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Original article

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Transepidermal medication application associated with photodynamic therapy in actinic keratosis treatment

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

SUMMARY

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

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

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.

INTRODUCTION

Photodynamic therapy (PDT) is based on chemical reaction activated by light used for the selective destruction of a tissue, requiring the presence of a photosensitizing agent such as aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), a source of light and oxygen.¹ the treatment of multiple actinic keratosis (AK) is among its main indications. Several other skin conditions such as infections, acne and photo rejuvenation, have also been described in the literature.²

The technique consists of two steps. At first, the photosensitizing agent is preferably accumulated in the tumor cells. Second step, the photosensitized target lesion is exposed to wavelength light that coincides with the absorption spectrum of the used photosensitizing agent. One of the limiting factors of this technique is the penetration and distribution ability of the photosensitizing agent used in the target tissue. It is known that the stratum corneum acts as a passage barrier of medications in the skin.³ Its objective to overcome this

Case Report

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Study conducted at the Hospital University Antônio Pedro (HUAP), Universidade Federal Fluminense (UFF) *Federal University Fluminense* - Niterói (RJ) Brazil.

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barrier; new technologies have been developed to allow better permeation of various substances – it is what is called transepidermal drug delivery, TED.³⁻⁸

Based on the fact that ablative fractional methods alter the skin barrier,^{3,7} a device that combines fractionated radio frequency (RF) and ultrasound (U.S.) has been developed by introducing the new TED concept. This technique is based on microscopic channels opening in the skin by the associated fractionated RF with an impact force of low US frequency to propel the molecules through these previously formed channels.

The use of the fractionated ablative method associated with the PDT has been described by Haedersdal et al.³ through animal testing, which demonstrated a greater MAL penetration into the deep dermis. Other studies also cite this technique in order to increase the effectiveness of topical PDT.⁸⁻¹⁰

In order to compare the clinical efficacy of the standard PDT treatment using standard incubation time of three hours with the modified protocol by combining fractional RF and US to the PDT with incubation time of one hour, the following case report of two patients with multiple AK is described.

CASE REPORT

Two female patients aged 59 and 63 years, phototypes II and III, were subjected to two treatment protocols. The standard MAL-PDT protocol was applied on the left forearm and the modified protocol on the other forearm (Figures 1 and 2). The standard protocol consisted on first cleaning the area to be treated with gauze and alcohol, superficial curettage of the keratotic lesions and application of MAL (one gram per treated area), followed by occlusion with plastic wrap and luminous protection with aluminum foil for three hours. In the modified protocol, after the skin hygiene procedure, fractionated RF was performed with Accent Legato® equipment (Alma Lasers Limited., Israel) with a 45 watt pin roller, two cross passages in the whole area were carried out (Figure 3). The MAL was applied immediately after the RF (Figure 4). The second step consisted of using US impact (27kHz) with the following parameters: 50 hertz frequency and 80% pulse impact (Figure 5). It was applied in a circular motion for 60 seconds in each area of 10x10cm. Subsequently, the occlusion was performed in the same manner as in the standard protocol, but for a reduced time of one hour. The standard incubation period of three hours on the left side was reduced to one hour on the right side, where it was done with fractionated RF preparation and prior US. Before the lighting, the excess cream was removed with gauze and 0.9% saline. The skin was illuminated with red LED 630nm Aktelite® (Photocure ASA, Norway). The LED parameters were 37J/cm² per treatment period (seven to ten minutes), on each side. Both patients underwent only one treatment session. They were followed up in a private practice after 24 and 48 hours, seven, 14 and 30 days, three and six months.

During the procedure with the fractionated RF, the patients complained of mild pain with a burning sensation or



Figure 1: Patient 1 before treatment



Figure 2: Patient 2 before treatment

low intensity burning. US caused only local heat. Pain intensity was reported as medium to high during the light exposure on both sides, without any difference in intensity. Postoperatively, erythema and edema was observed, and crusting occurred on both sides, although it was more evident on the treated side with the modified protocol.

The clinical efficacy evaluation was based on reducing the AK number and improving skin texture as well as color. There was a reduction in the AK number after one month and six months of treatment. Improvements in the texture and pigmentation of the skin was observed on both sides, but was more evident on the side previously treated with RF and US.

During the revaluations, an objective decrease of the AK number was observed on both sides, especially on the treated side with the modified protocol (Table 1). Patient 1 showed 34 lesions in the forearm and 54 lesions on the right contralateral forearm. After six months of the protocol implementation, there were eight injuries on the right side (pre-



Figure 3: Application of fractionated RF in the right forearm of patient 2



Figure 6: Patient 1, six months after treatment



Figure 4: Application of MAL after fractionated RF in the right forearm of patient 2



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

Table 1: Percentage reduction of AK six months after PDT on the right side (modified protocol) and left (default MAL-PDT).

Right forearm	Patient 1	Patient 2
Modified Pre-PDT	34	24
Modified post-PDT (6 months)	8	2
Reduction	76,4%	91,6%
Left forearm	Patient 1	Patient 2
Standard pre-PDT	54	21
Standard Post-PDT (6 months)	34	6
Reduction	37%	71.4%

modified protocol) and 34 on the left side (standard MAL-PDT). In patient 2, initially with 24 lesions on the right forearm and 21 on the left forearm, after the PDT, two lesions were counted on the right side (modified protocol) and six lesions on the left (Standard MAL-PDT) Figures 6 and 7).

DISCUSSION

PDT is a relatively new therapeutic modality in non-melanoma skin cancer treatment.¹ It shows advantages such as high efficiency, fast recovery time and excellent cosmetic results.² However, some proposals are described as a development of new sensitization topics and association of techniques in the preparation of skin for PDT in order to increase the clinical efficacy of topical PDT.⁸⁻¹⁰ Fractionated ablative methods such as laser and RF associated with US can increase the capacity of hydrophilic substances and macromolecules penetration into the dermis, and are described as an innovative mechanism for transepidermal application of drugs.^{3,6,8-10}



Figure 7: Patient 2, six months after treatment

The clinical efficacy evaluation was based on reducing the AK number and improving skin texture and color. There was a reduction in the AK number after one month and six months of treatment. Improvements in the texture and pigmentation of the skin was observed on both sides, but was more evident on the side previously treated with RF and US.

It is believed that the increased penetration of MAL in the AK treatment through transepidermal exposure may contribute in reducing the incubation time of the MAL. Through this clinical trial, it was observed that the PDT associated with transepidermal application of the MAL with an incubation time of one hour is not only effective in the AK treatment, but also showed better results than the standard protocol. More studies are needed to evaluate the new application concept and PDT preparation. ●

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