

Transepidermal application of medication combined with photodynamic therapy in the treatment of actinic keratosis

Aplicação transepidérmica de medicamento associado a terapia fotodinâmica no tratamento de ceratoses actínicas

ABSTRACT

Topical photodynamic therapy is an established method of treating some types of non-melanoma skin cancers. Modifications to the standard protocol have recently been adopted that increase its therapeutic efficacy. This case study describes two female patients with multiple actinic keratoses who were simultaneously treated with the standard and modified protocols for methyl aminolevulinate and fractional radiofrequency combined with ultrasound in two different, symmetrically located, affected areas. This study's objective is to evaluate the effectiveness of the transepidermal application of drugs in photodynamic therapy combined with new methods such as the proposed treatment.

Keywords: photochemotherapy; aminolevulinic acid; keratosis, actinic; ablation techniques.

RESUMO

A terapia fotodinâmica (TFD) tópica é método consagrado no tratamento de alguns tipos de cânceres de pele não melanoma. Recentemente, vem sendo descritas modificações no protocolo-padrão com o objetivo de aumentar sua eficácia terapêutica. Relatam-se casos de duas pacientes com ceratoses actínicas múltiplas tratadas simultaneamente com o protocolo-padrão de metilaminolevulinato (MAL-TFD) e com um protocolo modificado, pelo uso de radiofrequência fracionada (RF) associada ao ultrassom (US), em duas áreas diferentes, simetricamente acometidas. O objetivo deste trabalho é avaliar a eficácia da aplicação transepidérmica de medicamento na TFD através da associação de métodos como nova proposta terapêutica.

Palavras-chave: fotoquimioterapia; ácido aminolevulínico; ceratose actínica; técnicas de ablação.

INTRODUCTION

Photodynamic therapy (PDT) is based on a light-activated chemical reaction, which is used to selectively destroy tissue. The process requires a photosensitizing agent (such as aminolevulinic acid or methyl aminolevulinate, MAL), a source of light, and oxygen.¹ The treatment of multiple actinic keratoses (AKs) is among the main applications of PDT, and its use is recommended in the literature for many other dermatoses such as infections, acne, and photorejuvenation.²

The PDT technique consists of two steps. First, the photosensitizing agent is preferentially accumulated in tumorous cells. Second, the photosensitized target lesion is exposed to light with a wavelength that matches that of the photosensitizing agent's absorption spectrum. One of the limitations of this technique is the photosensitizing agent's capacity to penetrate and distribute within the target tissue, where the stratum corneum acts as a barrier to drug penetration.³ In order to overcome this barrier, new technologies such as transepidermal drug delivery (TED) have been developed to facilitate a better penetration of

Case Report

Authors:

Luiza Erthal de Brito Pereira Kassuga¹
 Maria Cláudia Almeida Issa²
 Natália Stroligo Chevrand³

¹ Resident Dermatologist Physician, Universidade Federal Fluminense (UFF) – Niterói (RJ), Brazil

² Associate Professor of Clinical Dermatology, Universidade Federal Fluminense (UFF)

³ Resident Dermatologist Physician, Universidade Federal Fluminense (UFF) – Niterói (RJ), Brazil

Correspondence:

Dra. Maria Cláudia Almeida Issa
 Praia de Icaraí número 139, apto. 702
 Icaraí
 Cep: 24230-001 - Niterói – RJ, Brazil
 E-mail: mariaclaudia@predialnet.com.br

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diverse substances in the skin.³⁻⁸

Since fractional ablative methods can cause changes in the cutaneous barrier,^{3,7} a new device that combines fractional radiofrequency (RF) and ultrasound (US) was developed, introducing the new concept of TED. This technique consists of opening microscopic channels in the skin through fractional RF, which is combined with the impact force of low frequency US that propels the substance's molecules through those channels. Haedersdal and colleagues described the use of the fractional ablative method combined with PDT;³ they demonstrated a deeper penetration of MAL in the deep dermis of laboratory animals. Other studies also refer to this technique as a means of increasing the efficiency of topical PDT.⁸⁻¹⁰

This study described two cases of patients with multiple AKs to compare the clinical efficacy of standard PDT treatment (using a three-hour incubation time) with a modified protocol that combines fractional RF and US with PDT (using a one-hour incubation time).

CASE REPORT

Two female patients (59 and 63 years old, phototypes II to III) underwent two treatment protocols. The standard MAL-PDT protocol and the modified protocol were applied to the left and right arms, respectively (Figures 1 and 2). The area to be treated using the standard protocol was cleansed with gauze and alcohol, with the subsequent superficial curettage of the keratotic lesions and application of MAL (1.0 g/treated area), followed by occlusion with plastic film and aluminum foil, which provided protection from light for three hours. In the modified protocol, after the skin asepsis, fractional RF was performed using a Legato Accent[®] device (Alma Lasers Ltda., Israel), with a 45 W roller tip and two crossed passes over the area (Figure 3). MAL was applied immediately after RF (Figure 4). In the second step, the impact US (27 kHz) was applied (50 Hz frequency and 80% pulse impact) (Figure 5) with circular movements for 60 seconds in areas of 10x10 cm. Next, a similar occlusion to that applied on the standard protocol arm was performed, however for only one hour. The standard 3-hour incubation period used on the left side was reduced to one hour on the right side, where the area previously received fractional RF and US. Before the light was beamed, the excess cream was removed with gauze and 0.9% saline solution. The skin was then beamed with 630 nm red LED (Aktelite[®], Photocure ASA, Norway), at 37 J/cm² per time of treatment (7-10 minutes) on each side. Both patients underwent a single treatment session and were followed up at a private practice after 24 and 48 hours; 7, 14 and 30 days; and 3 and 6 months.

During the fractional RF procedure, the patients complained of mild pain with a high-intensity stinging or burning sensation. The US caused only local heat. High- or medium-intensity pain was reported during the exposure to light on both sides, with no differences between the sides. Erythema, edema, and crust formation were observed on both sides after the procedure, however those effects were more evident on the side treated with the modified protocol.



Figure 1: Patient 1 before treatment



Figure 2: Patient 2 before treatment

Clinical efficacy was evaluated based on the reduction in the number of AKs and in the improvement of the texture and color of the skin. A reduction in the number of AKs was observed after one and six months of treatment. Improved texture and pigmentation of the skin were observed on both sides, nevertheless improvements were more evident on the side treated with RF and US.

During the follow-up evaluations, a clear reduction in the number of AKs was observed on both sides, especially in the group treated with the modified protocol (Table 1). Before the treatment, Patient 1 presented 34 lesions on the right forearm and 54 on the inside of the forearm. Six months after the application of the protocols, there were eight lesions on the right side (modified protocol) and 34 on the left side (standard MAL-PDT). Patient 2 presented 24 lesions on the right forearm and 21 on the left forearm. After PDT, there were two lesions on the right side (modified protocol) and 6 lesions on the left side (standard MAL-PDT) (Figures 6 and 7).



Figure 3: Fractional RF applied on the right forearm of patient 2



Figure 6: Patient 1 six months after treatment



Figure 4: Application of MAL after fractional RF on the right forearm of patient 2



Figure 5: Application of impact US on the right forearm of patient 2

Table 1: Percentage reduction of AKs 6 months after PDT on the right side (modified protocol) and left side (standard MAL-PDT).

Right forearm	Patient 1	Patient 2
Before modified PDT	34	24
After modified PDT (6 months)	8	2
Reduction	76,4%	91,6%
Left forearm	Patient 1	Patient 2
Before standard PDT	54	21
After standard PDT (6 months)	34	6
Reduction	37%	71,4%

DISCUSSION

PDT is a relatively new therapeutic modality in the treatment of non-melanoma skin cancers 1. Its advantages include high efficacy, fast recovery time, and excellent esthetical results 2. Nevertheless, some proposals that would increase the clinical efficacy of topical PDT, such as the development of new topical sensitizers or combining techniques in the preparation of the skin for TED, are described in the literature.⁸⁻¹⁰ Fractional ablative methods, such as laser and RF combined with US, can increase the penetration capacity of hydrophilic substances and macromolecules to as far as the dermis, and are described as innovative mechanisms for the application of transepidermal medications.^{3,6,8-10}

The clinical efficacy evaluation was based on the reduction in the number of AKs and the improvement of the skin's texture and color. A reduction in the number of AKs was observed at one month and six months after treatment. Improved texture and pigmentation of the skin were observed on both arms,



Figure 7: Patient 2 six months after treatment

however improvements were more evident on the side that was treated with RF and US.

The increased penetration of MAL in the transepidermal treatment of AK appears to help reduce its incubation time. This clinical trial demonstrated that PDT combined with transepidermal application of MAL and an incubation time of one hour was not only effective in the treatment of AKs, but also presented better outcomes than the standard protocol. Further studies are needed to evaluate this new concept of preparation for and application of PDT. ●

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