cosmetics

MDPI

Article

Fluorescent Light Energy (FLE) Generated through Red LED Light and a Natural Photoconverter Gel as a New, Non-Invasive Approach for Facial Age Control: A Pilot Study

Giuseppe Scarcella [1], Roberta Tardugno [2,*], Pasquale Crupi [3], Marilena Muraglia [2], Maria Lisa Clodoveo [3] and Filomena Corbo [2]

[1] Laser & High Tech Department of ISPLAD, International-Italian Society of Plastic-Regenerative and Oncologic Dermatology, 70125 Verona, Italy; info@giuseppescarcella.it
[2] Department of Pharmacy—Drug Science, University of Bari Aldo Moro, 70126 Bari, Italy
[3] Department of Interdisciplinary Medicine, University of Bari Aldo Moro, 70126 Bari, Italy
* Correspondence: roberta.tardugno@uniba.it

Abstract: This study, for the first time, evaluated the safety and efficacy of a new natural-based topical gel containing a spirulina extract. This photoconverter gel generates fluorescent light energy (FLE) via a red LED light device, which is proven to be effective for age control of facial skin. This was a one-centre, observational, uncontrolled pilot trial. Eight healthy female subjects aged 35 to 65 years old, with Fitzpatrick skin types II–V were recruited. The duration of the study was five treatment sessions of one treatment every seven days, with a final follow-up at one month after the last treatment session. The images and the related data were acquired with the SONY® Mod. DSCRX10M3, the Canfield VISIA Facial Imaging System®, and QUANTIFICARE 3D® analysis. Patient compliance was excellent (100%) and the treatment was described as warm and pleasant by the patients. After 30 days, VISIA parameters such as wrinkles, texture, red areas, and Trueskin Age® had improved. The safety and efficacy of the FLE treatment assessed in this trial were achieved for overall rejuvenation of facial skin, focusing on wrinkles evaluated via the specific VISIA algorithms.

Keywords: fluorescent light energy (FLE); photobiomodulation; skin; rejuvenation; spirulina; wrinkles; VISIA

Citation: Scarcella, G.; Tardugno, R.; Crupi, P.; Muraglia, M.; Clodoveo, M.L.; Corbo, F. Fluorescent Light Energy (FLE) Generated through Red LED Light and a Natural Photoconverter Gel as a New, Non-Invasive Approach for Facial Age Control: A Pilot Study. *Cosmetics* **2023**, *10*, 74. https://doi.org/10.3390/cosmetics10030074

Academic Editor: Antonio Vassallo

Received: 24 March 2023
Revised: 18 April 2023
Accepted: 8 May 2023
Published: 9 May 2023

1. Introduction

Non-invasive procedures for skin rejuvenation to improve patients' medical and aesthetic dermatologic conditions are increasing in demand [1].

According to the American Society of Plastic Surgeons' statistics, the growth of non-invasive procedures is outpacing that of surgical procedures in aesthetic medicine [2,3].

Part of the increase in non-invasive procedures can be due to the rise of new technologies. Low-level laser therapies (LLLT), light-emitting diodes (LED), broadband visible light lamps, and energy-based devices have been developed within the last few decades. These have been used for the aesthetic treatment of fine wrinkles, photoaged skin, scars, and photorejuvenation [3,4]. LED have been used in medicine since the 1960s because of their non-thermal biostimulation and promising results in slowing the aging process of the skin, improving inflammatory skin conditions and healing lesions [5–7].

Photobiomodulation (PBM) is the term used to describe the application of low-level light energy at specific wavelengths, power densities, and dosages to induce regeneration or protect tissues that have been injured or are degenerating [8].

Blue, green, yellow, red, and infrared LED have different clinical applications, depending on the wavelengths.

In particular, red light has the deepest tissue penetration, reaching the entirety of the dermis [9] exerting vascular activation, reducing inflammation, and increasing the produc-

tion of collagen [10–12]. The low-level light energy at specific wavelengths provides safe, non-ablative, non-thermal, atraumatic remedies with high patient satisfaction rates [13].

In this context, fluorescent light energy (FLE) is a biophotonic platform offering a unique approach to dermatology, aesthetic medicine, and wound care [8,10,14]. To generate FLE, chromophores translate light energy into a low-energy fluorescence emission. The FLE platform differs from other LED modalities, as the photoconverter gel emits hyperpulsed, polychromatic fluorescent light which covers the continuum of the visible spectrum. This platform showed superior results when compared with an equivalent mimicking non-fluorescent light and conventional LEDs. In addition, FLE is different from photodynamic therapy (PDT), due to the chromophores' topical activity [7,15]. The return of mitochondrial homeostasis and enhanced ATP production are key mechanisms of FLE supporting tissue regeneration in several skin conditions [8]. Furthermore, FLE treatment has been shown to enhance the production of fibroblastic collagen, attenuate inflammatory processes, and enhance angiogenesis [7,10].

This study examined a chromophore gel containing an extract of spirulina microalgae (*Arthrospira platensis*), which is an established natural product in both the food and skincare markets. Regarding its bioactivities on the skin, spirulina can repair the signs of early skin aging, can exert a tightening effect, stimulate the synthesis of collagen, prevent the formation of stria, and reduce the formation of wrinkles [16]. The spirulina extracts have high nutraceutical and cosmetic value due to their content in biologically important chemical constituents, including provitamins, minerals, proteins, polyunsaturated fatty acids, phenolic acids, tocopherols, and unique pigments such as chlorophylls, phycobilins, and β-carotene [6–18]. The phytocomplex of spirulina, due to the presence of chlorophylls, phycobilins, and β-carotene chromophores, can generate hyperpulsed FLE when illuminated with yellow-red light (590–630 nm) and re-emit it through the Stoke shift physical mechanism of fluorescence within the red and near-infrared (NIR) spectra, with high potential for beneficial effects on skin tissues.

Red LED phototherapies, according to recent studies, can slightly improve the signs of wrinkles, according to different protocols [19]. The synergistic effect of the combination of red LED and LED–NIR irradiation has been demonstrated in the rejuvenation of peri-orbital skin [20].

This study, for the first time, evaluated the safety and efficacy of FLE technology with a new natural gel, activated via a red LED light device for the rejuvenation of facial skin. The results were evaluated through the use of VISIA and Quantificare 3D photographic images and data.

2. Materials and Methods

2.1. Fluorescent Light Energy (FLE) System

The fluorescent light energy (FLE) platform consisted of a topical photoconverter gel and an LED lamp.

The photoconverting FLE gel consisted of two components: the carrier gel (A) and the chromophore gel (B). These components were divided into two separate tubes. The photoconverter gel was produced by mixing the carrier gel (A) with the chromophore gel (B).

The chromophore gel contained an extract of *Arthrospira platensis* (Nordstedt) Gomont or *Spirulina platensis* (spirulina). Immediately before application to the skin, 5 mL of the chromophore gel (B) was mixed with 50 mL of the carrier gel (A). A 2 mm thick layer of the extemporaneously prepared topical photoconverter gel was applied to the face, and the entire amount of the mixed (A) + (B) gels (55 mL) was used to cover the face of each patient.

The FLE gel activator was a red LED lamp device delivering photons with a 635 nm wavelength and a power density of 30 mW/cm^2. It was placed 10 cm from the treatment area for 13 min (the average time of treatment for red led light therapies). The FLE gel, upon illumination by the LED lamp, produced fluorescence with a broad spectrum of

wavelengths within the red and near-infrared wavelengths. At the end of the treatment, excess exhausted gel was promptly removed with a spatula, and the face was rinsed with water.

2.2. Testing Methods of the Clinical Study

This was a one-centre, observational, uncontrolled trial. Eight healthy female subjects aged from 35 to 65 years old, with Fitzpatrick skin types II–V were recruited; the effective demographic data are reported in Table 1. There were restrictions in the inclusion criteria, whereby the subjects had to be in good general health. Exclusion criteria for the treatment included pregnant subjects, patients with major uncontrolled medical disorder(s), subjects with conditions known to induce severe photosensitivity (such as porphyria), and patients with known skin hypersensitivity. Enrolment was based on the investigator's opinion and on clinical information that the FLE treatment was an appropriate option.

Table 1. Patients' demographic data.

Pt. n.	Sex	Age	Fitzpatrick Skin Type
1	F	45	II
2	F	30	III
3	F	31	III
4	F	65	III
5	F	59	V
6	F	57	II
7	F	62	II
8	F	43	III

Total number of patients: 8 (n = 8).

On the day of treatment, the subjects cleaned their faces with a gentle cleansing product provided by the physician before and after the treatment. The physician collected facial images of the subjects and measured the skin elasticity and skin tightness of the subjects' faces.

The protocol for the treatment was 5 sessions in total, with 1 treatment every 7 days (total: 28 days $\pm$ 2 days).

The images and related data were captured with a SONY® Mod. DSCRX10M3 14 Mpixel, a Canfield VISIA Facial Imaging System®, and QUANTIFICARE 3D® analysis at baseline/T0 (before the first treatment), T28 days (before the fifth/last treatment), and at T60 (one month after the fifth/last treatment).

2.3. Endpoints

The primary endpoint was to assess the efficacy of the FLE treatment on overall rejuvenation of the facial skin with a focus on wrinkles and an evaluation via the specific VISIA® algorithms, the SONY® digital camera, and QUANTIFICARE 3D images during treatment and the follow-up visits.

The secondary endpoints were a confirmation of the safety and tolerability of FLE treatments on patients' faces and overall treatment compliance. These assessments were performed through an evaluation of the following parameters: the rate of adverse events, the rate of serious adverse events, and the rate of device incidents related to the treatment with the gel and the lamp within the planned schedule of the visits.

2.4. Analysis and Assessment of the Skin

High-resolution digital photographs taken by VISIA® (Canfield Imaging Systems, NJ, USA) were used to provide an objective measurement, using standard incandescent, cross-polarized, and ultraviolet light settings [5,14]. Assessments of the number of wrinkles, skin surface spots, texture, pores, ultraviolet (UV) spots, porphyrins, red areas, and brown

spots on the skin were taken at baseline/T0, before the fifth treatment (approx. T30), and one month after the last session/T60.

All assessments were performed with the skin free from makeup, and the face cleansed with a gentle cleansing product provided by the physician prior to the VISIA analysis.

The height of the stool for the VISIA system was adjusted so the participant was sitting in a neutral facing position with their eyes closed. Photographs for digital analysis were taken by VISIA of the frontal, left, and right oblique positions. The total scores for each parameter in the left and right oblique positions were recorded at baseline and at the follow-up visits. A percentage of the increase or decrease in the VISIA values was calculated.

SONY Digital Camera and QUANTIFICARE 3D images were taken before the treatment, before the fifth and last session, and one month after the last session during post-treatment follow-up in the same room with no daylight under controlled ambient conditions and with open eyes.

2.5. Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization and Good Clinical Practice Guidelines.

Prior to their participation in this clinical study, the investigators gave a detailed explanation to the patients regarding all aspects of the study that were relevant to the patients' decision to participate in the study or not.

The informed consent was documented by means of a written, signed, and dated informed consent form (ICF) prior to the start of the study. The ICF was available in Italian and written in a form that was understandable to the patients. The investigators also signed and dated the ICF.

2.6. Data Analysis

Percentage variation data were calculated with Excel and given as a percentage as follows

$$\%\Delta M \text{ (M = measurements: } \Delta\% = [(M_{T60} - M_{T0})/M_{T0}] \times 100),$$

where T0 is the measurement before the first session and T60 is the measurement taken after 30 days after the end of the FLE treatment course (5 sessions).

The data were analysed statistically by the STATISTICA 12.0 (StatSoft Inc., Tulxa, OK, USA) software package. After testing their normal distribution by Shapiro–Wilk's W test (except the case of Trueskin age), a principal component analysis (PCA) was performed in order to describe the roles of the VISIA parameters on the clustering effects of patients before and after the FLE treatment.

3. Results

Demographic data such as sex, age, and Fitzpatrick skin type were recorded and are reported in Table 1.

Eight healthy female individuals, with a mean age of 49 $\pm$ 17 years (ranging from 30 to 65 years), were included and completed the study. Their Fitzpatrick skin types ranged from II to V, with Type III being the most common (4/8).

This study evaluated the data as a longitudinal comparison. The values selected for the analysis were taken at baseline (T0, before the commencement of any FLE treatment) and at follow-up (T60, 30 days after the last FLE treatment).

Improvements in several of the analysed skin parameters were mirrored by significant patient satisfaction, thereby suggesting that the FLE treatment is beneficial for the rejuvenation of facial skin.

The protocol used in this study was well tolerated. All participants completed the study without any complications, and no serious side effects or irritation were reported in relation to the application of the FLE treatments.

There were no specific adverse events to report in this study. No serious adverse events were reported during the study period. Of all the local skin responses which occurred during this study, none of them were considered clinically significant by the investigator.

Based on the participants' diaries, compliance with the treatment regimen was considered excellent (100%). No treatment visits were missed during the study protocol. No patient refused a study treatment during a visit.

All participants reported the treatment as warm and pleasant during the sessions. Participants reported positive feedback and a satisfactory improvement in their skin texture after a few weeks after the initiation of the treatment.

The VISIA non-invasive skin analysis device was used to evaluate the clinical outcomes of the FLE treatment. The image analysis provided a useful evaluation of the facial parameters that can often be difficult to detect clinically [21].

The VISIA camera can analyse eight skin criteria (spots, wrinkles, skin texture, pores, UV spots, brown spots, red marks, and porphyrin). For the criterion of wrinkles, three measurements were recorded: the feature count, the absolute score, and the percentile. The feature count was used to track how the treatment was progressing. The absolute score captured the total size and area of skin characteristics, as well as the intensity. The percentile provided a comparison of a person's individual complexion, compared with a pool of people with similar skin characteristics. A fall in the values of the feature count and absolute score defined an improvement, whereas an increase in the value in the percentile indicated an improvement [22].

Table 2 shows the results at baseline (T0) compared with after 30 days (T60) from the end of the treatment. All three of the VISIA values, namely the feature count, score, and percentile related to the wrinkle criterion, are reported. The values decreased over time in six out of eight patients, with an average value of −22.1%, while the absolute score decreased over time in seven out of eight patients, with an average value of −34.9%. The value of the percentile increased over time in six out of eight patients, with an average value of +32.8%. The reduction in wrinkles and the improvement in the appearance of the remaining features are summarised in Scheme 1 and highlighted in Figures 1–3. These data confirm the efficacy of the non-invasive FLE treatments assessed in this trial for overall rejuvenation of facial skin, with a focus on wrinkles and an evaluation via the specific VISIA algorithms.

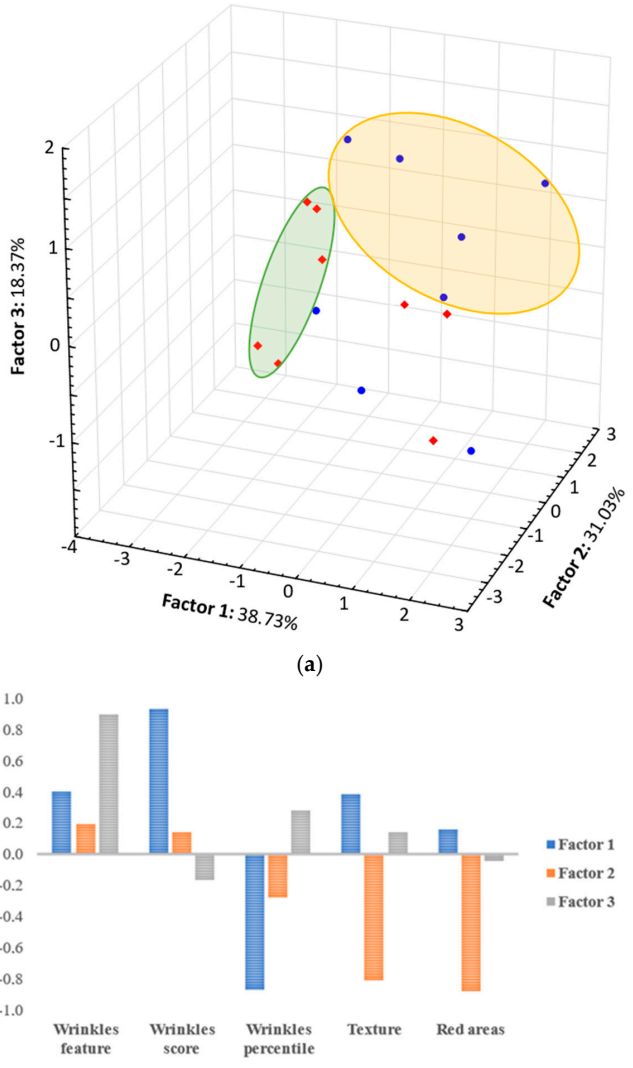
Table 2. VISIA wrinkle parameters before and after the FLE treatment.

		Wrinkles		
Patient no.	**Before/After**	**Feature**	**Score**	**Percentile**
Patient 1	Before	22	17,637	61
	After	7	4486	92
	%	−68.2	−74.6	50.8
Patient 2	Before	13	13,946	48
	After	19	5365	80
	%	46.2	−61.5	66.7
Patient 3	Before	23	8031	71
	After	16	7023	71
	%	−30.4	−12.6	0.0
Patient 4	Before	22	36,500	55
	After	16	30,127	65
	%	−27.3	−17.5	18.2
Patient 5	Before	26	44,234	34
	After	17	11,192	87
	%	−34.6	−74.7	155.9

Table 2. *Cont.*

Patient no.	Before/After	Wrinkles		
		Feature	Score	Percentile
Patient 6	Before	11	42,271	34
	After	17	33,576	47
	%	54.5	−20.6	38.2
Patient 7	Before	15	16,950	81
	After	13	13,312	86
	%	−13.3	−21.5	6.2
Patient 8	Before	17	25,656	40
	After	11	28,474	35
	%	−35.3	11.0	−12.5
	Average before	17	22,803	47
	Average after	13	14,839	63
	%	−22.1	−34.9	32.8

Total number of patients: 8 (n = 8).



Scheme 1. (**a**) Principal component scores of the eight patients before (blue circles) and after (red diamonds) the FLE treatment. Factors 1, 2, and 3 account for 88.13% of the total variance explained. (**b**) Factor loadings relative to the VISIA parameters.

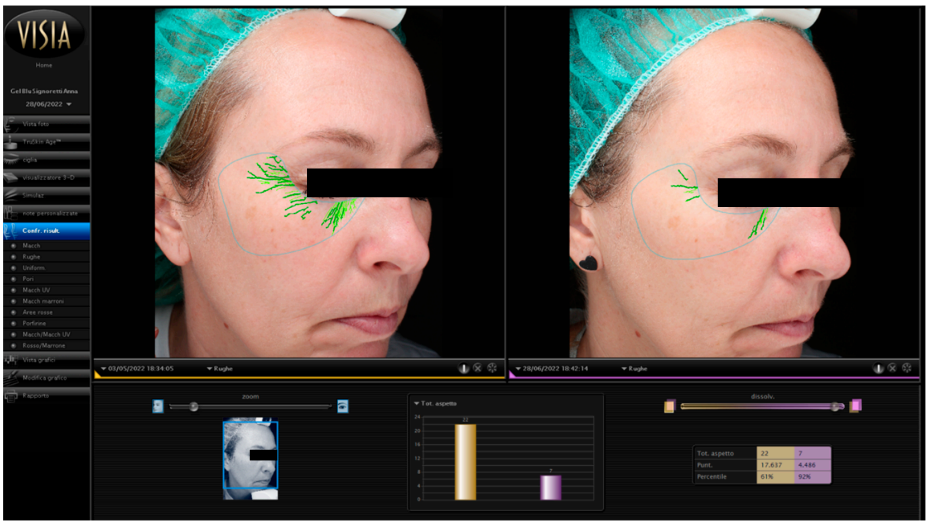
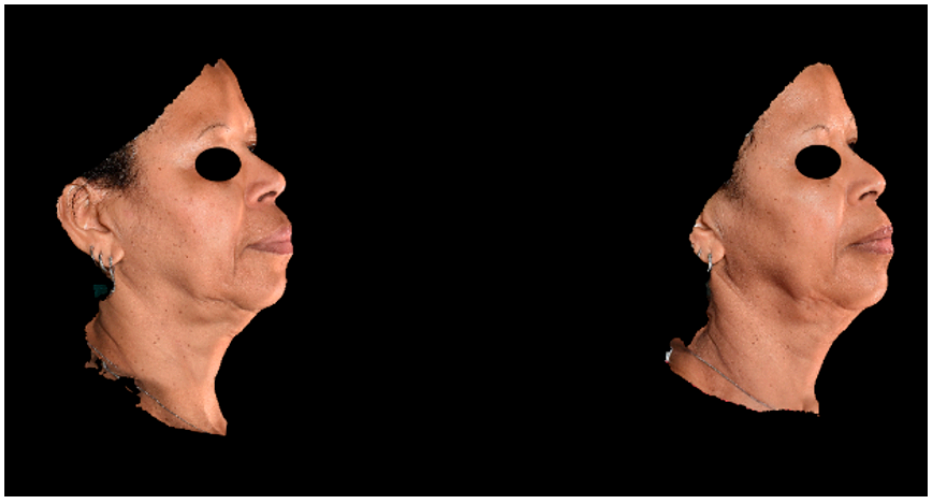


Figure 1. Patient 1: 45 years old, skin Type II. VISIA wrinkle mask before (T0, **left**) and 1 month after the last session (T60, **right**).

(**a**)



(**b**)

Figure 2. (**a**) Patient 5: 59 years old; skin type V. VISIA wrinkle mask images before (T0, **left**) and 1 month after the last session of the FLE treatment (T60, **right**); (**b**) Patient 5; QUANTIFICARE 3D images before (T0, left-hand 3D image) and 1 month after the last session (T60, right-hand 3D image).

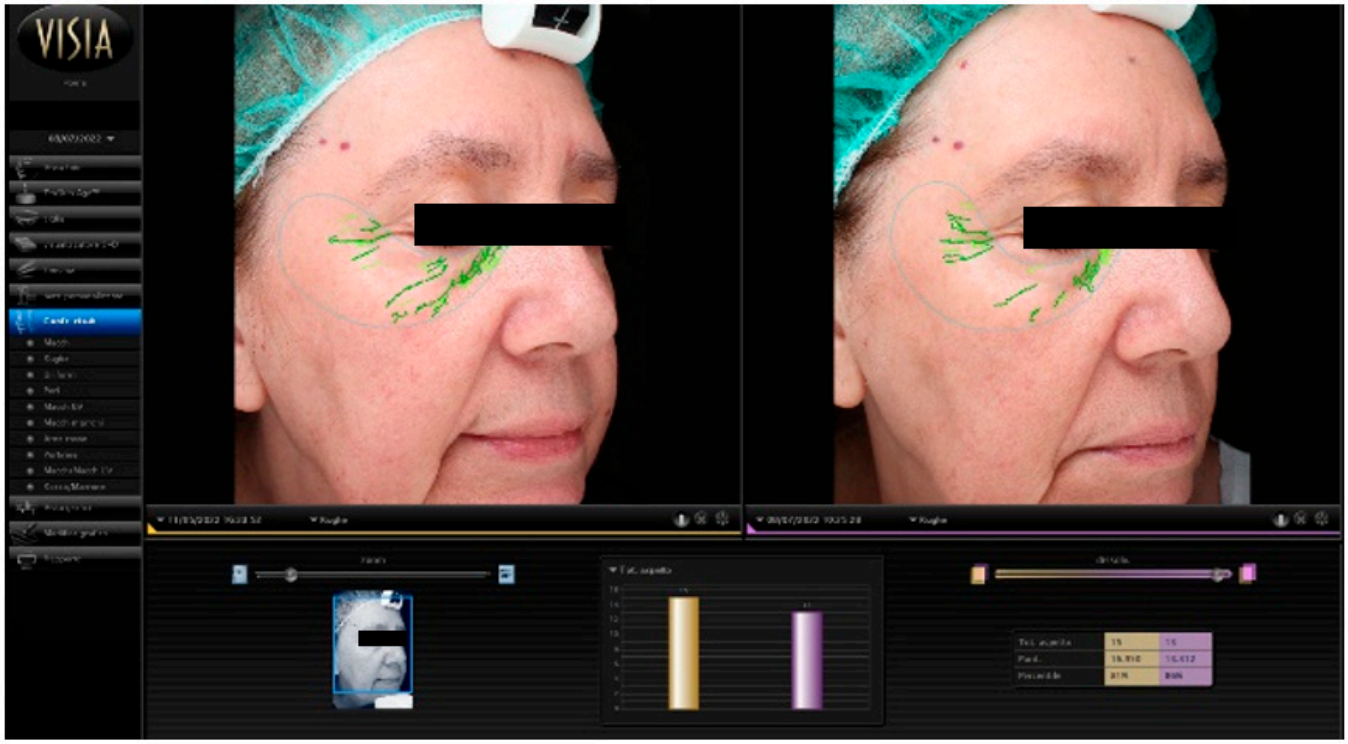


Figure 3. Patient 7: skin type II. VISIA wrinkle analytical images before (T0, **left**) and one month after the last FLE session (T60, **right**).

VISIA texture, the criterion of red areas, and the Trueskin age algorithm were taken into consideration as primary endpoints, and are reported in Table 3. Only the feature count was selected, as it provides easy-to-understand information about a feature of interest of the skin before and after the treatment. A rise in the value of the texture count as well as a fall in the value of the red areas and Trueskin age scores indicate an improvement. The value texture increased over time in five out of eight patients, with an average value of +8.2%. The red areas decreased over time in six out of eight patients, with an average value of −5.1%. The Trueskin age algorithm decreased over time, with an average value of −17.8%. This resulted in an overall improvement in the skin's aspect, which made the patient's skin look younger. The 3D images also demonstrated an improvement in the overall face profile and skin of the jawline. These improvements were evaluated by comparing the 3D images before and after, as highlighted in Figures 1–3. These data reinforce the efficacy of the non-invasive FLE treatments assessed in this trial for the overall rejuvenation of facial skin, with a focus on wrinkles and an evaluation via the specific VISIA algorithms.

To corroborate this result, a PCA analysis was conducted only on the normally distributed VISIA parameters. Scheme 1a illustrates the tridimensional PCA score of the three factors accounting for 88.13% of the total variance explained, which shows how the eight patients before and after the FLE treatment were rather clearly clustered, mainly along Factor 1, which was more correlated to the wrinkle score and the percentile having positive (0.9302) and negative (−0.8650) factor loadings, respectively (Scheme 1b). Texture and red areas made negative contributions to Factor 2 (−0.8084 and −0.8755, respectively) and, to a lesser extent, on Factor 3, wrinkles also contributed to the ability to discriminate between the two groups. This means that treated patients tended to present a decrease in the wrinkle score and percentile, and an improved texture with reduced red areas.

Table 3. VISIA values of texture, red areas, and Trueskin age before and after the FLE treatment.

Patient n.	Before/After	Texture	Red Areas	Trueskin Age
Patient 1	Before	229	122	49
	After	269	88	35
	%	17.5	−27.9	−28.6
Patient 2	Before	1045	265	n.d.
	After	931	203	n.d.
	%	−10.9	−23.4	0.0
Patient 3	Before	715	189	n.d.
	After	717	178	n.d.
	%	0.3	−5.8	0.0
Patient 4	Before	1627	208	n.d.
	After	1455	166	n.d.
	%	−10.6	−20.2	0.0
Patient 5	Before	1177	160	63
	After	1269	119	49
	%	7.8	−25.6	−22.2
Patient 6	Before	640	189	67
	After	612	183	59
	%	−4.4	−3.2	−11.9
Patient 7	Before	1336	252	62
	After	1667	315	55
	%	24.8	25.0	−11.3
Patient 8	Before	945	135	n.d.
	After	1428	190	n.d.
	%	51.1	40.7	0.0
	Average before	857	169	48
	Average after	928	160	40
	%	8.2	−5.1	−17.8

Total number of patients: 8 (n = 8).

4. Discussion

The principle of FLE treatments is based on photobiomodulation, where the photons emitted by LEDs are absorbed by the endogenous chromophores of the skin (e.g., mitochondrial, cytochrome C, melanin, and endogenous protoporphyrins), stimulating skin receptors such as opsin proteins and G-coupled receptors, as well as several biological activities [7,19,23]. In addition to the classical PBM mechanisms, after illumination by a red–yellow light delivered by the LED lamp, the FLE gel containing the natural chromophore molecules, namely chlorophylls, phycobilins, and β-carotene, acted as a photoconverter, absorbing the photons of the yellow–red light (590–650 nm). Such molecular systems excite and re-emit a dynamic spectrum of hyperpulsed and polychromatic fluorescent light up to 700 nm, which is specific to FLE technology and capable of producing multiple wavelengths in the red and near-infrared spectra in a single treatment. Red LED or LED–NIR light can strongly activate fibroblast growth factors, increase MMP-9 and type 1 procollagen, and reduce metalloproteinase-1, which are important factors in skin rejuvenation [19]. Moreover, opsins can be activated by the light stimuli modulating various physiological processes of the skin, including wound healing, melanogenesis, photoaging, and hair growth [23,24].

The hyperpulsed photons of FLE can show superior results with respect to conventional LED light [7,10,25]. In fact, pulsed light having 'quench periods' can deliver the energy deeper into the tissues while generating less heat at the surface layers [26–28]. The logic in favour of pulsed light is that the cells may need periods of rest, without which, they can no longer be stimulated further. If the light is pulsed, multiple photodissociation events could occur, while in continuous mode, the number of dissociations may be much smaller [26–28].

Hyperpulsed wavelengths of fluorescent light, compared with continuous wavelengths, appear to produce favourable biostimulation for the production of ATP and collagen [7,12,15]. The FLE treatment was able to promote collagen remodelling after skin grafting on mice, reducing the risk of developing fibrotic and chronic scars [29]. Furthermore, FLE has demonstrated improvements in mitochondrial morphology and increased the expression of genes involved in the production of mitochondrial ATP in human skin fibroblasts in vitro [8]. Based on FLE's reported effect on mitochondrial activity, it was hypothesized that cytochrome c oxidase (CCO) is an important acceptor for FLE [7,8].

Among the studied cellular mechanisms related to the biological activities stimulated by FLE, the reduced secretion of pro-inflammatory cytokines (IL-6 and TNF-α), the stimulation of collagen by the fibroblasts, and the promotion of the mechanisms of angiogenesis can have a role in skin rejuvenation processes [7,30]. The optimization of the FLE treatment tailored to the features of each opsin can maximize the benefit to the skin [23].

FLE has been proven to modulate healthy and diseased skin and tissues [7,14], providing a unique method for managing a wide range of skin conditions and representing a new approach to photobiomodulation. FLE can be used in combination with other invasive and non-invasive therapies, as an adjunct to the regenerative processes of the skin [5,14]. Further studies with large cohorts of participants and control groups may be required to better understand the characteristics and potential of FLE technology on skin rejuvenation and age control.

5. Conclusions

All the subjects involved were very satisfied with the results and tolerability of the treatment, which was described as pleasant by the patients. Improvements in the skin in terms of laxity, texture, and wrinkles were noticeable after the first two or three treatment sessions, although the best results were documented one month after the last session. There were no specific adverse events to report in this study. No serious adverse events were reported during the study period.

This study confirmed the safety and efficacy of FLE treatments generated through red LED light and a natural photoconverter gel for the rejuvenation of facial skin.

Author Contributions: Conceptualization, G.S. and R.T.; methodology, G.S.; software, G.S. and P.C.; investigation, G.S.; resources, G.S.; data curation, R.T. and P.C.; writing—original draft preparation, R.T. and G.S.; writing—review and editing, R.T. and M.M.; supervision, F.C. and M.L.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This was an observational study where approval of the ethics committee or an institutional review board was not mandatory for the investigation.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ablon, G. Phototherapy with Light Emitting Diodes: Treating a Broad Range of Medical and Aesthetic Conditions in Dermatology. *J. Clin. Aesthet. Dermatol.* **2018**, *11*, 21–27. [PubMed]
2. American Society of Plastic Surgeons Release. 2018 Plastic Surgery Statistics Report. Available online: https://www.plasticsurgery.org/documents/News/Statistics/2018/plastic-surgery-statistics-full-report-2018.pdf (accessed on 11 October 2022).
3. Avci, P.; Gupta, A.; Sadasivam, M.; Vecchio, D.; Pam, Z.; Pam, N.; Hamblin, M.R. Low-level laser (light) therapy (LLLT) in skin: Stimulating, healing, restoring. *Semin. Cutan. Med. Surg.* **2013**, *32*, 41–52. [PubMed]
4. Chung, H.; Dai, T.; Sharma, S.K.; Huang, Y.Y.; Carroll, J.D.; Hamblin, M.R. The nuts and bolts of low-level laser (light) therapy. *Ann. Biomed. Eng.* **2012**, *40*, 516–533. [CrossRef]
5. Edge, D.; Schødt, M.; Nielsen, M.C.E. Biophotonic Therapy Induced Photobiomodulation. In *Technology in Practical Dermatology*; Fimiani, M., Rubegni, P., Cinotti, E., Eds.; Springer: Cham, Switzerland, 2020. [CrossRef]

6. Edge, D.; Mellergaard, M.; Dam-Hansen, C.; Corell, D.D.; Jaworska, J.; Scapagnini, G.; Nielsen, M.C.E. Fluorescent Light Energy: The Future for Treating Inflammatory Skin Conditions? *J. Clin. Aesthet. Dermatol.* **2019**, *12*, E61–E68. [PubMed]
7. Ding, J.; Mellergaard, M.; Zhu, Z.; Kwan, P.; Edge, D.; Ma, Z.; Hebert, L.; Alrobaiea, S.; Iwasaki, T.; Nielsen, M.; et al. Fluorescent light energy modulates healing in skin grafted mouse model. *Open Med.* **2021**, *16*, 1240–1255. [CrossRef]
8. Farber, S.E.; Epps, M.T.; Brown, E.; Krochonis, J.; McConville, R.; Codner, M.A. A review of nonsurgical facial rejuvenation. *Plast. Aesthet. Res.* **2020**, *7*, 72. [CrossRef]
9. Ferroni, L.; Zago, M.; Patergnani, S.; Campbell, S.E.; Hébert, L.; Nielsen, M.; Scarpa, C.; Bassetto, F.; Pinton, P.; Zavan, B. Fluorescent Light Energy (FLE) Acts on Mitochondrial Physiology Improving Wound Healing. *J. Clin. Med.* **2020**, *9*, 559. [CrossRef]
10. Gerber, P.A.; Scarcella, G.; Edge, D.; Nielsen, M.C.E. Biophotonic pretreatment enhances the targeting of senile lentigines with a 694 nm QS-ruby laser. *Photodermatol. Photoimmunol. Photomed.* **2020**, *36*, 159–160. [CrossRef]
11. Gunes, S.; Tamburaci, S.; Dalay, M.C.; Deliloglu Gurhan, I. *In vitro* evaluation of *Spirulina platensis* extract incorporated skin cream with its wound healing and antioxidant activities. *Pharm. Biol.* **2017**, *55*, 1824–1832. [CrossRef]
12. Hashmi, J.T.; Huang, Y.Y.; Sharma, S.K.; Kurup, D.B.; De Taboada, L.; Carroll, J.D.; Hamblin, M.R. Effect of pulsing in low-level light therapy. *Lasers Surg. Med.* **2010**, *42*, 450–466. [CrossRef]
13. Henseler, H. Validation of the Visia® Camera System for skin analysis through assessment of the correlations among the three offered measurements—The percentile, feature count and absolute score—As well as the three capture perspectives, from the left, front and right. *GMS Interdiscip. Plast. Reconstr. Surg DGPW* **2022**, *11*, Doc04. [PubMed]
14. Kurtti, A.; Nguyen, J.K.; Weedon, J.; Mamalis, A.; Lai, Y.; Masub, N.; Geisler, A.; Siegel, D.M.; Jagdeo, J.R. Light emitting diode-red light for reduction of post-surgical scarring: Results from a dose-ranging, split-face, randomized controlled trial. *J. Biophotonics* **2021**, *14*, e202100073. [CrossRef] [PubMed]
15. Jalili, A. Chromophore gel-assisted phototherapy. *J. für. Ästhetische Chir.* **2018**, *20*, 1–5. [CrossRef]
16. Mellergaard, M.; Fauverghe, S.; Scarpa, C.; Pozner, V.L.; Skov, S.; Hebert, L.; Nielsen, M.; Bassetto, F.; Téot, L. Evaluation of Fluorescent Light Energy for the Treatment of Acute Second-degree Burns. *Mil. Med.* **2021**, *186*, 416–423. [CrossRef] [PubMed]
17. Migliardi, R.; Tofani, F.; Donati, L. Non-invasive peri-orbital rejuvenation: Radiofrequency dual radiowave energy source (rf) and light emission diode system (LED). *Orbit* **2009**, *28*, 214–218. [CrossRef]
18. Ngoc, L.T.N.; Moon, J.Y.; Lee, Y.C. Utilization of light-emitting diodes for skin therapy: Systematic review and meta-analysis. *Photodermatol. Photoimmunol. Photomed.* **2022**, 12841. [CrossRef]
19. Nikolis, A.; Bernstein, S.; Kinney, B.; Scuderi, N.; Rastogi, S.; Sampalis, J.S. A randomized, placebo-controlled, single-blinded, split-faced clinical trial evaluating the efficacy and safety of KLOX-001 gel formulation with KLOX light-emitting diode light on facial rejuvenation. *Clin. Cosmet. Investig. Dermatol.* **2016**, *13*, 115–125. [CrossRef]
20. Oh, P.S.; Jeong, H.J. Therapeutic application of light emitting diode: Photo-oncomic approach. *J. Photochem. Photobiol. B* **2019**, *192*, 1–7. [CrossRef]
21. Olinski, L.E.; Lin, E.M.; Oancea, E. Illuminating insights into opsin 3 function in the skin. *Adv. Biol. Regul.* **2020**, *75*, 100668. [CrossRef]
22. Quinlan, D.J.; Ghanem, A.M.; Hassan, H. Topical growth factors and home-based microneedling for facial skin rejuvenation. *J. Cosmet. Dermatol.* **2022**, *21*, 3469–3478. [CrossRef]
23. Ragusa, I.; Nardone, G.N.; Zanatta, S.; Bertin, W.; Amadio, E. Spirulina for Skin Care: A Bright Blue Future. *Cosmetics* **2021**, *8*, 7. [CrossRef]
24. Scarcella, G.; Gerber, P.A.; Edge, D.; Nielsen, M.C.E. Effective removal of solar lentigines by combination of pre- and post-fluorescent light energy treatment with picosecond laser treatment. *Clin. Case Rep.* **2020**, *8*, 1429–1432. [CrossRef] [PubMed]
25. Scarcella, G.; Dethlefsen, M.W.; Nielsen, M.C.E. Treatment of solar lentigines using a combination of picosecond laser and biophotonic treatment. *Clin. Case Rep.* **2018**, *6*, 1868–1870. [CrossRef]
26. Sommer, A.P. Revisiting the Photon/Cell Interaction Mechanism in Low-Level Light Therapy. *Photobiomodul. Photomed. Laser Surg.* **2019**, *37*, 336–341. [CrossRef] [PubMed]
27. Sonbol, H.; Brenaut, E.; Nowak, E.; Misery, L. Efficacy and Tolerability of Phototherapy with Light-Emitting Diodes for Sensitive Skin: A Pilot Study. *Front. Med.* **2020**, *7*, 35. [CrossRef] [PubMed]
28. Sorrenti, V.; Castagna, D.A.; Fortinguerra, S.; Buriani, A.; Scapagnini, G.; Willcox, D.C. Spirulina Microalgae and Brain Health: A Scoping Review of Experimental and Clinical Evidence. *Mar. Drugs* **2021**, *19*, 293. [CrossRef]
29. Suh, S.; Choi, E.H.; Atanaskova Mesinkovska, N. The expression of opsins in the human skin and its implications for photobiomodulation: A Systematic Review. *Photodermatol. Photoimmunol. Photomed.* **2020**, *36*, 329–338. [CrossRef]
30. Wunsch, A.; Matuschka, K. A controlled trial to determine the efficacy of red and near-infrared light treatment in patient satisfaction, reduction of fine lines, wrinkles, skin roughness, and intradermal collagen density increase. *Photomed. Laser Surg.* **2014**, *32*, 93–100. [CrossRef]