Photodiagnosis and Photodynamic Therapy 18 (2017) 105–110

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Efficacy of iontophoresis-assisted ablative fractional laser photodynamic therapy with short incubation time for the treatment of actinic keratosis: 12-month follow-up results of a prospective, randomised, comparative trial

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ARTICLE INFO

Article history:
Received 1 December 2016
Received in revised form 8 January 2017
Accepted 29 January 2017
Available online 3 February 2017

Keywords:
Ablative fractional laser
Actinic keratosis
Iontophoresis
Incubation time
Photodynamic therapy

ABSTRACT

Background: Iontophoresis is a transdermal drug-delivery technique that enhances the transport of ionic species across membranes and may have significant benefit for the treatment of actinic keratosis (AK) by ablative fractional laser–primed photodynamic therapy (AFL-PDT). The aims of this study were to compare the efficacy, recurrence rate, cosmetic outcome and safety of iontophoresis-assisted AFL-PDT with 2 h of incubation vs. those of conventional AFL-PDT with 2- and 3-h incubation in patients with facial and scalp AK.

Methods: Patients were randomly assigned to iontophoresis-assisted AFL-PDT with a 2-h incubation time (group A) and conventional AFL-PDT with a 2-h (group B) and 3-h (group C) incubation time. All patients underwent AFL-PDT, and group A patients were assigned to treatment with iontophoresis after methyl-aminolevulinate (MAL) application. After 2 or 3 h, MAL-applied lesions were irradiated using a red light. Patients were followed up at 1-week, 3 months and 12 months after treatment. Efficacy, cosmetic outcomes and adverse events were assessed.

Results: In total, 41 patients (160 AK lesions) completed the study and were evaluated. Efficacy was significantly higher in Group A (88.7%) than in Group B (73.2%); the efficacy of groups A and C (92.2%) at 3 months follow-up was comparable. The recurrence rates were not significantly different between the groups at 12 months ($P = 0.841$). The three groups did not differ in terms of cosmetic outcomes and safety.

Conclusions: Iontophoresis-assisted AFL-PDT showed higher efficacy than AFL-PDT with short incubation time. Iontophoresis may effectively reduce the incubation time in AFL-PDT.

1. Introduction

Many strategies to increase the production of protoporphyrin IX (PpIX) have been studied to improve the efficacy of photodynamic therapy (PDT). Pre-treatment with fractional laser resurfacing is a novel technique to improve the efficacy of PDT for AK. Our previous studies showed that ablative fractional laser-primed PDT (AFL-PDT) offered higher efficacy than conventional MAL-PDT in the treatment of many diseases, such as AK, actinic cheilitis, Bowen's disease and basal cell carcinoma [1–4].

Iontophoresis is a transdermal drug-delivery technique using electric current to enhance the transport of ionic species across membranes. Mizutani et al. [5] reported 5 AK patients successfully treated with direct-current pulsed iontophoresis – assisted 5-aminolevulinic acid (ALA)-PDT. Boddé et al. [6] studied iontophoretic transport of ALA quantitatively in vitro and demonstrated enhanced transport of ALA by iontophoresis.

In our previous study, though AFL-PDT with a 2-h incubation time showed enhanced efficacy than MAL-PDT with the 3-h incubation time, it showed significantly lower efficacy than AFL-PDT with 3-h incubation time [7].

The aim of our study was to evaluate efficacy of iontophoresis in AFL-PDT with short incubation time for AK treatment. Consequently, we compared efficacy, recurrence rate, cosmetic outcome and safety between iontophoresis-assisted AFL-PDT with 2-h incu-

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http://dx.doi.org/10.1016/j.pdpdt.2017.01.184
1572-1000/

bation time and conventional AFL-PDT with 2-h and 3-h incubation times.

2. Materials and methods

The study was designed as a three-armed, randomised, double-blinded, comparative trial. The study was approved by the Institutional Review Board and conducted in accordance with the guidelines of the 1975 Declaration of Helsinki. The trial was registered in the U.S National Institutes of Health clinicaltrials.gov database (identifier: NCT02670655).

2.1. Patients

Between June 2014 and January 2015, Korean patients aged ≥18 years who had biopsy-confirmed AK were enrolled in this study. We excluded lactating or pregnant women; patients with porphyria or a known allergy to the MAL cream and lidocaine; patients with history of melanoma, tendency of melasma development or keloid formation, any AK treatment of the area in the previous 4 weeks, or any conditions associated with a risk of poor protocol compliance; and patients on immunosuppressive treatment. Further exclusion criteria were: metal-containing device (cardiac pacemaker, orthopaedic implants, gynaecological devices), cardiac arrhythmia and large skin erosion. All patients were provided information regarding the nature of the study verbally and in writing, and signed informed consent was obtained in advance.

2.2. Study design

Participants were randomly divided into three groups, in a 1:1:1 ration, using a computer-generated random-number sequence. Group A was treated with iontophoresis-assisted AFL-PDT with 2-h incubation time. Group B was treated with conventional AFL-PDT with 2-h incubation time, and Group C was treated with conventional AFL-PDT with 3-h incubation time (standard).

2.3. Therapeutic intervention

Each AK lesion was photographed, numbered and graded at baseline. For AFL pre-treatment, lidocaine/prilocaine (5%) cream (EMLA; Astra Pharmaceuticals, LP, Westborough, MA, USA) was applied to the treatment area under occlusion for 30 min. After the anaesthetic cream was removed, AFL therapy was performed using a 2940-nm Er:YAG AFL (Joule; Sciton Inc., Palo Alto, CA, USA) at 300–550 μm ablation depth, level 1 coagulation, 22% treatment density and a single pulse. Immediately after treatment, MAL (Metvix, PhotoCure ASA, Oslo, Norway) was applied around the lesion with 5 mm-surrounding normal tissue. The area was covered with an occlusive dressing (Tegaderm, 3 M, St. Paul, MN, USA). In Group A, ionotophoresis was performed on MAL-applied sites. We used iontophoresis (vitaliont II®, ITC Inc, Korea) with a patch. The active electrode was the anode, and 0.50 mA/cm^2 current was applied to each AK lesion for 10 min. Subsequently, further 110-min incubation was added with an occlusive dressing. After incubation, the area was cleansed with saline. The area was irradiated with a red light-emitting diode lamp (Aktilite CL128; PhotoCure ASA, Oslo, Norway) with peak emission at 632 nm, placed 5 cm away from the skin surface, and a total light dose of 37 J/cm^2. After the illumination, a cold fan (UF92A Series; Fulltech, Taoyuan, Taiwan) was used to reduce pain. During illumination, patients were asked to evaluate pain intensity using an 11-point visual analogue scale (VAS).

2.4. Study evaluation

The same blinded investigators evaluated the response at 3 and 12 months after treatment by inspecting, photographing, and palpating each lesion in accordance with the guidelines of Olsen et al. [8] The response was classified as either complete response (complete disappearance of the lesion) or incomplete response (incomplete disappearance). In addition, the recurrence rate was evaluated at 12 months. For the histopathologic evaluation of treatment response, at the 12-month follow-up visit, a 3-mm punch biopsy was performed in all cases of clinically incomplete response. The overall cosmetic outcome was assessed 12 months after treatment by investigators, and graded as excellent (slight redness or pigmentation change), good (moderate redness or pigmentation change), fair (slight-to-moderate scarring, atrophy, or induration), or poor (extensive scarring, atrophy, or induration).

Adverse events reported by the patient were noted at each follow-up visit, including severity, duration and need for additional therapy. All events due to PDT were described as phototoxic reactions.

2.5. Statistical analysis

We compared the differences in efficacy, cosmetic outcomes and local adverse events between each group. All statistical analyses were performed using the Statistical Package for Social Sciences software (version 18.00; SPSS, Inc., Chicago, IL, USA). The categorical variables were analysed using Pearson's chi-square test and Fisher's exact test, and the continuous variables were analysed using one-way analysis of variance and Student's *t*-test. A *P* value of <0.05 was considered statistically significant.

3. Results

3.1. Patient demographics

Forty-four patients (21 men, 23 women) were enrolled in the study. 15 patients (62 lesions), 15 patients (60 lesions) and 14 patients (51 lesions) were treated with iontophoresis-assisted AFL-PDT with 2-h, AFL-PDT with 2-h and AFL-PDT with 3-h. A total of 41 patients (Group A, 13 patients, 53 lesions vs. Group B, 14 patients, 56 lesions vs. Group C, 14 patients, 51 lesions) completed the study and were analysed. Three subjects dropped out prematurely: one because of protocol violation and two because of loss to follow-up. A flow chart of patient disposition is presented in Fig. 1. Patient characteristics are summarized in Table 1.

3.2. Efficacy

Group A was significantly more effective with an efficacy of 88.7% (95% confidence interval [CI], 80.1%–97.3%) at 3 months compared to 73.2% (61.5%–84.9%) in Group B ($P = 0.041$). Although Group A showed lower efficacy than group C (92.2%, 84.7%–99.6%), the difference was not statistically significant ($P = 0.548$).

At the 12-month follow-up, the response rates (95% CIs) decreased to 83.0% (72.8%–93.2%), 66.1% (53.6%–78.6%) and 84.3% (74.2%–94.4%) in groups A, B and C, respectively. Group A also showed higher efficacy than group B at 12-month follow-up ($P = 0.043$). In addition, the difference of efficacy between groups A and C was also not statistically significant ($P = 0.646$). Clinical photographs and fluorescence images of treatment areas at baseline and 12 months after treatment are shown in Fig. 2. The complete response rates in the groups A, B and C are summarized in Fig. 3.