

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

*Aplicação transepidérmica de medicamento na terapia fotodinâmica com a luz do dia para o tratamento da pele fotodanificada: estudo piloto*

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## 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 (CO<sub>2</sub> laser, micro-abrasion or microneedling) and daylight-PDT. Two sessions were performed with two weeks intervals. MAL was applied after micro-abrasion and after CO<sub>2</sub> 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:** CO<sub>2</sub> 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 CO<sub>2</sub> 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 ceratoses actínicas 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 da 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 ceratoses actínicas foram submetidos à associação de métodos (laser de CO<sub>2</sub>, micro-abrasão ou microagulhamento) e TFD com a 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 CO<sub>2</sub>, 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 CO<sub>2</sub> 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 CO<sub>2</sub>.

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

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

## Original Articles

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## 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.<sup>1</sup> 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.<sup>2,3</sup>

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.<sup>4-11</sup>

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/cm<sup>2</sup>. 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 after 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.<sup>4-11</sup>

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 deliv-

ery (TED). Among the most recently described techniques for performing TED are microneedling<sup>12-14</sup> and the fractional ablative methods, such as fractional ablative radiofrequency and the CO<sub>2</sub> and Erbium lasers.<sup>15-19</sup> 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.<sup>20-24</sup> 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.<sup>15</sup> The association of TED with DLPDT however, is still rarely mentioned in the medical literature. The efficacy in the association of the CO<sub>2</sub> laser with the DLPDT in the treatment of actinic keratosis in transplanted patients was recently reported by Togsverd-Bo et al in 2015.<sup>25</sup>

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 keratosis. Patients who were smokers, pregnant, diagnosed with photosensitivity, malignant neoplasm, collagenosis, 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 CO<sub>2</sub> laser (I-Pixel CO<sub>2</sub> – Alma Lasers, Caesarea, Is-

Table 1: Differences between conventional PDT and PDT with daylight

	c-PDT	DLPDT
PREPARATION	Curettage	Curettage + Chemical sunscreen
INCUBATION OF PHOTOSENSITIZER (MAL)	3 hours under occlusion	Maximum of 30 minutes without occlusion
LIGHT SOURCE	Artificial (Light-Emitting Diode / LED)	Daylight (Fraction of Visible Sunlight)
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 (Doctor-roller-2,5mm, Moohan 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 CO<sub>2</sub> ablative laser). In some cases, cosmeceuticals, such as vitamin C and depigmenting agents (Sk-inceuticals, 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 (Met-vix®, GALDERMA, Paris, France) in the amount of 1 gram per session (face or cleft) in all patients. However, the order it was applied varied according to the method of TED that was used. Thus, the MAL was applied after the microdermabrasion and after the CO<sub>2</sub> laser, however it was always applied before the microneedling. It was only in one patient that two TED techniques were used in the same area in one single session. In this case, the MAL was applied after the microdermabrasion and before the microneedling. In every situation, however, the MAL was applied after the sunscreen.

All patients were exposed to daylight within 30 minutes of the MAL application, remaining exposed for 2 hours (open and well-lit space) before returning to the clinic for the skin cleansing with 0.9% Saline, reapplication of sunscreen and clinical evaluation of the immediate effects.

## TECHNIQUES FOR TRANSEPIDERMAL APPLICATION OF DRUGS

1. Aluminum Oxide Crystal Microdermabrasion (Crystal Peeling):

Before the simple curettage and the application of MAL, many scrubs in different directions were performed (vertical, horizontal and oblique) until a homogeneous erythema in the entire area was reached.

2. Microneedling:

The derma roller with 2.5mm needles was used immediately after the application of the MAL photosensitizer. Several scrubs in different directions were performed (like an asterisk), without causing bleeding.

3. Fractional Ablative CO<sub>2</sub> Laser:

It was applied after the curettage of the lesions, and im-

mediately 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<sup>26</sup>, 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-DLPDT in combination with the fractional CO<sub>2</sub> ablative laser on the right hemiface and microneedling on the left hemiface (Figure 1).

**Post Immediate:** Side treated with the CO<sub>2</sub> 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 CO<sub>2</sub> 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 CO<sub>2</sub> 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 CO<sub>2</sub> 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 micronee-

Table 2: Demographic data and classification of lesions

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

Legenda: \*: 1 lesão hipercrômica. D: direita. E: esquerda.



**FIGURE 1: Case 1** - Procedure: Right side with CO2 laser before the application of MAL. Left side, application of MAL before microneedling



Table 3: Clinical evaluations after Session 1

c	Gender	AGE	Treated Area	PROCEDURE USED IN THE FIRST SESSION		15 DAYS AFTER THE FIRST SESSION							
				RIGHT SIDE	LEFT SIDE	RIGHT SIDE				LEFT SIDE			
						Texture	Wrinkles	Pigmentation	Actinic Keratosis	Texture	Wrinkles	Pigmentation	Actinic Keratosis
1	M	70	FACE	CO <sub>2</sub> + MAL	Derma Roller	Moderate + MAL	Absence of improvement	Absence of improvement	50% Clinical Cure	Minimal	Absence of improvement	Absence of improvement	100% Clinical Cure
2	M	73	FACE	Derma Roller + MAL	Derma Roller + MAL with depigmenting agent and vitamin C	Minimal	Minimal	Minimal	33,4% Clinical Cure 66,6% Improvement in the grade	Minimal	Minimal	Moderate	Not applicable
3	F	73	FACE	CO <sub>2</sub> + MAL	CO <sub>2</sub> + MAL with depigmenting agent and vitamin C	Moderate	Minimal	Minimal	Not applicable	Minimal	Minimal	Moderate	Not applicable
4	F	60	FACE	CO <sub>2</sub> + MAL	CO <sub>2</sub> + MAL	Minimal	Absence of improvement	Not applicable	100% Clinical Cure	Minimal	Absence of improvement	Not applicable	100% Clinical Cure
5	F	70	COLO	CO <sub>2</sub> + MAL	CO <sub>2</sub> + MAL	Moderate	Minimal	Moderate	60% Clinical Cure 40% Improvement in the grade	Moderate	Minimal	Moderate	100% Clinical Cure
6	F	72	FACE	Crystal + MAL	Crystal + MAL	Moderate	Minimal	Minimal	80% Cure	Moderate	Minimal	Minimal	Not applicable
7	F	54	FACE	Crystal + MAL + Derma Roller	Crystal + MAL + Derma Roller	Moderate	Minimal	Not applicable	77,7% Cure	Moderate	Minimal	Not applicable	66,6% Cure

Key - \*: Improvement evaluation according to Tina Alster's grading scale, which considers minimal improvement (<25%); moderate (25% - 50%); significant (51% - 75%); and excellent (>75%).



**FIGURE 2: Case 1** - Comparison of erythema 2 hours after it was exposed to the light. Right side (CO<sub>2</sub> laser + DLPDT) and left side (microneedling + DLPDT)

ding (left), 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% clinical

Table 4: Clinical Evaluations after Session 2

C	Gender	age	Treated area	Procedure used in the second	3 MONTHS AFTER THE SECOND SESSION OF TED + DLPDT								
					Right side	Left side	Right side			Left side			
							Textura	Wrinkles	Pigmentation	Actinic Keratosis	Texture	Wrinkles	Pigmentation
1	M	70	Face	Co2 + Mal	Derma Roller + Mal	51-75%	1-25%	1-25%	50% Clinical cure	26-50%	Absence of improvement	Absence of improvement	100% Clinical cure
2	M	73	Face	Derma Roller + Mal	Derma Roller + Mal with depigmenting agent and vitamin C	51-75%	1-25%	1-25%	83,3% Clinical cure 16,7% Improvement in the grade	51-75%	1-25%	26-50%	Not applicable
3	F	73	Face	Co2 + Mal	Co2 + Mal with depigmenting agent and vitamin C	51-75%	51-75%	26-50%	Not applicable	51-75%	51-75%	51-75%	Not applicable
4	F	60	Face	Co2 + Mal	Co2 + Mal	26-50%	1-25%	Not applicable	100% Clinical cure	26-50%	1-25%	Not applicable	100% Clinical cure
5	F	70	Chest	Co2 + Mal	Co2 + Mal	51-75%	26-50 %	26-50%	80% Cure + 20% Improvement	51-75%	26-50%	26-50%	100% Clinical cure
6	F	72	Face	Not applicable	Not applicable	26-50%	1-25%	1-25%	100% Clinical Cure	26-50%	1-25%	1-25%	Not applicable
7	F	54	Face	Not applicable	Not applicable	51-75%	51-75%	Not applicable	88,8% Cure + 11,2% Improvement	51-75%	51-75%	Not applicable	100%

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



**FIGURE 3: Case 1** - Improvement of fine wrinkles after 2 sessions of DLPDT combined with CO<sub>2</sub> laser

cal cure and 66.6% improvement in the actinic keratosis grade. On the side treated with a combination of microneedling and MAL + depigmenting agents with vitamin C (left), there was minimum improvement in texture and wrinkles, and moderate improvement in pigmentation. (Table 4).

**Results after 3 months:** On the side treated with a com-

bination 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:

**ID:** 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 CO<sub>2</sub> ablative laser on both hemifaces. On the right hemiface, the MAL was applied isolatedly, on the left hemiface the MAL was combined with a depigmenting agent + vitamin C.

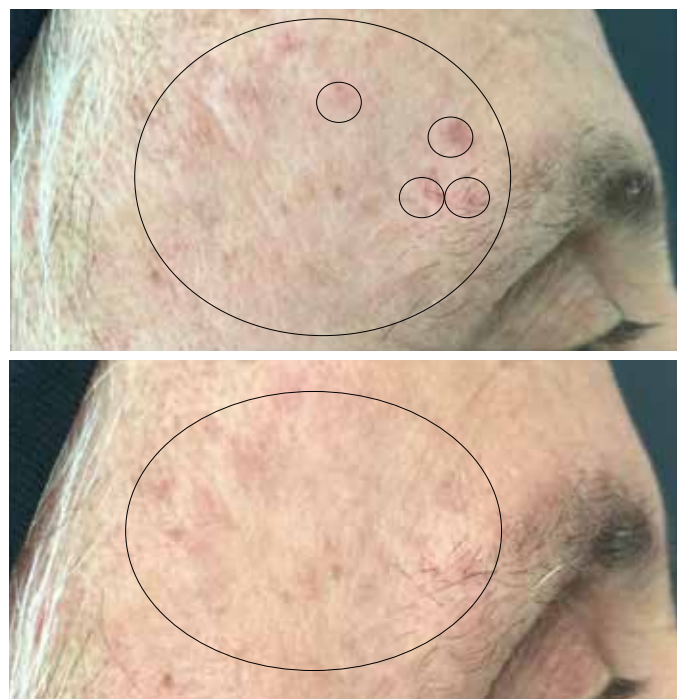
**Post immediate:** Intense pain and erythema and moderate edema on either side. (Table 3).

**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

Table 5: Clinical evaluation of side-effects

Patient	PROCEDURE USED		IMMEDIATE POST-PROCEDURE						2 hours after					
	FIRST SESSION													
	Right side	Left Side	Pain	Erythema	Edema	Pain	Erythema	Edema	Pain	Erythema	Edema	Pain	Erythema	Edema
1	CO <sub>2</sub> + MAL	Derma Roller + MAL	Moderate	Moderate	Mild	Mild	Mild	Absent	Mild	Moderate	Mild	Absent	Mild	Absent
2	Derma Roller + MAL	Derma Roller + MAL with depigmenting agent and vitamin C	Moderate	Mild	Absent	Moderate	Mild	Absent	Absent	Mild	Absent	Absent	Mild	Absent
3	CO <sub>2</sub> + MAL	CO <sub>2</sub> + MAL with depigmenting agent and vitamin C	Intense	Intense	Moderate	intensa	Intense	moderado	Absent	Moderate	Mild	Absent	Moderate	Mild
4	CO <sub>2</sub> + MAL	CO <sub>2</sub> + MAL	Moderate	Mild	Mild	Moderate	Mild	Mild	Mild	Moderate	Mild	Mild	Moderate	Mild
5	CO <sub>2</sub> + MAL	CO <sub>2</sub> + MAL	Moderate	Mild	Mild	Moderate	Mild	Mild	Mild	Moderate	Mild	Mild	Moderate	Mild
6	Crystal peeling + MAL		Mild	Mild	Mild	Mild	Mild	Absent	Mild	Mild	Absent	Mild	Mild	Absent
7	Crystal peeling + MAL + Derma Roller		Moderate	Intense	Moderate	Moderate	Intense	Moderate	Moderate	Intense	Moderate	Moderate	Intense	Moderate



**FIGURE 4: Case 2** - Improvement of actinic keratosis after 2 sessions of microneedling combined with DLPDT

of CO<sub>2</sub> and MAL (right), there was moderate improvement in texture; and minimum improvement in wrinkles and pigmentation. On the side treated with a combination of CO<sub>2</sub> 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 CO<sub>2</sub> 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 CO<sub>2</sub> 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).

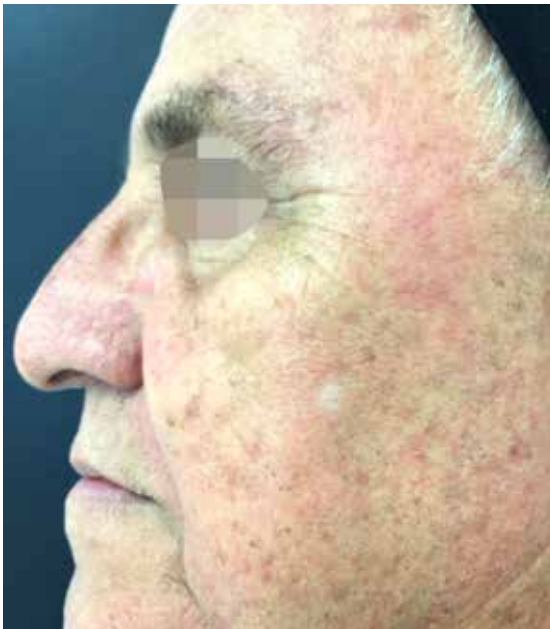
**Actinic Keratosis:** 2 AK lesions, grade II (1 on the right side and 1 on the left side).

**Aging Grade:** Glogau Type IV.

**Procedure: face:** Two sessions of MAL-DLPDT in combination with the fractional CO<sub>2</sub> 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).



**FIGURE 5: Case 2** - Improvement of texture and pigmentation after 2 sessions of microneedling combined with DLPDT (MAL + depigmenting agent and vitamin C)



**FIGURE 6: Case 3** - Improvement of texture, wrinkles and pigmentation after 2 sessions of CO<sub>2</sub> laser combined with DLPDT (MAL + depigmenting agent and vitamin C)



**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 CO<sub>2</sub> 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).





**FIGURE 7: Case 5** - Improvement of texture, wrinkles, pigmentation, and actinic keratosis after 2 sessions of CO<sub>2</sub> laser + DLPDT

**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.



**FIGURES 8 & 9: Case 7** - Overall improvement of texture, pigmentation, wrinkles, and actinic keratosis, after the combination of microdermabrasion and microneedling with DLPDT

**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 CO<sub>2</sub> 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 (moderate to intense) with protocols in which the CO<sub>2</sub> 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.<sup>22-24</sup> 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<sup>25</sup> have compared the efficacy of isolated DLPDT with DLPDT in combination with the fractional CO<sub>2</sub> ablative laser in the treatment of actinic keratosis with transplanted patients. In our study, we have evaluated the combination of DLPDT with the CO<sub>2</sub> 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<sup>25</sup> 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 CO<sub>2</sub> 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 CO<sub>2</sub> laser.

## CONCLUSION

Based on the methodology that was used, it is possible to state that the combination of methods such as the CO<sub>2</sub> 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. ●

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