Appendix S1

MATERIALS AND METHODS

Patients were recruited to this study in 2011. Both DL and LED treatments were implemented from mid-September to early October in 2011, from late April to early October in 2012 and from the beginning of June to early July in 2013. Eligible patients had to have a minimum of 3 clinically clearly detectable AKs on their face or scalp. Data on sex, age, occupation, skin photo-type (15), medication, and history of previous skin (pre)malignancy were recorded. Exclusion criteria were: a known history of porphyria or photodermatosis, allergy to the photosensitizer, immunosuppression, lactation and pregnancy.

Sample size

Based on previous publications, we assumed DL-PDT to be as effective as LED-PDT (13). As DL-PDT is assumed to be less costly due to less time spent at the clinic (14), we assumed the costs to be lower for DL-PDT. As no previous data on the costs of DL-PDT were available, we used the smallest acceptable difference of 20% between the costs of DL-PDT and LED-PDT. For the sample size calculator we used an alpha error of 0.05, beta error of 0.80 and sigma value of 0.3 for 2 independent samples, giving a sample size of 36 subjects per group.

Randomization

Patients were randomized to receive either DL-PDT or LED-PDT. At recruitment neither the patient nor the recruiting doctor knew which treatment the patient would receive. Randomization was generated using a web-based validated program (Research Randomizer®), which created a random assignment of the treatment to randomization numbers (1–2, 1=DL, 2=LED-PDT). The list was printed and concealed in an envelope, which was opened only during treatment visits.

Treatment procedure

All lesions were prepared with superficial curettage to remove crusts. Local anaesthesia (50:50 Lidocain c. adrenalin® 10 mg/ml + 10 µg/ml Orion Pharma and Naropin® 7.5 mg/ml AstraZeneca) was used for grades II–III lesions to reduce pain during illumination. No skin biopsies were taken.

For each patient the consumption of photosensitizer was determined by weighing (3 target lesions). In the LED-PDT group an approximately 1-mm thick layer of methylaminolaevulinate (MAL, Metvix®, Galderma, Paris, France) was applied to lesional target areas and kept occluded (Tegaderm™). After 3 h the excess MAL was wiped off and the area illuminated with a red-LED light (Aktilite® CL128 or CL16, peak irradiance 632 nm, Galderma, Paris, France) (17). The lamps were set to give a total light dose of 37 J/cm^2, achieved in approximately 9 min (CL128, mean irradiance 65 mW/cm^2), or in 7 min (CL16, mean irradiance 86 mW/cm^2) from a distance of 8 cm. Primarily, 1 lamp (CL128) was used, but if the lesions were far apart, 2 lamps (CL128 and CL16), and several illuminations were used.

For DL-PDT the lesions were prepared similarly. In addition, 15 min before the curettage, sunscreen (ACO Sun Kids High Protection Sun Spray® SPF 30, ACO; octocrylene, ethylhexyl salicylate, diethylamino hydroxybenzoyl hexyl benzoate, bisethylhexyloxyphenol methoxyphenyl triazine, methylene bis-benzotriazolyl tetramethylbutylphenol) was applied to all the sun-exposed skin areas including the treatment area. The sunscreen used had absorption peaks in the ultraviolet (UV)-region and only minimally overlapped the visible blue light region and thus was assumed not to affect the activation of protoporphyrin IX. Afterwards a thin visible layer (approximately 0.25 mm) of MAL was applied and the area left uncovered. The patients were instructed to start the daylight exposure 30 min after leaving the clinic, continue the exposure for 2 h, and then stay indoors for that day. Patients recorded the duration of the daylight exposure. Treatments were postponed on very dark or rainy days, or if the temperature was less than 10°C.

Assessment of effectiveness

Response was evaluated clinically (patient complete response, 3 target lesions cleared) at 6 months. Effectiveness was defined by the level as the probability of patient's complete response at 6 months. The probability of a patient's complete response was estimated by using a logistic regression estimation, where complete response was defined in cases where 3/3 lesions were clinically completely cleared (value = 1) and, respectively, no response if only 0–2/3 lesions were cleared (value = 0). Patients' age and sex, as well as treatment group were used as regressors in the logistic models.

Cost assessment

The nurses were instructed to record the time used for each task, including pre- and post-treatment guidance, cleaning the treatment area, assisting the doctor with curettage and MAL application, applying the occlusion sheet and performing illumination for the LED-PDT group. The time the doctors used for both groups was the same (approximately15 min), and thus was not recorded. In the assessment of the time cost we used the mean monthly salaries of nurses (€3,089) and doctors (resident €4,616) at Päijät-Häme Central Hospital. Patients' time consumption at the clinic included waiting for the reception, getting pre-and post-treatment guidance, pre-treatment procedures, MAL-application and illumination (LED or daylight). For DL-PDT we measured the application and absorption time for the sunscreen and for the LED-PDT group the MAL occlusion time. As all the patients in our study were pensioners, patients' time consumption for the treatment was monetary valued using the mean monthly retirement pension in Finland (€1,408 in 2012, source: Official Statistics in Finland).

Accurate costs were assessed in the 42 first patients and the values for each cost item were imputed item by item into a multivariate regression model using the following regressors: patients' age, sex, occupation (outdoors vs. indoors work), number of treatment sessions (1–2) and treatment group (daylight vs. LED light) to acquire estimated costs for all 70 patients included in the study.

Assessment of cost-effectiveness and statistical analysis

The analysis was performed using DL-PDT and LED-PDT as the intervention and control treatments, respectively. CEA was performed generating the incremental cost-effectiveness ratio (ICER), and uncertainty was assessed using 10,000 bootstrapping iterations. Results were presented in a cost-effectiveness (CE)-plane.

Baseline characteristics and lesion complete clearance rates were tested for statistical significance using Fisher's exact test, and patient's complete response using Pearson's χ^2 test. Total costs, time use, cost per complete responder and VAS pain scores were tested using the Mann-Whitney test. p-values < 0.05 were regarded as statistically significant. Two-tailed testing was used for all data analysis. The bootstrapping simulation technique and the CE-plane approach were used to represent uncertainty around the point estimate of the ICER.