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Photobiomodulation Original Research

Photobiomodulation Reduces Periocular Wrinkle Volume by 30%: A Randomized Controlled Trial

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Abstract

Objective: This study aimed to evaluate red and amber light-emitting diode protocols for facial rejuvenation at the same light dose.
Background: The demand for minimally invasive cosmetic procedures to address skin aging has grown throughout the world. *In vitro* red and amber photobiomodulation (PBM) has been shown to improve collagen synthesis. Meanwhile, red PBM has already been studied in clinical trials; however, a comparison of the use of different wavelengths at the same light dose to reduce periocular wrinkles has not yet been performed.
Methods: This split-face, randomized clinical trial recruited 137 women (40–65 years old) presenting with skin phototypes II–IV and Glogau photoaging scale types II–IV. The individuals received 10 sessions for 4 weeks of red (660 nm) and amber (590 nm) PBM (3.8 J/cm^2), one at each side of the face. The outcomes, measured before and after the treatments, were the periocular wrinkle volume measured by VisioFace® RD equipment; hydration measured by the Corneometer CM 825; skin elasticity measured by the Cutometer Dual MPA 580; and quality of life determined by adapted versions of validated questionnaires [Melasma Quality of Life Scale–Brazilian Portuguese (MelasQoL-BP) and Skindex-29].
Results: There was a significant reduction in wrinkle volume after red (31.6%) and amber (29.9%) PBM. None of the treatments improved skin hydration and viscoelasticity. Both questionnaires showed improvements in participants' quality of life.
Conclusions: PBM, both at red and amber wavelengths, is an effective tool for rejuvenation, producing a 30% wrinkle volume reduction. The technique has strong potential in patients with diabetes or those presenting with keloids, conditions for which highly inflammatory rejuvenating procedures are not indicated.
Clinical trial registration number: REBEC-6YFCBM.

Keywords: low-intensity laser, low-level laser therapy, phototherapy, skin aging, wrinkles

Introduction

The search for cosmetic treatments has increased in recent years due to the increase in life expectancy. According to the United Nations, in 2021, around 10% of the world's population was over 65 years. The average life expectancy exceeds 70 years in both men and women around the world.[1] According to the 2020 statistics from the American Society of Plastic Surgeons, the number of facelift surgeries was 234,374 in the United States, while worldwide, the five most applied minimally invasive procedures reached 10.5 million applications.[2]

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The data presented by the Brazilian Society of Plastic Surgery showed a reduction in surgical procedures from 82.6% in 2014 to 50.1% in 2018, while there was an increase in nonsurgical procedures from 17.4% to 49.9% during the same period.[3] Thus, the demand for minimally invasive cosmetic procedures to address skin aging has grown throughout the world.

Some of the current approaches being used, with the aim of rejuvenation, are peels, fillers, botulinum toxin, cosmetic products, radiofrequency, microneedling, and various forms of phototherapy [intense pulsed light, ablative laser, low-intensity laser, or light-emitting diodes (LEDs)].[4–8] Photobiomodulation (PBM) is a technique based on the use of a low-intensity laser device, or an LED, in a way that the photons are absorbed by the target tissue, producing a biological response.[6,9–11] The clinical use of PBM has shown many promising results in inflammatory conditions, tissue repair, wound healing, and others.[9,12]

For rejuvenation, *in vitro* data have suggested an increase in procollagen I production and gene expression, as well as a reduction in the gene and protein expression of matrix metalloproteinase 1 (MMP-1).[10,13] A few published clinical trials have assessed the effect of PBM on rejuvenation.[12,14–22] However, most of them have evaluated red PBM when compared with a nontreated control, compared or associated with infrared wavelengths, or where there was no comparison with a control group. Hence, clinical trials considering these limitations and those designed to reduce the risk of bias are still needed.

The choice of wavelength is an important parameter for the effectiveness of PBM therapy. *In vitro* and *in vivo* studies, as well as clinical trials, have shown good skin response to red light, associated with repair, healing, anti-inflammatory effects, metabolic improvements, increase in collagen synthesis, and reduction in MMP-1 expression.[23] On the other hand, amber light has been shown to reduce MMP-1 expression and increase collagen production.[24]

Both red and amber wavelengths are absorbed by the chromophore, cytochrome *c* oxidase, which has been considered as one of the main photon-absorbing molecules that mediate the effects of PBM.[25,26] However, red light penetrates the deeper layers of the skin.[27,28] Nam et al.[18] compared red and amber PBM for skin rejuvenation, but the device for applying amber light was polychromatic (411–777 nm, with a central wavelength of 594 nm). Because the irradiance was the same for both devices (7.5 mW/cm^2), the effective light dose for amber light in the polychromatic device was lower.

There are no clinical reports comparing the efficacy of these wavelengths in skin rejuvenation when using the same light dose in monochromatic devices. Thus, in this study, the authors aimed to compare these wavelengths at the same light dose to determine whether the efficacy varied due to the wavelength or the light dose. The study evaluated the periocular wrinkle volume and percentage reduction when treated with red and amber LEDs and compared the efficacy between the wavelengths.

The researchers have hypothesized that the amber and red wavelengths produce similar rejuvenating effects on the face because they both reduced the MMP-1 expression and increased collagen production by activating cytochrome *c* oxidase.

Methods

Trial design

A two-arm, parallel, randomized, double-blind (patients and the outcome assessors), split-face (1:1 allocation ratio), unicentric clinical trial was performed to evaluate the effects of PBM on facial rejuvenation. The study was conducted at the Universidade Nove de Julho, Brazil, between May 2018 and November 2018. This work has been written according to the CONSORT Statement (See Supplementary Table S1, CONSORT 2010 Checklist.)

Ethics and registration

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Research Ethics Committee of Nove de Julho University (Acceptance No.: 2.550.732). The trial has already been registered in the Registro Brasileiro de Ensaios Clínicos (REBEC No.: RBR-6YFCBM) on June 17th, 2017, and described in detail in the published protocol.[29] Informed consent was obtained from all of the individual participants who were included in the study.

Eligibility criteria

Eligibility was assessed for all of the women who registered at the website. This trial included women (40–65 years old) who presented with skin phototypes II, III, and IV (Fitzpatrick Scale) and with signs of aging II, III, and IV (Glogau Scale).

Participants who demonstrated uncontrolled thyroid disorders or any pathology of the skin; had undergone any facial esthetic procedure; had received a facial filling in the last 12 months; were pregnant or breastfeeding; were professional drivers; were presenting great laterality of skin aging; and were using retinoic acid, any vitamin A derivative, cosmetics, or medications that may increase the photosensitivity of the skin were excluded from the study.

Eligible participants were informed about the objectives, risks, and benefits of the study and were asked to fill out an informed consent form.

Interventions

All of the participants had their faces cleaned with a neutral cleansing soap and received eye protection with goggles, covering the entire globe of each eye. These participants received PBM to treat their periocular wrinkles using red (660 ± 10 nm as the control group) and amber (590 ± 10 nm) LED devices, with one color on each hemiface (determined by randomization). Both of the devices emitted the same sounds and were similar in shape.

The therapist was aware of the wavelength emitted by each device. Each LED device (Cicatrillux, Cosmedical, Brazil) comprised 36 LED units that were uniformly distant from each other (1.5 cm), in a total area of 66.5 cm^2 (9.5×7 cm), while delivering at 6.4 mW/cm^2 for 10 min (600 sec) and 3.8 J/cm^2 at continuous emission (Fig. 1 and Table 1).

Group A (control) received PBM with a red LED device on the right side of their face and an amber LED device on the left side of their face. Group B received the opposite; the participants received PBM with a red LED device on the left

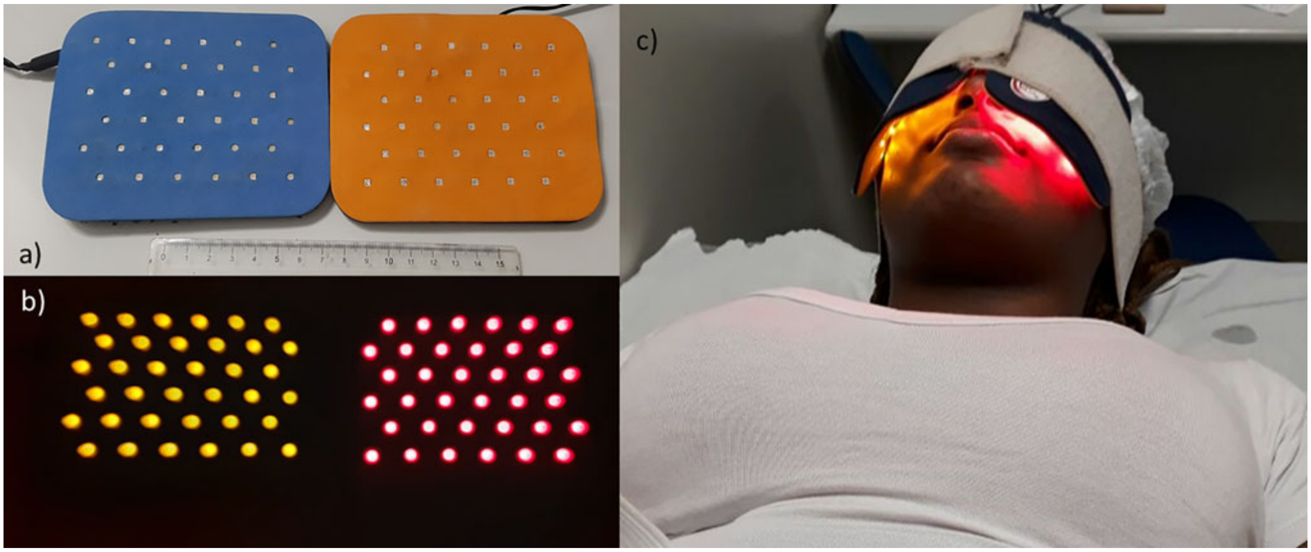

FIG. 1. LED devices—Cicatrillux, Cosmedical, Brazil. **(a)** Amber (left) and red (right), with LED devices turned off, **(b)** turned on, and **(c)** the patient receiving the treatment. LED, light-emitting diode.

side of their face and an amber LED device on the right side of their face (Fig. 1c). Thus, each patient received both red (control) and amber treatments. Each session lasted for 10 min (at each wavelength). The device was applied by contact with the skin, as positioned by the researcher, with an automatic timer.

The complete treatment comprised 10 sessions (2–3 sessions/week, within 1 month).

Procedures. The blinded assessor welcomed the participants and checked whether they were eligible for participation. Demographic and personal habits were collected alongside the outcome measures. The participants were then allocated into groups based on previously randomized envelopes. Each participant received a total of 10 sessions. After completing the treatment, the outcomes were measured again.

Randomization and blinding. Randomization and blinding were described in detail in the study protocol.[29] Briefly, randomization was performed by a researcher who was not directly involved in the patient's treatment, using Excel 2013 software (Microsoft, USA). The allocation information was written on paper and placed into sequentially numbered, sealed, and opaque envelopes. The researcher responsible for the treatment opened the envelope, in sequence, immediately before performing the procedure. This researcher was instructed to not disclose the group allocation to the other researchers, assessors, or participants in the study.

For blinding, patients received goggles for eye protection and to avoid knowing the color of light that was applied to each hemiface. Besides, the researcher applying the procedures was different from the ones assessing the outcomes.

Outcomes

The primary outcome was the volume of wrinkles in the periocular region. The secondary outcomes were hydration in the temporal region, skin elasticity, and quality of life.

Table 1. The Light Parameters That Were Used for the Study

Parameter	*Amber LED*	*Red LED*
Central wavelength (nm)	590	660
Spectral width (nm)	10	10
Operation mode	Continuous	Continuous
Average radiant power (one LED/mW)	5	5
Beam area on target tissue—one LED (cm^2)	1.28	1.28
Total number of LEDs	36	36
Irradiated area per application (cm^2)	66.5	66.5
Irradiance at the target (mW/cm^2)	6.4	6.4
Exposure duration (sec)	600	600
Radiant exposure (J/cm^2)	3.84	3.84
Radiant energy per application (J)	255.4	255.4
Total area irradiated (cm^2)	66.5	66.5
Application technique	Contact	Contact
Number and frequency of sessions	10 Sessions, 2–3 times/week	10 Sessions, 2–3 times/week

LED, light-emitting diode.

The volume of wrinkles in the periocular region (crow's feet) was measured by using the VisioFace® RD (CK Electronic, Cologne, Germany) equipment. The device registered a high-resolution image, with standardized lighting and distance from the patient's face to the camera, to allow a comparison of the pictures.[30,31] The equipment analyzed the area, depth, and volume of the wrinkles in square pixels, pixels, and cubic pixels, respectively. The wrinkle volume was converted to cubic millimeters (mm^3).

The Corneometer® CM 825 (CK Electronic) probe was used to evaluate skin hydration.[32–34] The measurement was based on the capacitance evaluated by the dielectric constant of the skin, which varied as a function of the water content. It evaluated a depth of around 10–20 μm in the epidermis, mainly in the stratum corneum. The results obtained varied on a scale from 0 to 100, where the higher the capacitance value, the greater the hydration.

The viscoelasticity of skin was evaluated with the Cutometer® Dual MPA 580 (CK Electronic) instrument. The measurement was based on negative pressure suction of the skin to be analyzed, drawing the skin into the equipment aperture and releasing it after a specific time. The ability of the skin to return to the initial position, called elasticity, was presented here by the R1 parameter.[35] A decrease in the R1 parameter meant an improvement in the skin reverting to the initial position after the application of stress. Measurements were performed in triplicate and the data are presented as average values.

The participants answered adapted versions of questionnaires that assessed the quality of life of participants with dermatological diseases: the Skindex-29 and Melasma Quality of Life Scale–Brazilian Portuguese (MelasQoL-BP). Due to the adaptations, these questionnaires were evaluated for reproducibility and internal consistency by using test–retest reliability. For this endeavor, 20 volunteers, external to the survey, answered the questionnaires twice, with a 30-day interval between the responses, and statistical analysis was performed.

The adapted MelasQoL-BP and Skindex-29 questionnaires were evaluated in terms of internal consistency (Cronbach's α) and reproducibility (Cohen's κ). Cronbach's alpha was 0.920 for the adapted MelasQoL-BP Questionnaire and 0.955 for the adapted Skindex-29 questionnaire. These values indicated excellent internal consistency.[36,37] In the reproducibility evaluation of the MelasQoL-BP questionnaire, 50% of the questions presented substantial agreement and 30% presented moderate agreement. Only one issue showed considerable agreement.

In the reproducibility evaluation of the Skindex-29 questionnaire, 60% of the questions presented substantial agreement, 30% presented moderate agreement, and ~10% presented excellent agreement. Only one issue showed considerable agreement.[38]

Sample size, statistical analyses, and characterization of the study population

While considering that no studies have reported on wrinkle volume using the VisioFace equipment, after designing the study protocol, a pilot study was performed to determine the effect size. Using the effect size obtained for 10 patients (0.214), α of 5%, and β of 20% and considering a *t*-test for the matched pairs, G*Power software (V3.1.9.2, Dusseldorf, Germany) was used to derive a sample size of 137 participants. While including a dropout of 5%, 143 participants were included in the study.

Table 2. Characteristics of the Participants at Baseline

Variables	n = *83 (100%)*
Age (years) (mean ± SD)	52.4 ± 6.8
Fitzpatrick scale, *n* (%)	
Phototype II	27 (32)
Phototype III	37 (45)
Phototype IV	19 (23)
Glogau scale, *n* (%)	
II	31 (37)
III	39 (47)
IV	13 (16)
Sun exposure,[a] *n* (%)	39 (47)
Healthy diet,[b] *n* (%)	79 (95)
Water intake,[c] *n* (%)	37 (45)
Sunscreen use,[d] *n* (%)	57 (69)

The categorical variables are presented as frequencies and percentages (%).
[a]2–5 Days/week from 10 a.m. to 4 p.m.
[b]Rich in proteins and vegetables and low in sugar, fat, and processed food.
[c]2 L/day.
[d]Daily use.
SD, standard deviation.

The Kolmogorov–Smirnov test was used to evaluate data normality. The parametric data are presented as average values with standard deviations; frequencies (absolute and relative %) are also used to describe the data (Table 1). The MelasQoL-BP and Skindex-29 scores before and after the treatments were compared using the Wilcoxon signed rank test. A value of α <5% was considered significant. These analyses were performed using OriginPro (Version 2020b) from OriginLab Corp. (Northampton, MA, USA).

General mixed models were used to analyze the treatment differences in wrinkle volume, hydration, and elasticity (descriptive and inferential) (Table 2). Normal and gamma distributions were considered as two possibilities for data distribution. The quality of the proposed models was evaluated by the Akaike information criterion value. For the volume, gamma distribution and an autoregressive (AR1) covariance matrix were the best fit, while using a generalized linear mixed model. For hydration, gamma distribution and an autoregressive (AR1) covariance matrix were used (also with a generalized linear mixed model).

Finally, for elasticity, normal distribution of the data was used, combined with a diagonal covariance matrix, in a general mixed model. In all of the cases, the treatment group (red or amber) and the time point analysis were considered fixed factors. Indeed, the subject was considered a random effect due to the observations of the graphical analysis of data and/or the intraclass correlation coefficient >0.10. This data analysis was performed using SPSS (Version 22; IBM Corp., Armonk, NY, USA).

Results and Discussion

Recruitment and baseline data

A total of 189 participants were registered for participation. After the selection based on the inclusion/exclusion criteria, 143 individuals were randomized. During the treatment, 60 participants dropped out of the trial, claiming personal reasons, such as changes in job or personal life or vacation (which would cause the participant to not be assiduous in the sessions), and due to noncompliance. Thus, 83 participants received the complete treatment and they were assessed both at the baseline and the end of the treatment (Fig. 2).

The average age of the participants was 52 years (Table 2). Most of them presented with phototype III (45%), that is to say, a large part of the sample consisted of patients with light brown skin. In terms of wrinkles, 47% of the participants showed Glogau scale type III, that is, visible wrinkles and significant skin flaccidity. In terms of sun exposure, 47% of the participants exposed themselves 2–5 days a week between 10 a.m. and 4 p.m. and 53% of participants did not expose themselves to the sun or exposed themselves sporadically.

Most of the participants (69%) said they used sunscreen every day, while 31% used sunscreen sporadically or never. Almost all of the participants (95%) considered their diet to be healthy, that is, a diet rich in proteins and vegetables, in a balanced way, without excess sugar, fat, and industrialized foods. To check the water intake requirement, this research considered the consumption of 2 L of water per day as ideal, with 45% of participants affirming that they ingested ≥2 L of water per day.

Clinical outcomes

The volume of crow's feet was measured by the software of the VisioFace equipment with images that registered each patient at rest, before and after the treatments, as presented in Fig. 3.

The variables were quantified before and after the PBM treatments with red and amber LEDs; data are presented in Table 3. At baseline, there were no statistical differences between the wrinkle volumes for the treatment groups. The primary outcome, the wrinkle volume, was significantly reduced after both treatments, reaching a reduction of 62.8 and 55.6 mm^3 for red and amber PBM, respectively ($p < 0.001$). These values correspond to a 31.6% reduction for red PBM and 29.9% reduction for amber PBM.

The between-group analysis showed that red PBM was more effective than amber PBM in the wrinkle treatment, presenting an additional 7.2 mm^3 [95% confidence interval (CI) −11.2 to −3.20] reduction in the periocular wrinkle volume after the 4-week treatment. However, this improved effect may not be clinically relevant. The greater wrinkle reduction achieved with red PBM may not be perceived by the patient.

By comparing the results of the present study with other published protocols, the authors found that a protocol of 2–3 sessions per week presented a greater reduction in the wrinkle volume compared with daily applications.[20] Moreover, lower irradiance (6.4 mW/cm^2) was more efficient than higher irradiance (50–105 mW/cm^2),[13] and the lower radiant exposure (3.8 J/cm^2) produced better results than higher radiant exposure (66–1266 J/cm^2).[15,17] Longer treatment protocols (>4 weeks) when considering the above-mentioned parameters should be evaluated in additional clinical trials.

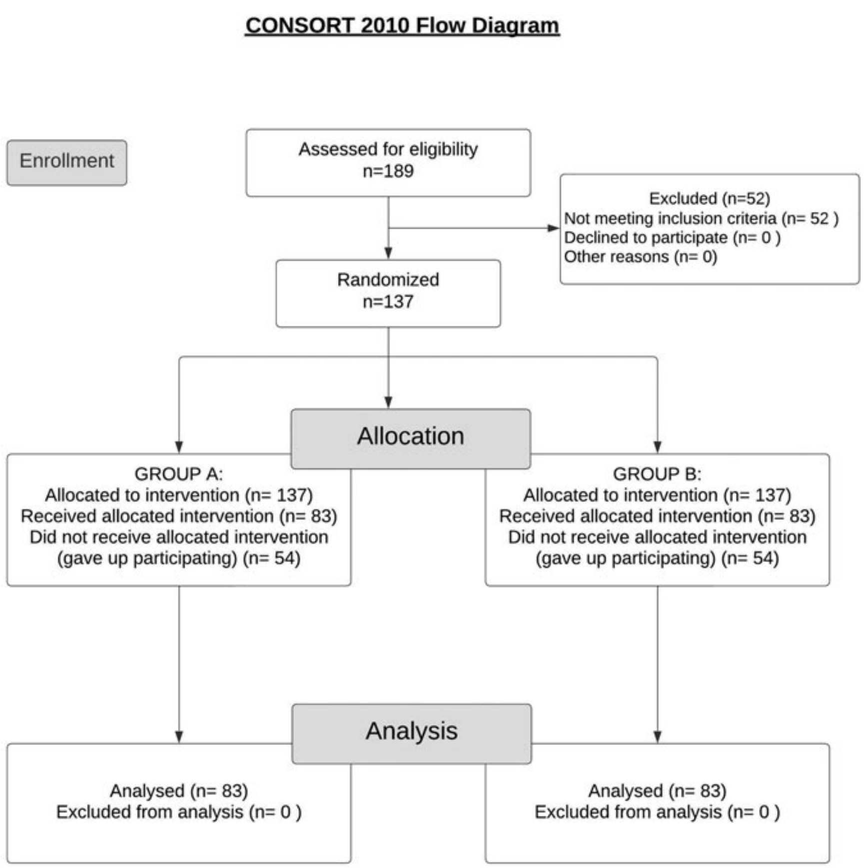

FIG. 2. CONSORT flow diagram.

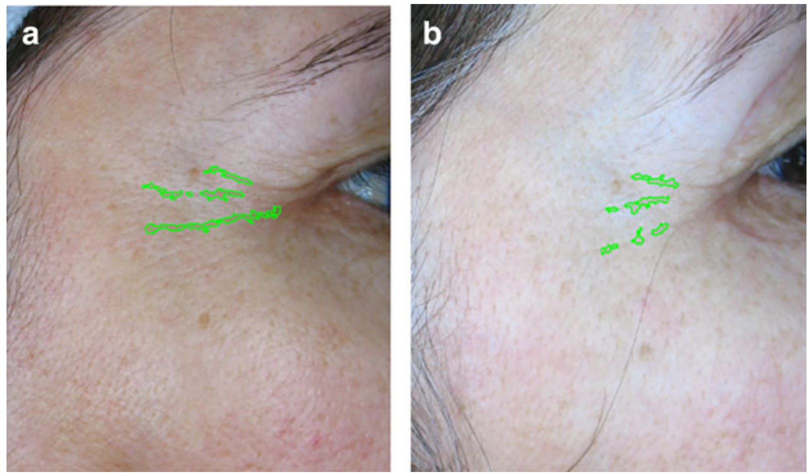

FIG. 3. Analysis of the volume of crow's feet **(a)** before and **(b)** after the treatment.

The Corneometer was used to measure the cutaneous capacitance in the periocular region to evaluate hydration. Within the groups (before and after the PBM treatment), there was no significant difference in skin hydration for amber PBM ($p > 0.05$), while there was a significant reduction in this parameter (-5.34 ± 2.59) after red PBM. When evaluating the between-group difference, there was significantly greater reduction in skin hydration with red PBM compared with amber PBM (−4.65, 95% CI −5.44 to −3.86).

The Cutometer was used to measure skin elasticity. The R1 value is an amplitude measurement and represents the skin's ability to return to its original state after deformation by vacuum suction. During the analysis, there were some problems with the files. Although the R1 values were collected for 83 patients, determined before and after the treatments with red and amber PBM, the researchers could only present the data for 38 patients. At baseline, there was no significant difference in R1 values between the groups. Besides, there was no significant difference before and after the PBM treatment for either group ($p > 0.05$).

Elasticity was not affected by PBM and hydration was reduced only by red PBM (-5.34 ± 2.59). In previous studies, hydration was not affected by intense pulsed light in both the T and U facial zones; it remained around 62 in the T area and around 75 in the U area.[39] However, in this study, after the red PBM treatment, hydration was 77.2 ± 1.63, which is higher than the values presented by Korean women.

Moreover, Bhat et al.[17] showed that red PBM did not change the elasticity or hydration.[40–42]

None of the participants reported pain, harm, or unintended effects.

Assessment of the quality of life

Participants answered the adapted Skindex-29 and MelasQoL-BP questionnaires before and after the PBM treatment. There was a significant reduction in the adapted Skindex-29 questionnaire total score, from 29 to 25 (median), which indicated that the participants presented less dissatisfaction after the treatment (Fig. 4a). The Skindex-29 questionnaire contains three domains (symptoms, emotions, and functioning).[43,44] The adaptations used in this work removed seven questions related to the symptom domain and two from the emotion domain.

The scores determined from the domains of the adapted Skindex-29 questionnaire that was used in this study (emotions and functioning) showed a significant reduction in the emotion domain (19–13, median data) and no changes in the functioning domain. The data that were obtained through the adapted MelasQoL-BP questionnaire showed a significant reduction in the total score, from 28 to 21 (median), after the treatment (Fig. 4b), which indicated a reduction in participants' dissatisfaction after the treatment.

Other studies have shown that esthetic treatments, topical cosmetic use, botulinum toxin type A, and minimally invasive cosmetic procedures improved the quality of life and self-esteem of patients.[40–42]

Limitations and generalizability of findings

This study presents some limitations. For example, the evaluation occurred at the end of the treatment. However, considering the effect of PBM on stimulating collagen synthesis, greater improvements might be observed after longer follow-up measurements, as seen in the study by Lee et al.[14]

Additionally, this study only included women aged 40–65 years, who presented with skin phototypes II, III, and IV. Indeed, the findings are not generalizable to men, individuals >65 years, and those with higher phototypes. Men and women show similar signs of aging; however, the perception of skin changes and hormonal levels may affect aging and the treatment results differently.[45–47]

Older individuals may have more severe wrinkles in the periocular region and may not respond to the same treatment as those who have mild wrinkles. Indeed, the higher melanin content in the epidermis interacts with light and thus the delivery of a suitable energy dose at the dermis could be affected. There is also an increased risk of adverse effects, such as an epidermal injury.

Nevertheless, the protocol is simple and can be reproduced in other parts of the world as long as the parameters used can be applied using locally available equipment. This technique may be very useful in clinics, especially for patients in whom highly inflammatory rejuvenation

Table 3. Continuous Outcomes for Each Group

Outcomes	*Groups*				*Within-group differences*		*Between-group difference*
	Before treatment		*After treatment*		*Final minus initial*		*Red minus amber*
	Amber	*Red*	*Amber*	*Red*	*Amber*	*Red*	
Volume (mm^3)	187 (22.1)	199 (23.6)	131 (15.5)	136 (16.1)	−55.6 (12.6, <0.001)	−62.8 (13.5, <0.001)	−7.2 (−11.2 to −3.20)
Hydration	79.6 (1.68)	82.6 (1.75)	78.9 (1.67)	77.2 (1.63)	−0.690 (2.57, 0.789)	−5.34 (2.59, 0.040)	−4.65 (−5.44 to −3.86)
Skin elasticity (0–1)[a]	0.104 (0.010)	0.098 (0.009)	0.111 (0.010)	0.097 (0.009)	0.014 (0.011, 0.186)	0.006 (0.011, 0.551)	−0.008 (−0.01 to 0.0)

The data are presented as follows: for "Groups," mean (SD); for "Within-group differences," mean difference (SD, p); and for "Between-group difference," mean (95% confidence interval).

[a]The data correspond to 38 participants from the 83 participants included.

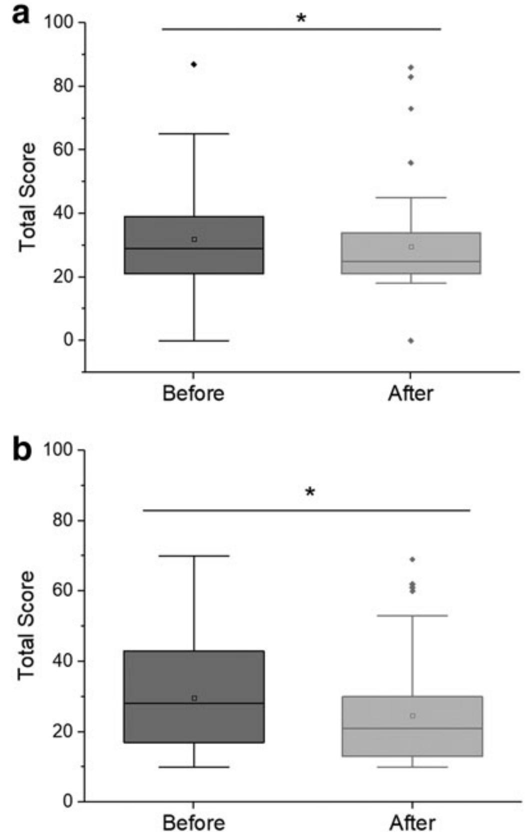

FIG. 4. Quality-of-life questionnaires: **(a)** The adapted Skindex-29 and **(b)** MelasQoL-BP questionnaires showed a significant reduction in the total score, evidencing an improvement in the quality of life. *$p < 0.05$ by the Wilcoxon signed rank test. MelasQoL-BP, Melasma Quality of Life Scale–Brazilian Portuguese.

procedures may not be indicated. Patients presenting with keloids, diabetes, or even a high Fitzpatrick skin phototype should avoid procedures such as TCA (trichloroacetic acid), peeling, and ablative lasers and they might benefit from PBM.

As far as the authors know, this study is the first to compare the effects of red and amber PBM at the same light dose on skin rejuvenation. These findings might be helpful in future studies that should investigate more deeply the effects of amber PBM on skin rejuvenation. Skin elasticity should be investigated with a larger sample size because this study presented data from only 38 patients. In addition, studies considering a longer follow-up should be performed.

Finally, studies on other cosmetic applications with amber light, such as melasma treatment, should also be considered.

Conclusions

In conclusion, PBM with red or amber LEDs was similarly effective for wrinkle volume reduction. Thus, the results of this study are compatible with the hypothesis that amber and red wavelengths produce similar rejuvenating effects on the face. The secondary outcomes, skin hydration and viscoelasticity, were not improved, while the quality of life was ameliorated by the PBM therapy.

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Authors' Contributions

All of the authors contributed to the study's conception and design. Data collection and curation were performed by L.R.M., I.d.S.D., T.R.G., and K.M.d.S.P.; data analysis was performed by D.d.F.T.d.S., O.C.N., and C.P.; L.J.M. adapted the questionnaires and performed the reproducibility and internal consistency analysis; A.C.R.T.H. generated the randomization; the first draft of the article was written by L.R.M.; and all of the authors commented on the previous versions of the article. All of the authors have read and approved the final article.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Table S1, CONSORT 2010 Checklist

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