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ORIGINAL ARTICLE

Efficacy and tolerability of 5-aminolevulinic acid 0.5% liposomal spray and intense pulsed light in wrinkle reduction of photodamaged skin

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Abstract

Background: Photodynamic therapy (PDT) with 5-aminolevulinic acid (5-ALA) is effective for the treatment of photoaging. *Objective*: To evaluate the efficacy and safety of PDT using a novel 0.5% liposome-encapsulated 5-ALA spray and an intense pulsed light (IPL) system (Ellipse Flex PPT®) in reduction of periorbital and nasolabial wrinkles. *Patients and Methods:* Thirty healthy volunteers, aged 35–65 years, skin type I–III, with type 2 photoaging underwent a baseline visit, three ALA-IPL treatments once every 3 weeks, an end-of-treatment visit and a final visit 3 months after the end-of-treatment visit. Wrinkle depth was evaluated according to the modified Fitzpatrick wrinkle scale (MFWS). At the final visit, patients rated their degree of overall improvement. *Results*: For periorbital and nasolabial wrinkles, the differences of the average MFWS evaluation between baseline versus end-of-treatment visit, baseline versus final visit and end-of-treatment visit versus final visit were statistically significant ($p < 0.001$). The average overall improvement was greater for periorbital than for nasolabial wrinkles ($p < 0.001$). No side effects were observed during and after treatment. The degree of overall improvement was scored as excellent by 47% of the volunteers. *Conclusions*: ALA-IPL treatment using 0.5% liposome-encapsulated 5-ALA spray and Ellipse Flex PPT system is effective and safe for the treatment of type 2 photoaging reducing the PDT-associated side effects.

Key words: *5-aminolevulinic acid, intense pulsed light, photodynamic therapy, photoaging*

Introduction

Photoaging is clinically characterized by telangiectasias or diffuse redness, solar lentigines, irregular pore size, wrinkles, rough texture and/or loss of elasticity. It is classified into type 1, which consists of pigmented and vascular lesions, and type 2, which includes thin facial wrinkles. Sun-damaged skin has been successfully treated on a short-term basis with topical retinoids, antioxidants, alfa-hydroxy acids, microdermabrasion, fractional photothermolysis, intense pulsed light (IPL) or photodynamic therapy (PDT) (1–3).

PDT has been used for several years for the treatment of non-melanoma skin cancers and acne vulgaris. Recently, PDT with 5-aminolevulinic acid (5-ALA) or its methyl ester (MAL) has proven effective for the treatment of photoaging (4,5). However, use of 20% 5-ALA under occlusion according to the standard treatment is often associated with several side effects. Christiansen et al. (6) demonstrated that the 5-ALA concentration can be lowered by a factor of 40 changing the vehicle from cream to liposome encapsulation, and such concentration is still able to induce the same skin fluorescence without need for occlusion. Recently, a new formulation of 5-ALA

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spray (0.5%) encapsulated in liposomes has been commercialized as a cosmetic device due to its low concentration.

IPL is a procedure based on selective photothermolysis, defined as the controlled destruction of a target tissue following conversion of light energy to heat energy in a very short period of time. The light emitted by an IPL system differs from the light of a laser because it is not just one single wavelength, but covers a spectrum of different wavelengths (420–720 nm). By changing different filters, IPL is used to treat a wide range of skin conditions, including photodamage, wrinkles and acne vulgaris, for long-term depilation, for removal of vascular lesions (angiomas and telangectasias) and epidermal pigmented lesions (ephelides and solar lentigines) and for improvement of skin texture (7,8). The conversion of light energy to heat energy indeed stimulates a recovery process with formation of new collagen that makes the skin more luminous and elastic, with less thin wrinkles and improved texture (9,10). A new IPL system (Ellipse Flex PPT®, Ellipse A/S, Horsholm, Denmark) with a specific program and a handful device for PDT has been recently introduced in the market. It allows a light emission spectrum between 420 and 720 nm which can activate protoporphyrin IX in all its five absorption peaks.

Our study aimed to evaluate the efficacy and safety of PDT using 0.5% liposome-encapsulated 5-ALA spray and IPL in reduction of periorbital and nasolabial wrinkles of patients with type 2 photoaging.

Patients and methods

Patients

In this multicenter study, 30 healthy volunteers aged 35–65 years, skin type I–III, affected by type 2 photoaging were enrolled at the Departments of Dermatology of the University of L'Aquila and Rome "Tor Vergata", Italy, and at the UOSD Prevenzione e Programmazione in Dermatologia ISG-IFO, Rome, Italy. Exclusion criteria included patients affected by melasma, photosensitizing disorders, abnormal healing processes, coagulation disorders or type I or II diabetes. In addition, subjects with contraindications to 5-ALA treatment (such as erythema during the pretreatment) and patients who were under treatment with anticoagulants, any photosensitizing medications within 1 week prior to the study or with topical or systemic corticosteroids or non-steroidal anti-inflammatory drugs which could reduce treatment efficacy, were also excluded. Written informed consent was obtained under Institutional Review Board-approved protocols respecting the Declaration of Helsinki's guidelines.

Treatment procedure

Study protocol included an initial screening visit (baseline), three IPL treatment sessions using 0.5% 5-ALA in spray formulation and Ellipse Flex PPT system once every 3 weeks, a visit 1 week after the last IPL treatment (end-of-treatment visit) and a final visit 3 months after the end-of-treatment (final visit).

The 0.5% 5-ALA spray formulation was applied on the entire face every 5 min for 1 h before treatment with the Ellipse Flex PPT system, which consisted of three complete passages of the PL-W applicator (approximately 80–100 spots per passage) using a specific wrinkle reduction program characterized by 3.5 J/cm^2 energy and 30 ms duration single spots for a total of 10.5 J/cm^2 energy released at each treatment.

Patient evaluation

Wrinkles were evaluated according to the modified Fitzpatrick wrinkle scale (MFWS), which scores severity of nasolabial fold wrinkling by wrinkle depth (11). The definition of interclasses in the MFWS allows easier and more precise assessment of wrinkle severity as compared with the original Fitzpatrick classification, which was more focused on general wrinkling and elastosis (12). Evaluation of wrinkle severity was carried out by one blinded evaluator per center, who were initially trained on wrinkle assessment according to the MFWS on a test set of patients. In our study, we used the MFWS classification to describe the depth of both nasolabial and periorbital wrinkles. According to the MFWS, nasolabial and periorbital wrinkling is classified as follows: *class 0* (no wrinkle; no visible wrinkle and continuous skin line); *class 0.5* (very shallow yet visible wrinkle); *class 1* (fine wrinkle; visible wrinkle and slight indentation); *class 1.5* (visible wrinkle and clear indentation, <1 mm wrinkle depth); *class 2* (moderate wrinkle, clearly visible, 1–2 mm wrinkle depth); *class 2.5* (prominent and visible wrinkle, >2 mm and <3 mm wrinkle depth) (11). Only patients with wrinkle severity ranging from class 0.5 to 2 were included in the study. Improvement in wrinkle severity was defined as the reduction of at least one class in the MFWS classification after treatment.

Photographic documentation was performed at the baseline visit and at the final visit using a high-resolution digital camera (Canon, USA) at a fixed distance and under standard conditions of illumination.

At the final visit, patients were invited to evaluate their outcome through a comparison of photographs taken at the baseline and at the final visit. Patients rated their satisfaction and the overall improvement according to the following scale: fair, good, excellent.

Statistical analysis

The number of classes by which the MFWS was reduced at the end-of-treatment visit and 3 months after the end-of-treatment visit compared with the baseline was used as a measure of "early" and "overall" improvement, respectively. The number of classes by which the MFWS was reduced 3 months after the end-of-treatment visit compared with the end-of-treatment evaluation was used as a measure of "late" improvement.

Spearman's correlation coefficients were estimated to examine correlation between all the variables. Paired t-test was used to compare means and Pearson's χ^2 test with Yates' correction for continuity was used to compare different groups within categorical variables.

Statistical significance was accepted at the 5% arbitrary level. The analysis was carried out using STATA version 10 (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp. LP).

Results

Thirty female volunteers, aged 35–65 years (median age: 48 years), were enrolled in this study. At baseline all volunteers were classified according to skin type: 3 of 30 (10%) patients were classified as skin type I; 13 of 30 (43%) patients as skin type II and 14 of 30 (47%) patients as skin type III. All subjects completed the study.

Periorbital and nasolabial wrinkle evaluations at baseline, at the end-of-treatment visit and 3 months after the end-of-treatment visit are summarized in Table I and illustrated in detail in Figure 1.

For periorbital wrinkles, the average MFWS evaluation was 1.52 ± 0.50 at baseline, 1.02 ± 0.33 at the end-of-treatment visit and 0.55 ± 0.15 3 months after the end-of-treatment visit. For nasolabial wrinkles, the mean scoring was 1.37 ± 0.43 at baseline, 1.12 ± 0.34 at the end-of-treatment visit and 0.78 ± 0.28 at the final visit (Table I and Figure 2).

No significant difference was found between the depth of periorbital and nasolabial wrinkles at baseline ($p = 0.20$) and at the end-of-treatment visit ($p = 0.28$), whereas a significant difference was detected at the final visit ($p < 0.001$).

Within the periorbital wrinkles, the differences between baseline and end-of-treatment visit, between baseline and final visit and between end-of-treatment visit and final visit were statistically significant ($p < 0.001$ for all), as well as for nasolabial wrinkles ($p < 0.001$ for all) (Figures 3 and 4).

The distribution of early, late and overall improvement after treatment is shown in Table II. At the end-of-treatment visit, a reduction of at least one class on the MFWS (early improvement) was obtained by the 73% of participants for periorbital wrinkles and by 50% for nasolabial wrinkles ($p = 0.003$). A late improvement of at least one class was obtained by the 80% of participants for periorbital wrinkles and by 67% for nasolabial wrinkles ($p < 0.001$). An overall improvement of at least one class was obtained by the 100% of participants for periorbital wrinkles and by 90% for nasolabial wrinkles ($p < 0.001$).

The average early improvement was significantly greater for periorbital wrinkles (0.50 ± 0.37) than for nasolabial wrinkles (0.25 ± 0.25) ($p = 0.005$). Similarly, the average overall improvement was greater for periorbital wrinkles (0.97 ± 0.47) than for nasolabial

Table I. Distribution of the MFWS values of periorbital and nasolabial wrinkles.

	Periorbital wrinkles			Nasolabial wrinkles		
MFWS	Baseline No. (%)	End-of-treatment visit No. (%)	Three months after end-of-treatment visit No. (%)	Baseline No. (%)	End-of-treatment visit No. (%)	Three months after end-of-treatment visit No. (%)
Class 0.5	–	6 (20)	27 (90)	2 (7)	4 (13)	14 (47)
Class 1	14 (47)	17 (57)	3 (10)	10 (33)	15 (50)	15 (50)
Class 1.5	1 (3)	7 (23)	–	12 (40)	11 (37)	1 (3)
Class 2	15 (50)	–	–	6 (20)	–	–
Mean (SD)	1.52 (0.50)	1.02 (0.33)	0.55 (0.15)	1.37 (0.43)	1.12 (0.34)	0.78 (0.28)

MFWS = modified Fitzpatrick wrinkle scale.

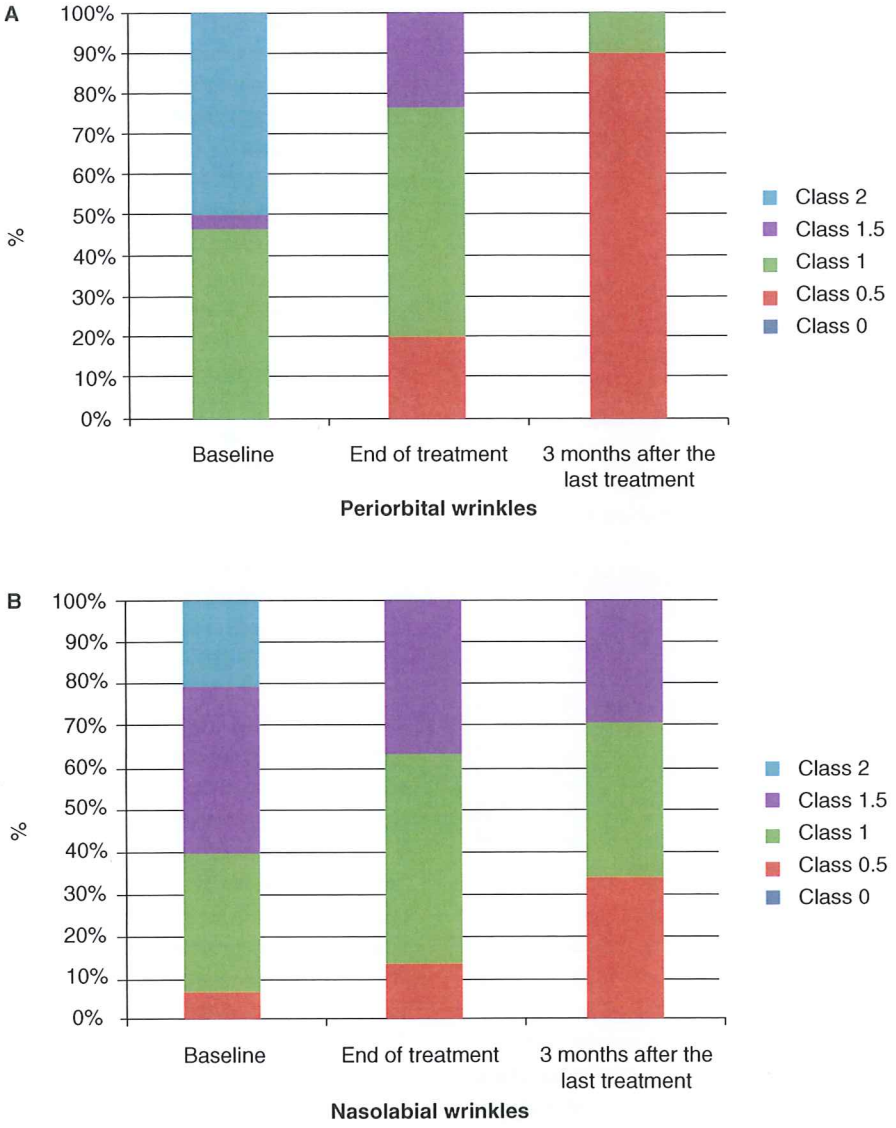

Figure 1. Evaluation of the severity of (A) periorbital wrinkles and (B) nasolabial wrinkles according to the modified Fitzpatrick wrinkle scale (MFWS) at baseline, at the end-of-treatment visit and 3 months after the end-of-treatment visit.

wrinkles (0.58 ± 0.30) ($p < 0.001$). Conversely, no significant difference in average late improvement was found between periorbital (0.47 ± 0.29) and nasolabial (0.33 ± 0.29) ($p = 0.07$).

The MFWS evaluations at baseline, at the end-of-treatment visit and 3 months after treatment were not correlated with skin type for either periorbital or nasolabial wrinkles.

A significantly negative correlation of early improvement in nasolabial wrinkles with skin type was observed (Spearman's rho = -0.38, $p = 0.04$), whereas late and overall improvements were not correlated with skin type.

There have been no side effects during the treatment and the 3 months follow-up period.

Three months after the end-of-treatment visit, 14 of 30 (47%) patients scored their degree of satisfaction and overall improvement as excellent, 12 of 30 (40%) patients as good and 4 of 30 (13%) patients as fair.

Discussion

Our study showed that IPL-PDT treatment using 0.5% 5-ALA spray and Ellipse Flex PPT system resulted in a significant "early", "late" and "overall" improvement of both periorbital and nasolabial wrinkles in patients with type 2 photoaging.

Photorejuvenation is a new application of PDT either with 20% 5-ALA or MAL (2,13–15). IPL has been recently demonstrated as a valid alternative

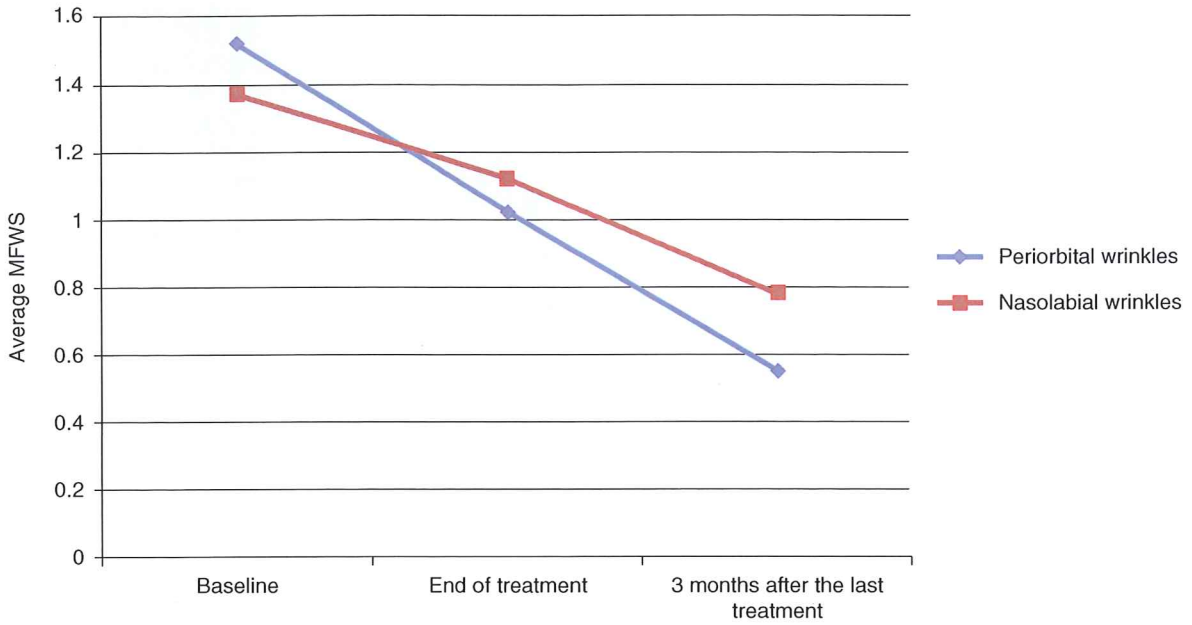

Figure 2. Average modified Fitzpatrick wrinkle scale (MFWS) evaluations for periorbital and nasolabial wrinkles at baseline, at the end-of-treatment visit and 3 months after end-of-treatment visit.

to standard light-emitting diode (LED) system as a light source for PDT. In a prospective randomized-controlled split-face study, complete regression and cosmetic outcome were equivalent for IPL-PDT and standard LED-PDT in the treatment of actinic keratosis (16). In addition, ALA-PDT using an IPL device showed significant better improvement as compared with IPL alone in the treatment of the different clinical aspects of photodamage and in the clearance rate of actinic keratosis (17). We used a new IPL system (Ellipse Flex PPT) with a specific program and a handful device for PDT (PL-W applicator) which has been recently introduced in the market.

PDT with 20% 5-ALA under occlusion according to the standard procedure is often complicated by side effects such as pain, erythema and post-treatment hyperpigmentation. Reduction of these side effects might be obtained by reducing the concentration or the application time of the photosensitizer or by reducing light fluences. The use of 5-ALA at concentrations of 1% or 2% applied several times, every 10–15 min and incubated for 30–60 min, improved photodamage and skin elasticity with high patient satisfaction (18). In the present study, we used a new formulation of 0.5% liposome-encapsulated 5-ALA spray to reduce PDT-related side effects.

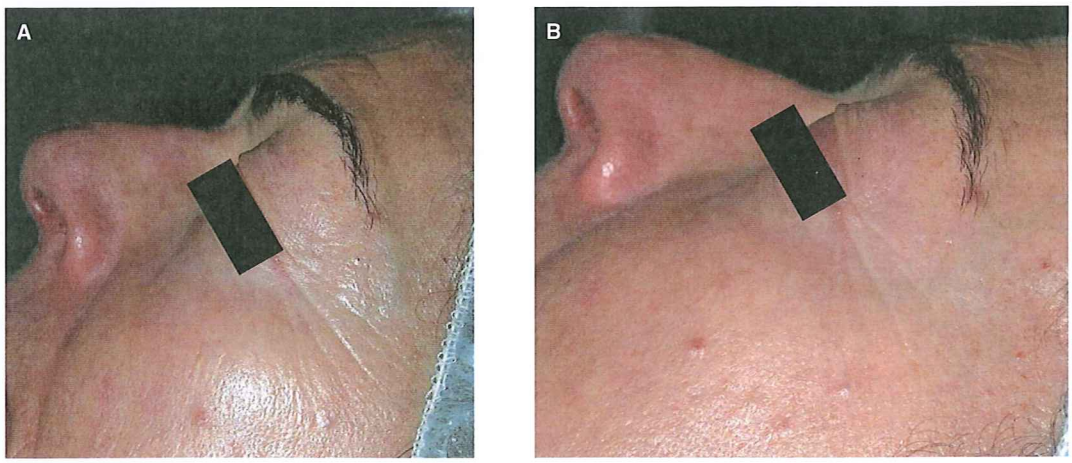

Figure 3. Periorbital wrinkles: a 57-year-old woman at (A) baseline and (B) 3 months after the last treatment.

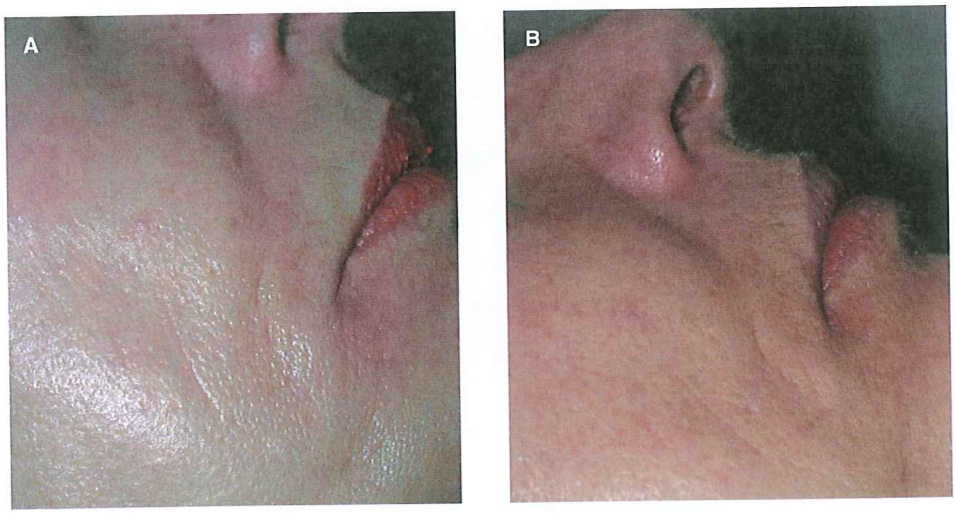

Figure 4. Nasolabial wrinkles: a 51-year-old woman at (A) baseline and (B) 3 months after the last treatment.

Changing the 5-ALA vehicle from a moisturizing cream to liposomes provides the opportunity to lower ALA concentration, still inducing the same effectiveness, but reducing the side effects (19). The similarity of lipid composition of liposomes and epidermal membranes allows the compounds encapsulated into liposomes to penetrate into the epidermal barrier to a higher extent as compared with other application forms. The level of skin fluorescence after 1 h spraying with this new 0.5% 5-ALA liposomal spray has been indeed shown to be identical to that obtained after 30 min application of 20% 5-ALA in a cream base (6). Clinically, liposome-encapsulated 0.5% 5-ALA has been shown to induce a statistically significant improvement in wrinkle reduction and skin texture, which was equivalent to that obtained with 20% ALA although with fewer side effects (20). In our study, an overall improvement of at least one class of the MFWS was observed in 100% of participants for periorbital wrinkles and in 90% for nasolabial wrinkles. Eighty-seven percent of the volunteers scored their degree of satisfaction as excellent or good. Notably, there have been no side effects during the treatment and the 3 months follow-up period.

Reduction of the clinical signs of photoaging after PDT has been confirmed by several histopathologic evidences (5,21). Histopathologic and morphometric changes after MAL-PDT have indeed demonstrated an increase of collagen fibers and a decrease of elastic fibers (21). Similarly, ALA-PDT resulted in restoration of photoaged skin with significant increase of the total collagen volume in the dermis and expression of type I and III protocollagen as well as decrease of the elastotic material and of fibrillin-1 and tropoelastin (5). We observed a significantly greater average overall improvement for periorbital wrinkles than nasolabial wrinkles probably due to the different skin

Table II. Early, late and overall improvement measured as classes of reduction in MFWS.

	Early improvement No. (%)		Late improvement No. (%)		Overall improvement No. (%)	
Reduction in MFWS (no. of classes)	Periorbital wrinkles	Nasolabial wrinkles	Periorbital wrinkles	Nasolabial wrinkles	Periorbital wrinkles	Nasolabial wrinkles
0	8 (27)	15 (50)	6 (20)	10 (33)	–	3 (10)
1	14 (46)	15 (50)	20 (67)	20 (67)	14 (47)	19 (63)
2	8 (27)	–	4 (13)	–	4 (13)	8 (27)
3	–	–	–	–	12 (40)	–
Mean (SD)	0.50 (0.37)	0.25 (0.25)	0.47 (0.29)	0.33 (0.29)	0.97 (0.47)	0.58 (0.30)

MFWS = modified Fitzpatrick wrinkle scale.

thickness at the both sites or to a more facial expression of the nasolabial area.

PDT using the 5-ALA 0.5% liposomal spray has been recently shown to be effective and safe also for the treatment of inflammatory acne, either alone or in combination with topical peeling agents (22,23).

In conclusion, our results demonstrated that IPL-PDT treatment using 5-ALA 0.5% liposomal spray and Ellipse Flex PPT system is effective and safe for the treatment of type 2 photoaging with reduced PDT-associated side effects.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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