Transepidermal drug delivery in daylight photodynamic therapy in the treatment of photodamaged skin: a pilot study

ABSTRACT

INTRODUCTION: Daylight photodynamic therapy (PDT) is a recent therapeutic modality for actinic keratoses and field cancerization. The association of techniques to PDT for transepidermal delivery of the photosensitizer is a new option for the treatment of photodamaged skin with actinic keratosis.

OBJECTIVE: To evaluate the clinical efficacy and the adverse events of photodamaged skin treatment through the transepidermal drug delivery and daylight-PDT.

METHODS: Seven patients with phototype II and III, aged 60-73 years, with photodamaged skin, with and without actinic keratoses, were submitted to the association of methods (CO₂ laser, micro-abrasion or microneedling) and daylight-PDT. Two sessions were performed with two weeks intervals. MAL was applied after micro-abrasion and after CO₂ laser, but before the micro-needling. All patients were exposed to daylight for a period of 2 hours. Clinical evaluations were performed before, 15 days and three months after treatment.

RESULTS: CO₂ laser associated with daylight-PDT was more effective in overall improvement of the skin (texture, pigmentation and wrinkles). Microneedling associated with daylight-PDT was effective in improving texture and pigmentation. Micro-abrasion proved to be effective when combined with microneedling. Excellent improvement of actinic keratosis lesions was achieved with all associations of techniques. Adverse events were transient and more intense with the association of CO₂ Laser.

CONCLUSION: Association of TDD with daylight-PDT was effective in the treatment of photodamaged skin and safe in all protocols.

Keywords: photodynamic therapy, photosensitizer, light, actinic keratosis, photoaging.

RESUMO

INTRODUÇÃO: A Terapia Fotodinâmica com a luz do dia é uma modalidade terapêutica recente para ceratose actínica e campo de cancerização. A associação de técnicas à TFD para aplicação transepidérmica do fotossensibilizante é uma nova opção para tratamento da pele fotodanificada com ceratose actínica.

OBJETIVO: Avaliar a eficácia clínica e os efeitos colaterais do tratamento de pele fotodanificada através da aplicação transepidérmica de medicamentos e TFD com luz do dia.

MÉTODOS: Sete pacientes fototipos II e III, 60-73 anos, com pele fotodanificada, com e sem ceratose actínica foram submetidos à associação de métodos (laser de CO₂, micro-abrasão ou microagulhamento) e TFD com luz do dia. Foram realizadas duas sessões com intervalo de duas semanas. O MAL foi aplicado após a micro-abrasão e após o laser de CO₂, entretanto antes do micro-agulhamento. Todos os pacientes foram expostos à luz do dia por um período de 2 horas. Avaliações clínicas foram realizadas antes, 15 dias e três meses após tratamento.

RESULTADOS: O Laser de CO₂ associado à DLPDT foi mais eficaz na melhora global da pele (textura, pigmentação e rugas). O micro-agulhamento associado à DLPDT foi eficaz na melhora da textura e da pigmentação. A micro-abrasão se mostrou eficaz quando associada ao microagulhamento. Excelente melhora das lesões de ceratose actínica foi alcançada com todas as associações de técnicas. Os efeitos colaterais foram transitórios e mais intensos com a associação de Laser de CO₂.

CONCLUSÕES: A associação de TED à DLPDT foi eficaz no tratamento da pele fotodanificada e segura em todas as protocolos.

Palavras-chave: terapia fotodinâmica; fotossensibilizante; luz; ceratose actínica; fotoenvelhecimento.
INTRODUCTION

Chronic exposure to sunlight increases the incidence of nonmelanoma skin cancer, to be included of actinic keratosis (AK), basal cellular carcinoma and spinocellular carcinoma. It is also responsible for the photoaging of the skin, observed clinically by the presence of wrinkles, erythema, coarseness, telangiectasia and irregular pigmentation. Among treatment options for photodamaged skin with AK, conventional photodynamic therapy (c-PDT) stands out due to its high efficacy and excellent cosmetic results. Some factors, such as side-effects (pain, erythema and edema), the incubation time of the methyl aminolevulinate (MAL) lasting 3 hours under an occlusive dressing and the need of an artificial lamp for the lighting, may be limiting for patients and doctors.2,3

Over the last few years, studies have reported the efficacy of a new technique, which follows the same principle of c-PDT, but uses daylight as a source of light (fraction of visible sunlight). Daylight Photodynamic Therapy (DLPDT) is well tolerated by the patient. Pain is either absent or discrete during the lighting, and cutaneous reaction in the period following the procedure, such as erythema and edema, are minimal.4-11

The treatment protocols of the conventional form and with the sunlight differ in several aspects (Table 1). With c-PDT, the MAL must be applied to the previously curetted skin, and maintained under occlusion for a period of 3 hours. After this incubation period, the skin is exposed to a source of artificial light (red LED) for approximately 10 minutes, which is equivalent to a dose of 37J/cm². With the DLPDT, the MAL is applied without occlusion over the previously curetted area and with the chemical sunscreen. The patient must be exposed to daylight, in up to 30 minutes of the procedure, and remain under it for a period of 2 hours. DLPDT minimizes the disadvantages of c-PDT, and maintains its efficacy in the treatment of actinic keratosis and cutaneous field cancerization.4,11

Regardless of the type of light that is being used, artificial or daylight, the penetration of the photosensitizer through the stratum corneum layer in the area of the skin that is to receive treatment remains a limiting factor of the technique. Inasmuch, a new possibility for the PDT is the association of techniques that may augment the penetration of the photosensitizer. This new therapeutic modality is called transepidermal drug delivery (TED). Among the most recently described techniques for performing TED are microneedling12-14 and the fractional ablative methods, such as fractional ablative radiofrequency and the CO₂ and Erbium lasers.15-19 Microneedling acts by “pushing” the medication through the perforations caused during its application on the cutaneous surface. The fractional ablative methods promote the production of pathways within the epidermis all the way to the papillary dermis, depending on the parameters being used, which permeate the substances applied topically. Microdermabrasion collaborates with simple curettage in order to remove the topmost layers of the epidermis.

Several studies have reported the association of fractional ablative methods with a method for potentializing the efficacy of the c-PDT.20-24 Also, it is mentioned that this clinical response, potentialized by the association of TED with c-PDT may be attained even with a time reduction in the incubation of MAL to one hour.15 The association of TED with DLPDT however, is still rarely mentioned in the medical literature. The efficacy in the association of the CO₂ laser with the DLPDT in the treatment of actinic keratosis in transplanted patients was recently reported by Togsverd-Bo et al in 2015.25

Based on recent data found in the medical literature, we have proposed this pilot study, which seeks to clinically evaluate the modifications induced by this association (TED + DLPDT), by comparing different protocols and techniques.

METHODOLOGY

CLINICAL TRIAL STUDY DESIGN

A non-randomized prospective pilot study was done with 7 patients from both genders, phototypes II and III, aged between 60 and 73 years old, presenting photodamaged skin on the face and chest (degrees III and IV on the Glogau scale), with and without actinic keratoses. Patients who were smokers, pregnant, diagnosed with photosensitivity, malignant neoplasm, collagenoses, local or systemic infections, immunodepression or were making use of photosensitive substances. All patients were photographed and signed a consent and clarification form in order to take part in the study. The procedures took place at the researcher’s private clinic, which allowed for the usage of her own CO₂ laser (I-Pixel CO₂ – Alma Lasers, Caesarea, Isra-

| Table 1: Differences between conventional PDT and PDT with daylight |
|-----------------|------------------|
| **c-PDT**       | **DLPDT**        |
| PREPARATION     | Curettage        |
| INCUBATION OF PHOTOSENSITIZER (MAL) | 3 hours under occlusion |
| LIGHT SOURCE    | Artificial (Light-Emitting Diode / LED) |
| EXPOSURE TIME TO LIGHT SOURCE | Approximately 10 minutes |
|                 | 2 hours          |
rael), her crystal peeling device (by the company Pan Electronic, Rio de Janeiro, Brazil), and donated the derma rollers (Doctorroller–2.5mm, Moohant Enterprise Ltd, Gwangju, South Korea). The MAL was donated by Galderma Pharmaceutical Industry (Galderma Indústria Farmacêutica). The patients had no financial expenditures but their transportation costs. The researchers involved received no remuneration.

The treatment was comprised of undergoing one or two MAL-TFD sessions with daylight, two weeks apart, in combination with the transepidermal application techniques of MAL (aluminum oxide crystal microdermabrasion – crystal peeling; microneedling; and fractional CO₂ ablative laser). In some cases, cosmeceuticals, such as vitamin C and depigmenting agents (Skinceuticals, L’Oréal, Paris, France) were combined with the MAL for drug delivery. After each session, the patients were told to apply a wound healing cream that contained dexpanthenol (3x/day for 7 days) and SPF50 sunscreen (Actinica® Galderma, Paris, France). Prophylaxis was carried out using an antiviral (acyclovir) at its full dosage for five days in all patients who underwent laser and microneedling procedures. Applying the sunscreen was the first step of the protocol, even before all other procedures, except for those cases in which microdermabrasion with crystal peeling was used.

The photosensitizer used was the 16% MAL cream (Metvix®, GALDERMA, Paris, France) in the amount of 1 gram per peeling. It was applied after the curettage of the lesions, and immediately before the application of MAL, with the following parameters: 60 watts of power, fluence of 20 mJ/pixel, spacing of 3 mm in between the pixels, with one single scrub of the whole area, using a roller tip.

CLINICAL EVALUATION

The patients had follow-ups for a period of 3 months in order to evaluate the cure rate of the actinic keratoses and the overall degree of improvement of the skin (texture, wrinkles and pigmentation). Evaluations took place before the procedures first began, 15 days after the first session and 3 months after the treatment.

Texture (coarseness), color (pigmentation) and wrinkles analysis were conducted by the means of qualitative parameters, using the Glogau Aging Scale. The degree of improvement was evaluated in accordance to the quartile scale proposed by Alster et al., which considers improvement as minimal (<25%); moderate (25%-50%); significant (51%-75%), and excellent (>75%).

The evaluation concerning the improvement in the actinic keratosis lesions was done with quantitative parameters (lesion count), and also qualitative in accordance to thickness levels (grades 1, 2 and 3). The side effects (pain, erythema and edema) were evaluated by an intensity scale varying from absent, mild, moderate and intense, in the periods immediately following the procedure and two hours after having been exposed to sunlight.

CLINICAL CASES

Case 1:
ID: Male, 70 years old, phototype III (Table 2).
Actinic Keratosis: 3 AK lesions, grade II (2 on the right side, one being hyperchromatic; and 1 on the left side).
Aging Grade: Glogau Type III.
Procedure: face: Two sessions of MAL-DLNPDT in combination with the fractional CO₂ ablative laser on the right hemiface and microneedling on the left hemiface (Figure 1).
Post Immediate: Side treated with the CO₂ laser (right): moderate pain; moderate erythema; mild edema. Side treated with the microneedling (left): mild pain; mild erythema; absence of edema (Table 3).
After 2 hours: Side treated with the CO₂ laser (right): mild pain; moderate erythema; mild edema. Side treated with the microneedling (left): absence of pain; mild erythema; absence of edema (Figure 2). (Table 3).
After 15 days: Side treated with the CO₂ laser (right): showed moderate improvement in texture; showed no improvement in wrinkles and pigmentation; and 50% clinical cure of the actinic keratosis lesions. Side treated with the microneedling (left): showed minimum improvement in texture; absence of improvement in wrinkles and pigmentation; and 100% clinical cure of actinic keratosis (Table 4).
Results after 3 months: On the side treated with the CO₂ laser (right), there was significant improvement in texture, minimum improvement in wrinkles and pigmentation (Figure 3). The cure rate of the AK was 50%, without improvement of the hyperchromatic lesion. On the side treated with microneedling (left), there was 50% improvement in texture, absence of improvement in wrinkles and pigmentation (Figure 4).
Table 2: Demographic data and classification of lesions

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>AGE</th>
<th>GENDER</th>
<th>PLACE</th>
<th>PHOTOTYPE</th>
<th>ACTINIC KERATOSIS NUMBER / AREA</th>
<th>GRADE / AREA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>M</td>
<td>FACE</td>
<td>III</td>
<td>3 (2D e 1E)</td>
<td>II (*)</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>M</td>
<td>FACE</td>
<td>III</td>
<td>6 (6D)</td>
<td>I- 3 Lesions</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>F</td>
<td>FACE</td>
<td>II</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>F</td>
<td>FACE</td>
<td>III</td>
<td>2 (1D e 1E)</td>
<td>II</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>F</td>
<td>CHEST</td>
<td>II</td>
<td>8 (5D e 3E)</td>
<td>II</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>F</td>
<td>FACE</td>
<td>III</td>
<td>5 (5D)</td>
<td>II</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>F</td>
<td>FACE</td>
<td>III</td>
<td>15 (9D e 6E)</td>
<td>II</td>
</tr>
</tbody>
</table>


**Figure 1: Case 1** - Procedure: Right side with CO2 laser before the application of MAL. Left side, application of MAL before microneedling.
There was moderate improvement in texture. There was no improvement in wrinkles nor in pigmentation. The AK lesion was cured (Table 5).

Case 2:

ID: Male, 73 years old, phototype III (Table 2).

Actinic Keratosis: 6 AK lesions on the right hemiface (3 grade II and 3 grade III).

Aging Grade: Glogau Type III.

Procedure: face: Two sessions of MAL-DLPDT in combination with microneedling on both hemifaces. On the right hemiface, MAL was used isolatedly, and on the left hemiface, MAL was combined with a depigmenting agent and vitamin C.

Post immediate: Moderate pain; mild erythema; absence of edema on either side. (Table 3).

After two hours: Absence of pain; mild erythema; absence of edema on either side. (Table 3).

After 15 days: On the side treated with a combination of microneedling and MAL (right), there was minimum improvement in texture, wrinkles and pigmentation; 33.4% clini-
Table 4: Clinical Evaluations after Session 2

<table>
<thead>
<tr>
<th>C/ID</th>
<th>Gender</th>
<th>Age</th>
<th>Treated area</th>
<th>Procedure used in the second session</th>
<th>3 MONTHS AFTER THE SECOND SESSION OF TED + DLPDT</th>
<th>Absence of improvement</th>
<th>Absence of improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right side</td>
<td>Left side</td>
<td>Right side</td>
<td>Left side</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>70</td>
<td>Face</td>
<td>Co2 + Mal + Derma Roller + Mal</td>
<td>51-75%</td>
<td>1-25%</td>
<td>1-25%</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>73</td>
<td>Face</td>
<td>Derma Roller + Mal with depigmenting agent and vitamin C</td>
<td>51-75%</td>
<td>1-25%</td>
<td>1-25%</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>73</td>
<td>Face</td>
<td>Co2 + Mal with depigmenting agent and vitamin C</td>
<td>51-75%</td>
<td>51-75%</td>
<td>26-50%</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>60</td>
<td>Face</td>
<td>Co2 + Mal</td>
<td>26-50%</td>
<td>1-25%</td>
<td>Not applicable</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>70</td>
<td>Chest</td>
<td>Co2 + Mal</td>
<td>51-75%</td>
<td>26-50%</td>
<td>26-50%</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>72</td>
<td>Face</td>
<td>Not applicable</td>
<td>26-50%</td>
<td>1-25%</td>
<td>1-25%</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>54</td>
<td>Face</td>
<td>Not applicable</td>
<td>51-75%</td>
<td>51-75%</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Obs: Cases 6 and 7 – The evaluation of patients took place 3 months after one single treatment session.

Results after 3 months: On the side treated with a combination of microneedling and MAL (right), there was significant improvement in texture, and minimum improvement in wrinkles and pigmentation. The cure rate of the AK was 83.3%, with 16.7% being reduced from grade III to grade II (Figure 4). On the side treated with a combination of microneedling and MAL + depigmenting agents with vitamin C (left), (Figure 5), there was significant improvement in texture; minimum improvement in wrinkles; moderate improvement in pigmentation (Table 5).

Case 3:
Descriptive parameters: Female, 73 years old, phototype III (Table 2).
Actinic Keratosis: absent
Aging Grade: Glogau Type III
Procedure: face: Two sessions of MAL-DLPDT in combination with the fractional CO2 ablative laser on both hemifaces. On the right hemiface, the MAL was applied isolat edly, on the left hemiface the MAL was combined with a depigmenting agent + vitamin C.
Post immediate: Intense pain and erythema and moderate edema on either side. (Table 3).
After 2 hours: Absence of pain; mild edema; moderate erythema on either side. (Table 3).
After 15 days: On the side treated with a combination...
of CO₂ and MAL (right), there was moderate improvement in texture; and minimum improvement in wrinkles and pigmentation. On the side treated with a combination of CO₂ and MAL + depigmenting agent + vitamin C (left), there was moderate improvement in texture; minimum improvement in wrinkles and pigmentation. (Table 4).

**Results after 3 months:** On the side treated with a combination of CO₂ and MAL (right), there was significant improvement in texture and in wrinkles, with moderate improvement in pigmentation.

On the side treated with a combination of CO₂ and MAL + depigmenting agent + vitamin C (left), (Figure 6), there was significant improvement in texture, wrinkles and pigmentation. (Table 5).

**Case 4:**

**ID:** Female, 60 years old, phototype III (Table 2).

**Actinic Keratosis:** 2 AK lesions, grade II (1 on the right side and 1 on the left side).

**Aging Grade:** Glogau Type IV.

**Procedure: face:** Two sessions of MAL-DLPDT in combination with the fractional CO₂ ablative laser on both hemifaces.

**Post immediate:** Moderate pain; mild erythema; mild edema, on both sides. (Table 3).

**After 2 hours:** Mild pain; moderate erythema; mild edema, on both sides. (Table 3).
After 15 days: There was minimum improvement in texture; there was no improvement in wrinkles nor in pigmentation; and 100% clinical cure of the actinic keratosis on both sides (Table 4).

Results after 3 months: Moderate improvement in texture, minimum improvement in wrinkles. The cure rate of the AK was 100% on both sides (Table 5).

Case 5:
ID: Female, 70 years old, phototype II (Table 2).
Actinic Keratosis: 8 AK lesions, grade II (5 on the right side and 3 on the left side).
Aging Grade: Glogau Type III.
Procedure: cleft: Two sessions of MAL-DLPDT in combination with the fractional CO₂ ablative laser on both sides of the cleft (divided by an imaginary line between the sternum furcula and the xiphoid process).
Post immediate: Moderate pain; mild erythema; mild edema on both sides. (Table 3).
After 2 hours: Mild pain; moderate erythema; mild edema on both sides. (Table 3).
After 15 days: On the right side, there was moderate improvement in texture and pigmentation, and minimum improvement in wrinkles; with 60% clinical cure and 40% improvement actinic keratosis grading. On the left side, there was moderate improvement in texture and pigmentation; and minimum improvement in wrinkles; with 100% clinical cure of actinic keratosis (Table 4).

Results after 3 months: Significant improvement in texture, moderate improvement in wrinkles and pigmentation on both sides (Figure 7). The cure rate of AK was 80%, with 20% improvement in the reduction grading of the keratosis (from II to I) on the right side. On the left side, the cure rate was 100% (Table 5).

Case 6:
ID: Female, 72 years old, phototype III (Table 2).
Actinic Keratosis: 5 AK lesions, grade II, right side.
Aging Grade: Glogau Type III.
Procedure: face: One single session of MAL-DLPDT in combination with microdermabrasion (crystal peeling) on both hemifaces.

Post Immediate: Mild pain and erythema; absence of edema on either side. (Table 3).
After 2 hours: Mild pain and erythema; absence of edema on either side. (Table 3).
After 15 days: There was moderate improvement in texture, and minimal improvement in wrinkles and pigmentation on both sides.

On the right side, there was 80% clinical cure and 20% improvement in the actinic keratosis grading. (Table 4).

Results after 3 months: Moderate improvement in texture, minimal improvement in wrinkles and pigmentation.
The cure rate of the AK was of 100% (Table 5).

Case 7:
ID: Female, 54 years old, phototype III (Table 2).
Actinic Keratosis: 15 AK lesions, grade II (9 on the right side and 6 on the left side).
Aging Grade: Glogau Type III.
Procedure: face: One single session of MAL-DLPDT in combination with microdermabrasion (crystal peeling) +
microneedling on both hemifaces.

**Post Immediate:** Moderate pain and edema; intense erythema on both sides. (Table 3).

**After 2 hours:** Moderate pain and edema; intense erythema on both sides. (Table 3).

**After 15 days:** For both hemifaces, there was moderate improvement in texture; and minimal improvement in wrinkles. On the right side, there was 77.7% clinical cure and 22.3% improvement in the actinic keratosis grading. On the left side, there was 66.6% clinical cure and 33.4% improvement in the actinic keratosis grading (Table 4).

**Results after 3 months:** Significant improvement in texture and in wrinkles on both sides (Figures 8 and 9). The cure rate of the AK was 88.8% on the right side, with an improvement in the actinic keratosis grading (from II to I) in 11.2%. On the left side, the cure rate of the keratosis was 100% (Table 5).

**RESULTS**

The CO₂ Laser in combination with DLPDT was more effective in the overall improvement of the skin, mainly in the improvement of wrinkles, when compared to microneedling. Microneedling in combination with DLPDT has proven to be effective in the improvement of texture and pigmentation, mainly when combined with cosmeceutical depigmenting agents. The combination of two TED (microdermabrasion with microneedling) techniques with DLPDT was more effective in the improvement of texture, pigmentation and wrinkles when compared to the use of techniques isolatedly. Excellent improvement in the actinic keratosis lesions was attained with techniques that were combined with TED and DLPDT.

Among all possible side-effects, pain, erythema and edema were observed in most patients. However, these side-effects were observed with greater intensity (moderato to intense) with protocols in which the CO₂ Laser was used. Side effects were mild to moderate when using microdermabrasion or microneedling. The case in which two techniques were combined, microdermabrasion and microneedling to DLPDT, erythema, edema and pain were more intense.

**DISCUSSION**

Several studies have already shown an increase in effectiveness of conventional PDT in the treatment of actinic keratosis and field cancerization, in combination with methods to increase the permeation of the photosensitizer. However, there is a lack of studies regarding the combination of TED with PDT while using daylight. This pilot study is the first of its kind to be conducted in Brazil with the goal to evaluate TED technique with DLPDT.

In the international medical literature, Togsverd-Bo et al have compared the efficacy of isolated DLPDT with DLPDT in combination with the fractional CO₂ ablative laser in the treatment of actinic keratosis with transplanted patients. In our study, we have evaluated the combination of DLPDT with the CO₂ laser and, also, with microneedling and microdermabrasion in the treatment of photodamaged skin with and without actinic keratosis in immunocompetent patients. Togsverd-Bo et al have reported erythema and edema to be more intense in the areas treated with DLPDT when combined with the laser after the procedure, with no long-term change in pigmentation. In our cases, we have also observed a mild increase of erythema and edema immediately after the laser treatment and, also, after daylight exposure, which were transitory, not leading to postinflammatory pigmentation. We have also observed the overall improvement of the skin (texture, fine wrinkles and pigmentation) in varying intensity, according to the other techniques (laser and non-laser) in combination with DLPDT. The clinical response was more evident when combined with the CO₂ laser, and also when we combined the DLPDT to the microdermabrasion with microneedling. The response in pigmentation was slightly better when we combined depigmenting agents and vitamin C to the MAL, either before the microneedling or after the CO₂ laser.

**CONCLUSION**

Based on the methodology that was used, it is possible to state that the combination of methods such as the CO₂ laser, microdermabrasion and microneedling with DLPDT has proven to be effective in the treatment of photodamaged skin, with improvement of actinic keratosis, texture, pigmentation and wrinkles. The combination of TED and DLPDT was safe in all protocols that it was used.

**REFERENCES**


16. Letada PR, Shumaker PR, Uebrilhoer NS. Demonstration of protoporphyrin IX (PpIX) localized to area of palmar skin injected with 5-aminolevulinic acid (ALA) and pre-treated with a fractionated CO2 laser prior to topically applied ALA. Photodiagnosis Photodyn Ther. 2010; 7(2): 120-2.


