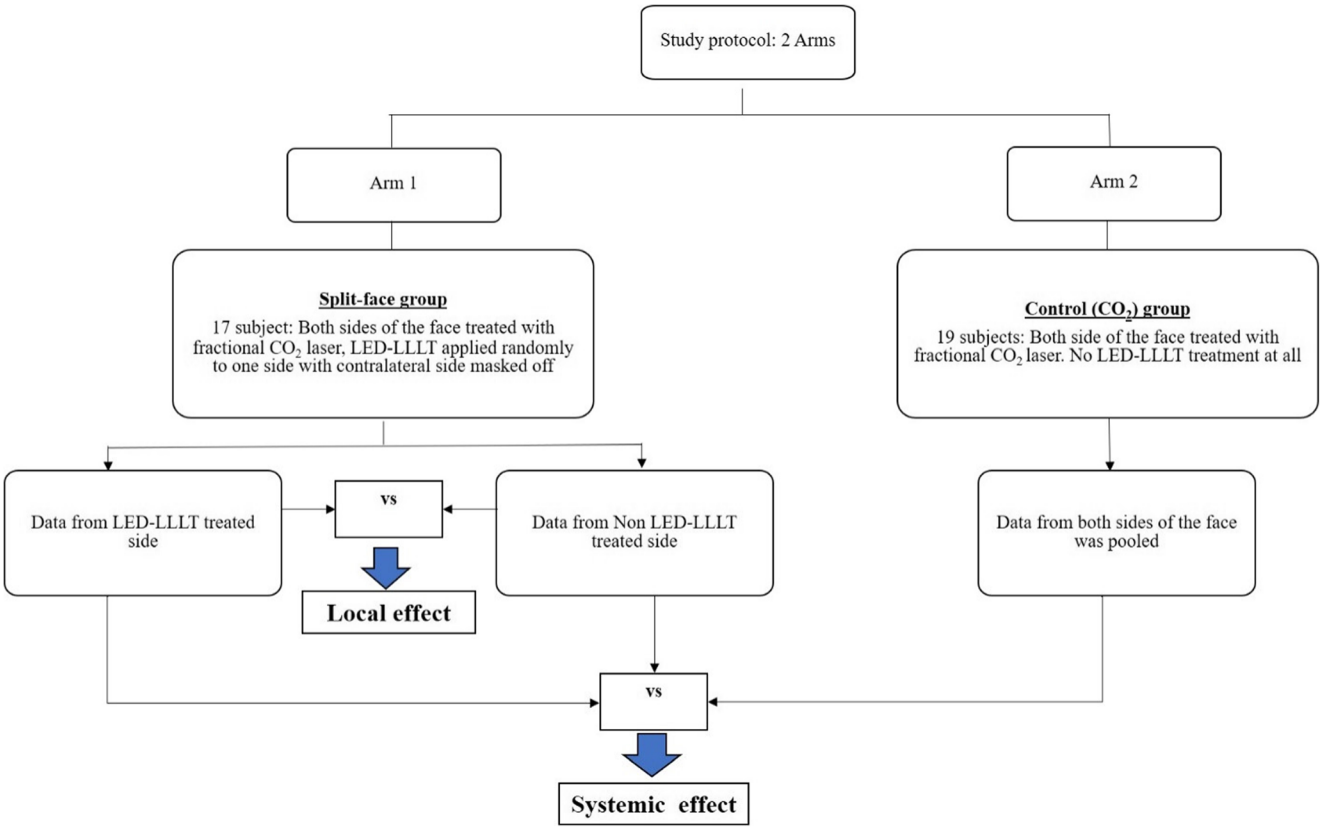

Fig. 1 Study protocol

spectrum UVA/B sunscreen with a sun protection factor of 30 or more after crusting had completely spontaneously separated.

Evaluations

Post-laser erythema, the primary outcome of this study, was evaluated by photographic documentation which was performed at baseline and daily follow-up visits for 7 days posttreatment. Photographs were obtained with identical camera settings, lighting, and patient positioning with facial photo fixture using a Canon PowerShot G9 stand-off camera (OMNIA Imaging System, Canfield Scientific, Inc., Fairfield, NJ). The fixture ensured a fixed distance and fixed angles between the patient and the camera. The duration of erythema was evaluated by a blinded dermatologist via the clinical photographs. The erythema index assigned as an objective evaluation was measured with a Mexameter® (MX18 TM300, Cutometer Dual MPA580, EnviroDerm Services [UK] Ltd.) during the daily 7-day posttreatment follow-up using an identical area of the face.

We also evaluated the skin barrier function determined by the duration of the scab shedding, data being collected from all subjects, and transepidermal water loss measured with a Tewameter® (TM300, Cutometer Dual MPA580, EnviroDerm Services [UK], Ltd.) during the daily 7-day posttreatment follow-up using an identical area of the face.

Statistical analyses

The SPSS statistical package (Version 18, SPSS Inc., Chicago, IL, USA) was applied to compute all data. For the split-face comparison, a paired *T* test was used to compare the duration of the post-laser erythema, duration of scab shedding, erythema index, and transepidermal water loss between each side of the face. A repeated-measure ANOVA was performed to analyze the trend of the erythema index and transepidermal water loss over time. To compare the split-face group with the control CO2 group, data from both left and right cheeks of the additional 19 cases (CO_2 group) were pooled for analysis (n = 38). We used a Kruskal-Wallis test and post hoc testing with a Dunn-Bonferroni test to compare the duration of the post-laser erythema, duration of scab shedding, percentage of difference in the erythema index, and transepidermal water loss from baseline among those groups. The p value that was equal to or less than 0.05 was considered to indicate a statistically significant difference.

Table 1 Demographic data

	CO_2 ($n = 19$)	Split face ($n = 17$)
Age, mean (SD)	28.8 (3.7)	34.7 (6.9)
Gender		
Female, *n* (%)	17 (89.5%)	13 (76.5%)
Male, *n* (%)	2 (10.5%)	4 (23.5%)
Fitzpatrick skin type		
Skin type III	2 (10.5%)	2 (11.8%)
Skin type IV	16 (84.2%)	15 (88.2%)
Skin type V	1 (5.3%)	–

Results

Arm I: split-face study

There were 17 cases (split-face group) enrolled in this arm of the study consisting of 13 females (76.5%) and 4 males (23.5%) with a mean age of 34.7 ± 6.9 years. Most of them were Fitzpatrick skin type IV (88.2%) while the remainder were skin type III (11.8%). (Table 1).

A mild degree of post-laser erythema was found in all cases (Fig. 2). The mean duration of post-laser erythema on the non-LED-treated side and LED-treated side were equal (mean ± SD = 7.4 ± 2.8 days) and the mean duration of scab shedding between the two sides was comparable which was 5.8 days in the non LED-treated side and 6 days in LED-treated side (p value = 0.34). The objective evaluation by the erythema index and transepidermal water loss showed no statistically significant difference either (p values = 0.99 and 0.78 respectively, Figs. 3 and 4).

Arm II: control CO_2 only group

We enrolled an additional 19 patients (CO_2 group). Patients received only fractional CO_2 laser on both cheeks without LED treatment and data from both cheeks were collected for analysis ($n = 38$). The patient demographic data are shown in Table 1. The majority were females (89.5%) with Fitzpatrick skin type IV (84.2%). The mean age of patient was 28.8 ± 3.7 years old.

A mild degree of post-laser erythema was found in the CO2 group subjects, similar to the split-face group. The mean durations of the erythema and scab shedding were 8.3 days and 6.6 days, respectively. Compared with the data from the split-face group, the duration of scab shedding was comparable, whereas the duration of the erythema in the split-face group tended to be shorter than in the CO_2 group (7.4 days vs 8.3 days), however, there was no statistically significant difference (p value = 0.32, Table 2).

For the objective evaluation, the erythema index and transepidermal water loss baseline data of the CO_2 group and split-face group were not comparable (Tables 3 and 4). Therefore, we used the percentage difference from baseline for the statistical analysis among those groups. The percentage difference in the erythema index from the baseline of the split-face group was lower than the CO_2 group and statistically significant differences were found on days 1, 4, 5, and 7 after treatment (Table 3 and Fig. 5). The LED-treated side in the split face group provided the lowest percentage difference of the erythema index followed by the split-face without LED (non LED-treated side) and the CO_2 group. Post hoc analysis showed a significant lower percentage change in the erythema index in the LED-treated side of the split-face group than the CO_2 group on days 1, 4, 5, and 7, whereas the non

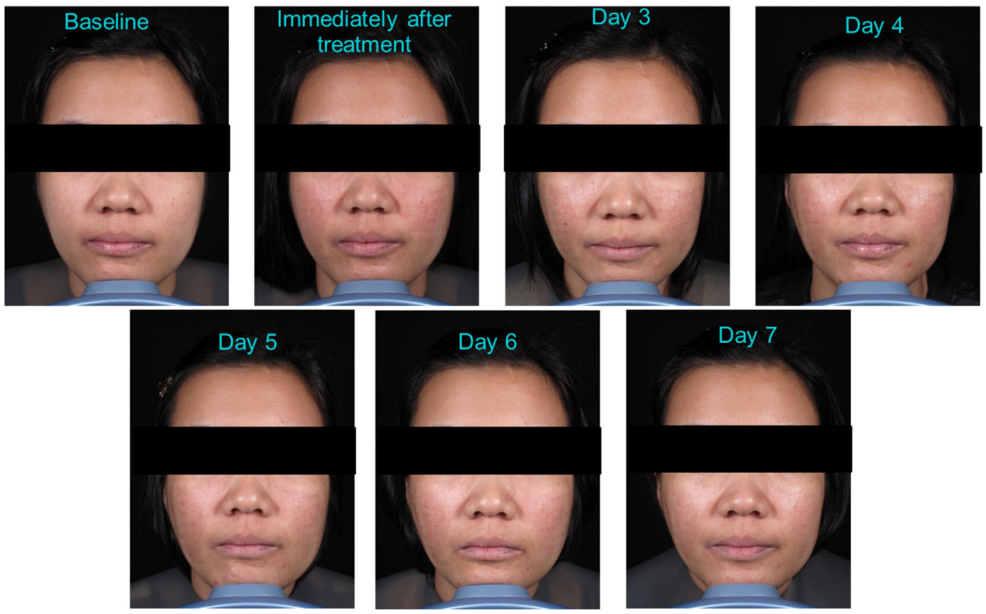

Fig. 2 These pictures illustrate one patient in the split-face group. She had a comparable degree of mild erythema between the non LED- and LED-treated sides on the 7th day of the follow-up period after treatment

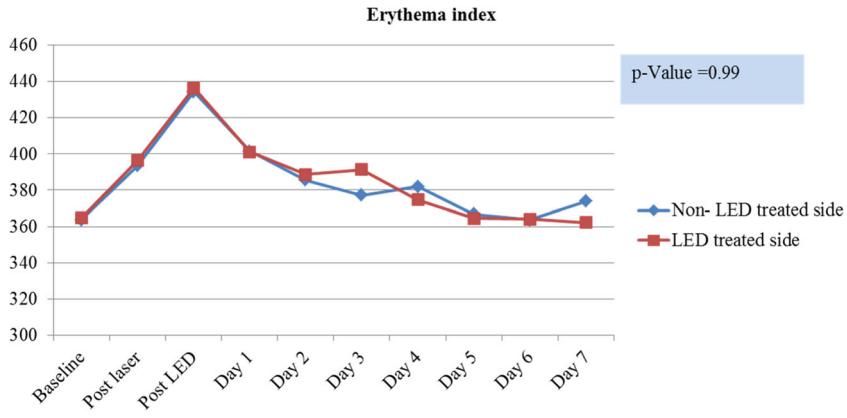

Fig. 3 Erythema index with a Mexameter in the split-face group

LED-treated side showed a significant lower percentage change in the erythema index than the CO_2 group only on day 1 (Table 4). On the other hand, the percentage difference of transepidermal water loss among all of the groups showed no statistical difference (Table 5 and Fig. 6).

Discussion

LEDs for clinical indications have been developed as a light source for low-level light therapy (LLLT). In an LLLT procedure, the incident photon to tissue energy exchange induces a response which is both athermal and atraumatic, but which is able to change the biological activities of the cells, referred to as "photobiomodulation" or "photoactivation". In 1998, NASA developed "NASA LEDs" in its Space Medicine Laboratory which have less divergence, much higher and more stable output powers, and quasimonochromaticity properties (the latter meaning that, although noncoherent, nearly all photons are at the rated wavelength). Furthermore, these properties, in combination with the intensity-enhancing photon interference phenomenon that is produced by planar arrays of LEDs, have the abilities to provide optimum beneficial bioreactions without heat or tissue damage. When compared with surgical lasers, the maximum power output of LEDs is measured in milliwatts. They provide a much gentler delivery of the same wavelengths of light at a substantially lower irradiance or power density.

Surgical lasers depend for their clinical effect on a mainly photothermal reaction, with certain short-pulsed lasers based on the theory of selective photothermolysis, whereby a pigment is the wavelength-specific target for the visible and near-infrared waveband and water for the longer infrared waveband. LEDs, on the other hand rely, on direct absorption in specific chromophores as the receptors to initiate their biological reaction. The main mechanism associated with photobiomodulation has been postulated to be mitochondrial in nature, resulting in enhanced ATP synthesis in addition to the induction of calcium ion (Ca^{++}) and proton (H^{+}) signaling compounds. In the case of visible light from the yellow and red wavebands, the major chromophore is the end terminal enzyme of the mitochondrial respiratory chain and cytochrome c oxidase (CCO) [15, 16]. CCO has its main absorption peak around 633 nm, but 590 nm also efficiently activates the mitochondrial respiratory chain components and results in the initiation of a photochemically-mediated cascade of intracellular reactions. These include increased ATP production, modulation of small levels of reactive oxygen species,

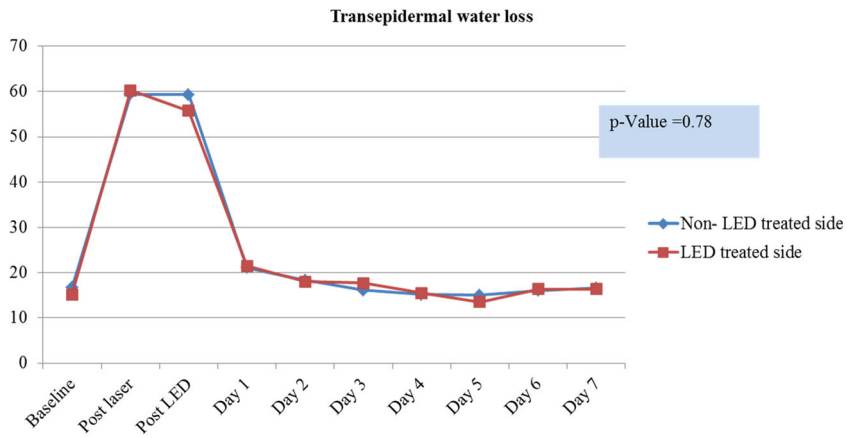

Fig. 4 Transepidermal water loss with a Tewameter in the split-face group

Table 2 Duration of erythema and scab shedding

Patient's evaluation	CO_2 group ($n = 38$)	Split face without LED ($n = 17$)	Split face with LED ($n = 17$)	p value
Duration of erythema (days)	8.3 (2.1)	7.4 (2.8)	7.4 (2.8)	0.32
Scab shedding (days)	6.6 (2.1)	5.8 (1.9)	6.0 (1.9)	0.39

reduction and prevention of apoptosis, stimulation of angiogenesis, increased blood flow, and induction of transcription factors. Moreover, these pathways can lead to fibroblasts proliferation and migration, cytokines, growth factors and inflammatory mediator modulation, and an increase in antiapoptotic proteins [1, 2, 12, 15, 16].

Five hundred ninety nanometers of LED has also been observed to provide a rapid increase in ATP production in mitochondria of cultured fibroblasts and the clinical outcomes showed global improvement in facial textures, fine lines, background erythema, and pigmentation [7]. More importantly, 590 nm can also target the abundant mitochondria in the epidermal stratum basale and Merkel cells, inducing a rapid increase of extracellular ATP, Ca^{++}, and H^{+} levels to ensure an improved epidermal general condition. In addition, preemptive treatment with 590 nm proceeding ahead of the main wavelength of 830 nm in the system used in the present study could precondition the dermal cells to enhance light/cellular and extracellular interaction with 830 nm LED.

On the other hand, the cellular interaction between near-infrared wavelengths, including 830 nm, is photophysical in nature rather than photochemical, whereby the principle target is cellular membrane chromophores resulting in rotational and vibrational changes in the membrane molecules [17]. This kick-starts the membrane transport mechanisms, in particular the sodium-potassium pumps, and leads to a secondary chemical cascade based on activation of the mitochondria due to the increased energy requirement of the target cells. The end result of both visible and near-infrared energy is however the same, a photoactivated cell, and three things can occur following photoactivation: if the cell is compromised or damaged, repair will occur if possible; if the cell has a function to perform, it will perform it better and faster; if there are not enough of a particular cell, others will be recruited in or mitosis is induced [15].

Near-infrared energy from 830 nm LED-LLLT is known to penetrate well into and beyond the subdermal layer, thus reaching all the target cells in the epidermis and dermis including the keratinocytes, fibroblasts, macrophages, and mast cells: the latter three are particularly important targets when considering post-laser wound healing and the enhanced resolution of sequelae such as inflammation and erythema. A controlled study following full-face laser resurfacing in 50 subjects with an LED-LLLT-treated group compared with a control group revealed wound healing in around half the time, and significantly faster resolution of posttreatment erythema, edema, and pain in the LED-LLLT group [10].

Until now, LED-LLLT has been used adjunctively in a variety of clinical practices, such as to accelerate wound healing after surgical procedure, for radiation therapy and infection, and in pain attenuation, skin rejuvenation, and acne treatment [3, 6, 8–12, 18]. LED-LLLT has also been used in stand-alone skin rejuvenation and acne treatment with excellent results [19, 20]. From the data in all these publications, the anti-inflammatory effect of 830 nm LED-LLLT has been well proven. In addition, the histological and ultrastructural data from the rejuvenation paper by Lee and colleagues show conclusively a renewed extracellular matrix with improvement in both collagen and elastin, and young, active fibroblasts in the LED-treated tissues [19]. The effect of 830 nm LED-LLLT on fibroblasts, among the other dermal cells, clearly accelerates wound healing [12].

Table 3 Erythema index and percentage difference of erythema index from baseline

Day of treatment		CO_2 group ($n = 38$)	Split face without LED ($n = 17$)	Split face with LED ($n = 17$)	p value
Erythema index	Baseline	281.8 (195, 392)	376 (191.5, 491.5)	360 (242.5, 466)	< 0.001
Percentage difference of erythema index (from baseline)	Day 1	23.7 (− 5.7, 65.1)	15.1 (− 15.7, 45.6)	9.1 (− 11.3, 47.6)	0.03
	Day 2	15.3 (− 14.1, 67.1)	9.7(− 19.7, 37.9)	0.4 (− 28.2, 68.4)	0.20
	Day 3	17.4 (− 24.1, 49.2)	4.3 (− 17.2, 37.9)	2.4 (− 16.8, 48.1)	0.1
	Day 4	16.6 (− 14.1, 52.4)	8.0 (− 12.6, 38.3)	0.7 (− 15.2, 34.4)	0.03
	Day 5	9.9 (− 32.3, 44.5)	3.5 (− 19.1, 25.9)	0.8 (− 32.4, 29.7)	0.03
	Day 6	9.6 (− 22.7, 89.8)	−0.3 (− 20.6, 24.7)	−4.1 (− 19.5, 33.2)	0.07
	Day 7	12 (− 17, 52.2)	3.2 (− 13.1, 32.4)	−0.8 (− 21.5, 16.7)	0.04

The median values of these data is shown (min, max)

Table 4 Post hoc testing with the Dunn-Bonferroni test for the percentage difference of erythema index from baseline

Day of treatment		*p* value
Day 1	CO_2 group split face without LED-treated side	0.046
	CO_2 group split face with LED-treated side	0.02
	Split face without LED-treated side—split face with LED treated	0.76
Day 4	CO_2 group split face without LED-treated side	0.058
	CO_2 group split face with LED-treated side	0.02
	Split face without LED-treated side—split face with LED treated	0.67
Day 5	CO_2 group split face without LED-treated side	0.05
	CO_2 group split face with LED-treated side	0.02
	Split face without LED-treated side—split face with LED treated	0.73
Day 7	CO_2 group split face without LED-treated side	0.14
	CO_2 group split face with LED-treated side	0.01
	Split face without LED-treated side—split face with LED treated	0.42

Returning to the present study, the results in the split-face group showed a comparable degree of erythema and skin barrier function on both cheeks (with or without LED treatment) in subjective and objective evaluations. On the other hand, results from the control group in the present study (CO2 fractional treatment only) demonstrated a shorter duration of erythema in the split-face group corresponding with a significantly lower percentage difference in the erythema index on days 1, 4, 5, and 7 in that group compared with the CO_2 group. This meant that patients who received LED on one side of their cheeks tended to show a significantly faster resolution of their erythema in both the LED-treated and -untreated sides, based on the objective erythema index findings, than patients who did not receive LED treatment at all and the maximum effect was found on the cheeks that directly received LED treatment. On the contrary, the duration of scab shedding and transepidermal water loss standing for skin barrier function among those groups were not different. These results could suggest that 830/590 nm LED-LLLT may provide both a local and a systemic effect in reducing erythema post-ablative laser resurfacing of human skin.

Lee et al. studied in a rodent model that the rats with fractional laser wounds to their backs which were subjected to 830/590 nm LED phototherapy (with the same system as used in the present study) of the abdomen showed significantly faster wound healing than the animals that did not receive any LED treatment and they strongly suggested that LED-LLLT may induce a systemic effect to the indirectly and untreated area: however, this study had the limitation of a small sample size [13]. The systemic effect of laser therapy on humans had been proposed previously

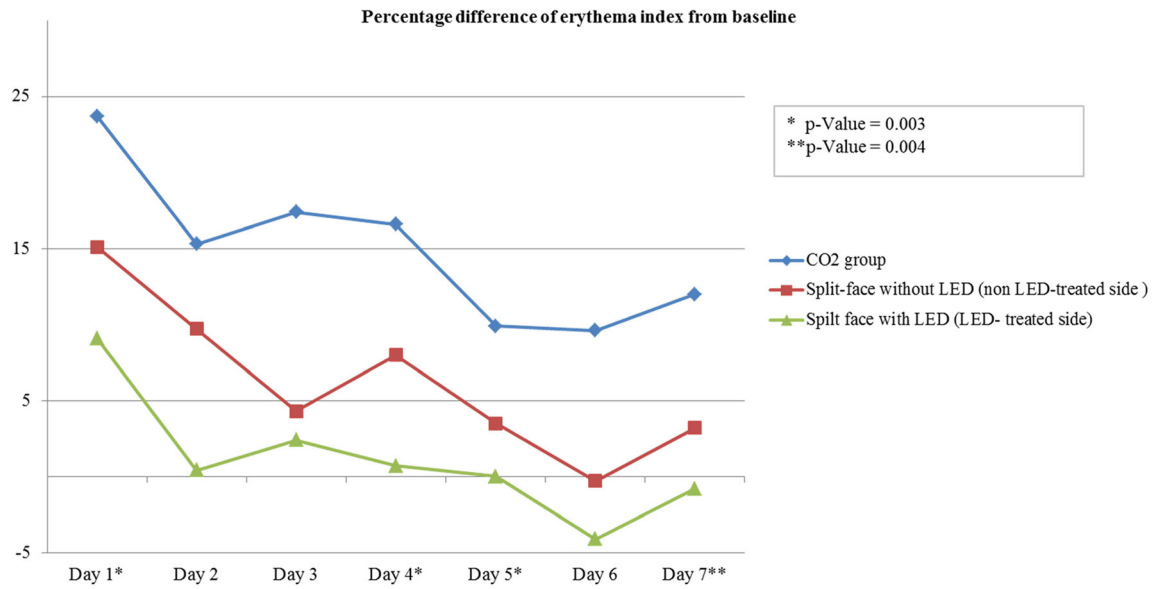

Fig. 5 Percentage difference in the erythema index compared between CO_2 and split-face groups. Lower values show decreasing erythema

Table 5 Transepidermal water loss and percentage difference of transepidermal water loss

Day of treatment		CO_2 group ($n = 38$)	Split face without LED-treated side ($n = 17$)	Split face with LED-treated side ($n = 17$)	p value
TEWL	Baseline	11.1 (4.9, 25.5)	14.9 (7.4, 33.8)	13.7(8.1, 32)	0.007
Percentage difference of TEWL (from baseline)	Day 1	34.0 (− 55.6, 554.4)	47 (− 29.1, 171.6)	59.5 (− 30.6, 127.2)	0.76
	Day 2	3.2 (− 63.9, 228.9)	− 5.7(− 44.6, 175.2)	22.6 (− 31.2, 125.7)	0.75
	Day 3	2.0 (− 72.7, 95.9)	− 2.1 (− 54.1, 122.3)	8.7 (− 6.3.8, 207.4)	0.67
	Day 4	− 5.4 (− 65.1, 79.6)	− 18.0 (− 60.4, 187.6)	− 7.1 (− 70.3, 183.2)	0.73
	Day 5	0.8 (− 68.3, 110.2)	− 18.1 (− 64.8, 311.4)	− 3.8 (− 77.8, 162.5)	0.47
	Day 6	0.1 (− 65.9, 91.8)	− 4.0 (− 60.1, 117.6)	4.0 (− 55.6, 101.0)	0.54
	Day 7	8.7 (− 65.9, 237.8)	− 17.6 (− 58.9, 303.9)	15.9 (− 60, 197)	0.45

These median values of these data are shown (min, max)

by Mester et al. [21]. They observed wound healing on patients with chronic unhealed leg ulcers who received laser therapy on the ulcers on one of their legs than patients who did not receive laser treatment. The authors also subsequently noted wound healing of ulcers on the contralateral unirradiated legs without any further treatment. Our study provides corroborative evidence supporting the hypothesis of the systemic effect associated with LED-LLLT on human skin; however, the exact mechanism is still unclear and further study is required.

We cannot demonstrate the significant local effect of LED in this study especially regarding the clinical outcome. That may be explained from some reasons other than the indirect or systemic effect of LED-LLLT. First, we observed that almost all of the subjects had a mild degree of post-laser erythema which may have resulted from the low fractional laser parameter setting of 5% skin surface coverage: therefore, the degree of post-laser erythema may have been too low to create any difference between local or systemic LED-LLLT treatment. Thus, we plan to increase the area of skin surface coverage in a further study to elicit a greater erythema response. Second, a single-LED treatment session immediately post laser is thought to be suitable and convenient for the patients; however, it may not be enough to provide significant clinical improvement. There have not been many previous studies using the 830/590 nm LED system as used in the present study. A study by Park et al. used 830/590 nm LED-LLLT to treat herpes zoster ophthalmicus in combination with an antiviral drug compared with the antiviral drug alone. In this study, LED-LLLT was applied every 3 days, for a total of four treatments. The healing time was 2–3 days shorter in the LED-treated group with statistical significance [3]. Another controlled study by Lee SY et al. used eight sessions of LED-LLLT for skin rejuvenation over a four-week period and the results showed that the skin roughness (i.e., rhytides) significantly decreased while collagenesis and elasticity significantly increased at a 12-week posttreatment follow up [6]. In the case of 590 nm LED-LLLT, a study by Delan et al. using daily LED treatment for radiation mucositis in which LED post radiation could decrease the severity of mucositis when

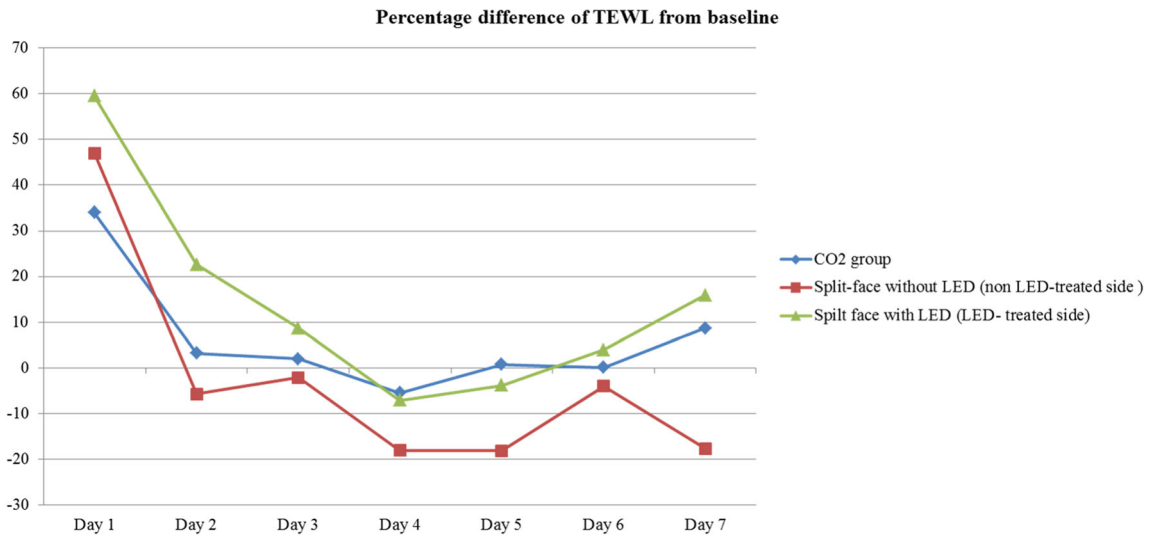

Fig. 6 Percentage difference in transepidermal water loss compared between the CO_2 and split-face groups

comparing with the control [19]. Hypertrophic scar formation following a thyroidectomy is almost inevitable, but in a controlled study by Park and colleagues, 830/590 nm LED-LLLT not only reduced the occurrence of hypertrophic scars compared with the unirradiated control group, but also showed significantly less redness based on Mexameter readings [22]. Again, the protocol required a treatment immediately postoperatively followed by two treatments a week for 3 weeks. The final study to consider is a split-face study by Alster et al., the design of which was similar to our study. They used a single 590-nm LED treatment post-fractional ablative laser and found that only 6 from 20 patients had less erythema on the LED-treated facial halves at 48 h post laser [8]. Of course, based on our and other studies, we have to consider the effect of the systemic influence on the unirradiated side. When comparing these studies, multiple LED treatments may provide a more favorable clinical outcome than a single treatment session. Some evidence has suggested that not only the irradiance and fluence but other modes of LED settings such as a pulsing mode, the frequency of treatment, and precise working distance can also affect the outcome of LED-LLLT. Moreover, the precise number of and intervals between treatment should be paid attention clinically [12].

In conclusion, based on our findings in the present study, near-infrared LED-LLLT was shown to provide both a local and systemic effect in reducing post-ablative fractional laser erythema on human skin compared with a non LED-LLLT control. However, appropriate protocol settings should be considered to maximize the clinical outcome.

Acknowledgements This research project is supported by Faculty of Medicine Siriraj Hospital, Mahidol University. The authors wish to thank Ms. Phassara Klamsawat and Ms. Phonsuk Yamlexnoi for their assistance in recruiting subjects and managing the database.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Avci P, Gupta A, Sadasivam M et al (2013) Low-level laser (light) therapy (LLLT) in skin: stimulating, healing, restoring. Semin Cutan Med Surg 32:41–52
2. Kim WS, Calderhead RG (2011) Is light-emitting diode phototherapy (LED-LLLT) really effective? Laser Ther 20:205–215
3. Park KY, Han TY, Kim IS et al (2013) The effects of 830 nm light-emitting diode therapy on acute herpes zoster ophthalmicus: a pilot study. Ann Dermatol 25:163–167
4. Minatel DG, Frade MA, Franca SC et al (2009) Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies. Lasers Surg Med 41:433–441
5. Caetano KS, Frade MA, Minatel DG et al (2009) Phototherapy improves healing of chronic venous ulcers. Photomed Laser Surg 27:111–118
6. Russell BA, Kellett N, Reilly LR (2005) A study to determine the efficacy of combination LED light therapy (633 nm and 830 nm) in facial skin rejuvenation. J Cosmet Laser Ther. 7:196–200
7. Weiss RA, McDaniel DH, Geronemus RG et al (2005) Clinical experience with light-emitting diode (LED) photomodulation. Dermatol Surg 31:1199–1205
8. Alster TS, Wanitphakdeedecha R (2009) Improvement of postfractional laser erythema with light-emitting diode photomodulation. Dermatol Surg 35:813–815
9. Sadick N (2009) A study to determine the effect of combination blue (415 nm) and near-infrared (830 nm) light-emitting diode (LED) therapy for moderate acne vulgaris. J Cosmet Laser Ther. 11:125–128
10. Trelles MA, Allones I (2006) Red light-emitting diode (LED) therapy accelerates wound healing post-blepharoplasty and periocular laser ablative resurfacing. J Cosmet Laser Ther. 8:39–42
11. DeLand MM, Weiss RA, McDaniel DH et al (2007) Treatment of radiation-induced dermatitis with light-emitting diode (LED) photomodulation. Lasers Surg Med 39:164–168
12. Barolet D (2008) Light-emitting diodes (LEDs) in dermatology. Semin Cutan Med Surg. 27:227–238
13. Lee GY, Kim WS (2012) The systemic effect of 830-nm LED phototherapy on the wound healing of burn injuries: a controlled study in mouse and rat models. J Cosmet Laser Ther 14:107–110
14. Manuskiatti W, Iamphonrat T, Wanitphakdeedecha R, et al. Comparison of fractional erbium-doped yttrium aluminum garnet and carbon dioxide lasers in resurfacing of atrophic acne scars in Asians. Dermatol Surg. 39:111–20
15. Karu TI (1999) Primary and secondary mechanisms of action of visible to near-IR radiation on cells. J Photochem Photobiol B 49:1–17
16. Karu TI (2007) Identifying the photoreceptors. In: Karu TI (ed) Ten Lectures on Basic Science of Laser Phototherapy. Prima Books AB, Grängesberg
17. : Calderhead RG. (2011)Light/tissue interaction in photosurgery and phototherapy. In Calderhead RG, Photobiological Basics of Photosurgery and Phototherapy: A Practical Introduction. Hanmi Medical Seoul, South Korea pp 47–89
18. Calderhead RG, Kim WS, Ohshiro T, Trelles MA, Vasily DB (2015) Adjunctive 830 nm light-emitting diode therapy can improve the results following aesthetic procedures. Laser Therapy 23:277–289
19. Lee SY, Park KH, Choi JW, Kwon JK et al (2007) A prospective, randomized, placebo-controlled, double-blinded, and split-face clinical study on LED phototherapy for skin rejuvenation: clinical, profilometric, histologic, ultrastructural, and biochemical evaluations and comparison of three different treatment settings. J Photochem Photobiol B 88:51–67
20. Lee SY, You CE, Park MY (2007) Blue and red light combination LED phototherapy for acne vulgaris in patients with skin phototype IV. Lasers Surg Med 39:180–188
21. Mester E, Mester AF, Mester A (1985) The biomedical effects of laser application. Lasers Surg Med 5:31–39
22. Park YJ, Kim SJ, Song HS, Kim SK, Lee JH et al (2015) Prevention of thyroidectomy scars in Asian adults with low-level light therapy. Derm Surg 42:526–534