Appendix S1.

METHODS

Study design

The current study is a prospective, open-label study with split-face design. Patients were treated with pulsed dye laser (PDL) mediated photodynamic therapy (PDT) on the left side of the face and conventional light emitting diode (LED)-mediated PDT on the right side of the face as was predefined in the study protocol. Both treatments took place on the same day with an interval of 1 min. Treatment order was counterbalanced to control for order effects. This was done to prevent an effect of treatment order on pain score for example.

The primary outcome measure was mean change in the number of lesions between baseline and 12-month follow-up. Secondary outcome measures were pain sensation, qualitative clinical improvement and adverse events.

Patients

Participants were recruited and treated at the dermatology department of a secondary dermatology referral centre in Eindhoven, the Netherlands, between November 2011 and August 2012. Patients were considered eligible if they were 18 years or older, had Fitzpatrick skin type I–III and a clinical diagnosis of actinic keratosis (AK) on the scalp and/or forehead. The AK had to cover a minimal area of 25 cm^2 with the potency to be divided into 2 equal halves. The diagnosis was based on clinical assessment. Exclusion criteria were suspicion for malignancy in the treatment area, the use of immunosuppressive medication, topical treatment of any kind in the past 6 months within the treatment area, known hypersensitivity for the photosensitizer or presence of other skin conditions in the treatment area. The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the local medical ethics review board (16). Prior to enrolment, all patients gave their written informed consent.

Procedures

At baseline the total number of target lesions in the treatment area of each individual participant was scored. Furthermore, lesion severity was assessed using the Olsen scale, based on the thickness of AK: 1 = mild (slightly palpable, more easily felt than seen); 2 = moderate (moderately thick, easy to see and feel); 3 = severe (very thick and/or obvious AK). Colour photographs were taken from the treatment area at baseline and at each follow-up visit. Furthermore, patients' concomitant medication and skin type according to the Fitzpatrick 6-point scale were registered. When the inclusion criteria were met, 2 clinically equal treatment areas were assigned. Subsequently, both areas were pre-treated with slight curettage of hyperkeratotic lesions, followed by methyl-aminolevulinate cream (Metvix®, Galderma Benelux, Rotterdam, The Netherlands) application. Both areas were covered with an occlusive dressing (Tegaderm®, 3M Health Care, Amsterdam, The Netherlands), a gauze, tinfoil and light-blocking tape, in order to increase penetration of the photosensitizer and prevent light exposure. After a 3-h incubation time, the cream residue was removed.

Subsequently, all participants received PDL illumination on the left side of the scalp and/or forehead (595 nm Pulsed Dye Laser, Vbeam, Candela Corporation®, Wayland, MA, USA, 7-mm spot size, fluence 7 J/cm^2, pulse duration 10 ms, epidermal cooling with Dynamic Cooling Device (DCD spray/delay) 30/10 ms, spots overlapping 50%) and regular LED illumination on the right side (Aktilite®, Galderma), 37 J/cm^2, 635 ± 18 nm, cooling was obtained with the incorporated fan. During illumination of either one of the areas, the other adjacent area was covered with occlusive dressing to prevent light exposure.

Time required for both illuminations was registered. Because of the treatment nature patients were not blinded for treatment.

Outcome assessment

Follow-up visits were scheduled at 3, 6, 9 and 12 months post-treatment and were performed by the same investigator (JK). During follow-up the remaining number of target AKs were calculated. Moreover, global clinical improvement in AK post-treatment was scored in a qualitative way as no clinical improvement vs. clinical improvement. In case of no treatment effect or an increase in AK after treatment, the same treatment(s) were repeated. When a histologically confirmed skin malignancy was confirmed within the treated area, this was registered.

Patients were asked to complete a detailed diary in which they recorded adverse events (erythema, crusting, infection and burning sensation) during the first 2 weeks post-treatment. In this diary, concomitant medication, such as antibiotic treatment, used within 2 weeks after treatment, was registered. Pain scores were assessed immediately after both treatments using a visual analogue scale (VAS) ranging from 0 (no pain at all) to 10 (worst pain imaginable).

Statistical analysis

The primary outcome measure was defined as the mean change in the number of lesions between baseline and 12-month follow-up. The decrease in number of AK lesions per patient in the treatment area was calculated. A *t*-test for paired samples was conducted to test the difference in mean decrease between treatments. The sample size of this study with 57 patients enabled detection of a between-treatment difference (in the mean decrease in AK lesions with a SD of 3) of 1.6 or more with a power of 80%.

Other continuous outcomes were also tested for statistical significance with a *t*-test for paired samples. Differences in proportions between treatments were tested using the McNemar test for paired proportions. All statistical analyses were performed on an intention-to-treat basis.

Data were collected and analysed with SPSS (version 19.9 for Windows). *p*-values smaller than or equal to 0.05 were considered as a significant difference.