Acta Derm Venereol 2016; 96: 241–244

CLINICAL REPORT

Photodynamic Therapy for Actinic Keratoses: A Randomized Prospective Non-sponsored Cost-effectiveness Study of Daylight-mediated Treatment Compared with Light-emitting Diode Treatment

Noora NEITTAANMÄKI-PERTTU[1,2], Mari GRÖNROOS[2], Toni T. KARPPINEN[2], Erna SNELLMAN[3] and Pekka RISSANEN[4]
Departments of Dermatology and Allergology, [1]Helsinki University and Helsinki University Hospital, Helsinki, [2]Päijät-Häme Central Hospital, Päijät-Häme, [3]Department of Dermatology, Tampere University and Tampere University Hospital, and [4]School of Health Sciences (Health Economics), Tampere University, Tampere, Finland

Daylight-mediated photodynamic therapy (DL-PDT) is considered as effective as conventional PDT using artificial light (light-emitting diode (LED)-PDT) for treatment of actinic keratoses (AK). This randomized prospective non-sponsored study assessed the cost-effectiveness of DL-PDT compared with LED-PDT. Seventy patients with 210 AKs were randomized to DL-PDT or LED-PDT groups. Effectiveness was assessed at 6 months. The costs included societal costs and private costs, including the time patients spent in treatment. Results are presented as incremental cost-effectiveness ratio (ICER). The total costs per patient were significantly lower for DL-PDT (€132) compared with LED-PDT (€170), giving a cost saving of €38 ($p = 0.022$). The estimated probabilities for patients' complete response were 0.429 for DL-PDT and 0.686 for LED-PDT; a difference in probability of being healed of 0.257. ICER showed a monetary gain of €147 per unit of effectiveness lost. DL-PDT is less costly and less effective than LED-PDT. In terms of cost-effectiveness analysis, DL-PDT provides lower value for money compared with LED-PDT. ***Key words: actinic keratoses; cost-effectiveness; daylight-photodynamic therapy.***

Accepted Aug 4, 2015; Epub ahead of print Aug 10, 2015

Acta Derm Venereol 2016; 96: 241–244.

Noora Neittaanmäki-Perttu, Department of Dermatology and Allergology, Helsinki University Hospital, Box 160 Meilahdentie 2, FIN-00029 Helsinki, Finland. E-mail: noora.neittaanmaki@fimnet.fi

Actinic keratoses (AK) are precursors with potential to develop into metastatic squamous cell carcinoma (SCC) (1). High incidence rates of AKs raise a significant economic issue. The prevalence of AK is estimated to be approximately 50% in Australia and 11–34% in the Northern hemisphere, with higher prevalence among elderly subjects (2–4). The total annual direct costs for AKs were 18 million Euros (€) in Sweden in 2011 and 1.2 billion USD in the US in 2004 (5, 6).

There are several topical treatment options for AKs (7, 8). Photodynamic therapy (PDT) is a recommended treatment option (9–11). A novel approach, using daylight (DL-PDT) in the treatment of AKs is considered to be as effective as treatment with conventional PDT using artificial light (light-emitting diode (LED)-PDT) (12, 13). The use of DL-PDT is thought to be less costly due to shorter visiting times at the clinics (13, 14). To our knowledge, the cost-effectiveness of DL-PDT for the treatment of AK has not been studied previously.

This study was a prospective randomized non-sponsored trial to assess the cost-effectiveness of DL-PDT compared with LED-PDT in the treatment of AKs.

MATERIALS AND METHODS

The study protocol followed the Declaration of Helsinki and was approved by the local ethics committee. All participants provided informed consent. For full details, see Appendix S1[1].

All patients who fulfilled the inclusion criteria were sequentially recruited from the Department of Dermatology, Päijät-Häme Central Hospital between 2011 and 2013. Inclusion criteria included a minimum of 3 clinically clearly detectable AKs on facial or scalp areas. Exclusion criteria are detailed in Appendix S1[1].

Patients were randomized to receive either DL-PDT or LED-PDT. Before treatments AK lesions were photographed, counted and classified into grades I–III (16).Three clearly detectable target lesions per patient were chosen for the study follow-up. If patients had more than 3 lesions, all lesions were treated according to the randomization. Grade I lesions were treated once and grades II–III lesions twice. The treatment procedure is detailed in Appendix S1[1].

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.

Costs included societal costs (including the working time of the nurse and doctor, treatment room rent, medication and equipment) and patients' costs (including treatment time and travel costs). The analysis adopted a societal perspective, including both healthcare and patients' costs (Table I). The costs of control visits or further treatments were not included.

Cost-effectiveness analysis (CEA) was performed using DL-PDT and LED-PDT as the intervention and control treatments, respectively, generating the incremental cost-effectiveness ratio (ICER). For a detailed description of the method, see Appendix S1[1].

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2205

RESULTS

Patients

Of the 73 randomized patients 3 were excluded; one due to an unrelated death, one for diagnosed SCC on the studied area before treatment, and one for severe diffuse photo-damage that hindered the count of AKs (Fig S1[1]).

A total of 70 patients completed the study, 39 men and 31 women, age range 59–93 years (mean 76 years). Eight patients had anamnestic skin photo-type I, 25 photo-type II, 34 photo-type III, and 3 photo-type IV. Forty-six patients had earlier received treatment for their AKs and 3 for carcinoma *in situ*. Six had had operations for SCC, 18 for basal cell carcinoma (BCC), 1 for melanoma and one for verrucous carcinoma, of which 2 BCCs, one SCC and verrucous carcinoma were in the studied skin areas. Twenty-four patients had previously received cryosurgery, 8 DL-PDT and 11 LED-PDT for AKs on the studied areas. In addition, 5 patients had received LED-PDT, 23 cryosurgery, 1 imiquimod, 1 diclofenac and 1 topical retinoid treatment for AKs in other skin areas. None of the patients had received both DL-PDT and LED-PDT. There was a wash-out period of at least 6 months from previous treatments to the studied areas.

Thirty-five patients received DL-PDT and 35 received LED-PDT. Seven patients in both groups received 2 treatments for thicker lesions 7–23 days apart (mean 12 days) and the rest received one treatment session. The mean time for daylight-exposure was 161 min (range 120–480 min). Patients did not visit or contact the hospital between treatments and control visits.

Three target lesions per patient were included in the study; thus, the number of lesions studied was 210, of whom 105 (92 grade I, 13 grade II–III) were treated with DL-PDT and 105 (93 grade I and 12 grade II–III) with LED-PDT ($p = 0.46$). Patient complete response rates (3/3 lesions cleared) were 15 of 35 (42.9%) with DL-PDT and 24 of 35 (68.6%) with LED-PDT ($p = 0.030$) (Fig S1[1]).

To better compare our results with previous DL-PDT studies, we also conducted per lesion clearance analysis. At 6 months LED-PDT cleared 94 of 105 (89.2%) and DL-PDT 76 of 105 (72.4%) lesions ($p = 0.0025$). In the LED-PDT group 93 grade I AKs receiving 1 and 12 grade II–III AKs 2 treatments showed 88.2% and 100% complete clearance, respectively ($p = 0.36$). In the DL-PDT group 92 grade I AKs received 1 treatment and 13 grade II–III AKs 2 treatments with 73.9% and 61.5% clearance rates ($p = 0.34$).

Costs

The imputed mean total costs per patient (1–2 treatments) were €132 (95% confidence interval (CI) 111.3–152.6) for DL-PDT and €170 (95% CI 126.0–213.5) for LED-PDT, resulting in incremental costs savings of –€38 ($p = 0.022$) (Table I).

Cost-effectiveness

The probabilities for patients' complete response were 0.429 (95% CI 0.414–0.443) for DL-PDT and 0.686 (95% CI 0.674–0.698) for LED-PDT, thus yielding a loss in the probability of being healed of 0.257. The ICER revealed a monetary gain of €147 per unit of effectiveness lost (Table II). The cost-effectiveness (CE)-plane showed that approximately 96% of the bootstrapped replica data yielded a result that lies in the south-western part of the plane, indicating that DL-PDT provided a lower value for money compared with LED-PDT (Fig S2[1]).

Additional data analysis

When dividing the mean cost per patient with the estimated probability for patient's complete response, the costs per complete responders were calculated as €308 for DL-PDT and €248 for LED-PDT ($p = 0.004$).

DL-PDT required significantly less of the nurses' time (median 51 vs. 78 min per treatment, $p = 0.003$) and less of the patients' treatment time (median 194.5 vs. 271 min, $p < 0.0001$) compared with LED-PDT.

As measured with the visual analogue scale (VAS, range 0–10) during and after the treatments until the pain had vanished, DL-PDT was significantly less painful, with a mean maximal pain value of 1.53 (range 0.1–6.0) compared with LED-PDT 4.36 (range 0.3–8.4), $p < 0.001$).

Table I. *Cost items, unit cost and mean total costs of daylight-mediated photodynamic therapy (DL-PDT) compared with light-emitting diode PDT (LED-PDT) for treatment of actinic keratoses (AK) (*p = *0.022)*

Cost item	Unit costs	DL-PDT, € $n = 35$[a] Mean ± SD	LED-PDT, € $n = 35$[a] Mean ± SD
Societal costs			
Nurses' time with the patient	€19/h	17.1 ± 4.3	24.9 ± 6.6
Doctors' time (resident) for the treatment	€30.2/h	9.0 ± 3.0	9.0 ± 3.0
Treatment room rent	€1.5/h	1.4 ± 0.3	2.0 ± 0.5
Photosensitizer (methylaminolaevulinate)	€163/g	37.2 ± 26.3	50.4 ± 31.8
Anaesthetic	€0.3/ml	0.25 ± 0.56	0.23 ± 0.53
Sunscreen	€0.1/ml	1.6 ± 0.53	–
Occlusion membrane	€0.3/20 cm	–	0.35 ± 0.12
LED light	€0.14/illumination	–	0.16 ± 0.05
Hospitalization	€385/night[b]	–	11
Patients' costs			
Patients' (pensioner) time used for the treatment	€8.6/h	40.4 ± 23.0	49.6 ± 21.8
Patients' travel costs	€0.45/km	25.0 ± 22.1	22.1 ± 30.9
Mean total costs		132 ± 62.3	170 ± 132.0

[a]28/35 patients received one treatment session, 7/35 patients received 2 treatments for grade II–III AKs. [b]Only 1 patient spent a night at the hospital due to pain in the treatment area after LED-PDT.

Table II. *Incremental cost-effectiveness ratio (ICER)*

	Effectiveness (E)		Costs (C)		ICER
	Probability of complete response	Incremental effectiveness	Per patient €	Incremental cost	€/Probability of complete response
DL-PDT	0.429		132		
LED-PDT	0.686	–0.257	170	–38	147

DL-PDT: daylight-mediated photodynamic therapy; LED-PDT: light-emitting diode photodynamic therapy.

DISCUSSION

The results of this study show that DL-PDT is less costly, but also less effective, than LED-PDT. DL-PDT was associated with an incremental cost saving of €147 and a decremental probability of being healed of –0.257. Thus, DL-PDT provides a lower value for money compared with LED-PDT.

The cost-effectiveness of LED-PDT compared with other treatments for AK has been evaluated in several studies. A limitation of many of these studies compared with our prospective study using accurate costs is that they use estimated costs; some of the studies included only the cost of the topical drug. To our knowledge there have been no cost-effectiveness evaluations of DL-PDT. The simulated costs per complete responder were €379 for MAL-PDT and €363 for cryotherapy, including the cost of yearly re-treatments, and valuing the cosmetic outcome. The incremental cost per extra complete responder was €401, with MAL-PDT being more expensive (18). When LED-PDT was compared with imiquimod using a decision-tree model estimating quality-adjusted life years (QALYs) and treatment costs, it was implied that imiquimod might be more cost-effective (19). A recent prospective head-to-head study found that MAL-PDT was more cost-effective compared with diclofenac + hyaluronic acid gel (DHA), with the costs per complete responder being €566.7 and €1,026.2 for MAL-PDT and €595.2 and €2,295.2 for DHA at 3 and 12 months, respectively (20). Our study showed that the costs per complete responder were €308 for DL-PDT and €248 for LED-PDT at 6 months. A limitation of our study is that we did not include the costs of further treatments or the quality of life analysis (QALY), and thus the numbers are not directly comparable with previous data.

PDT studies rarely report response rates at the patient level. In the Italian study, the patient complete response rate for LED-PDT was 68.4% at 3 months and 55.2% at 1 year (19). In another study, MAL-PDT was superior to a placebo, with a patient complete response of 59.2% vs. 14.9% at 3 months (21). Our results are in concordance with these findings, showing a 68.6% patient complete response rate for LED-PDT at 6 months. Our patient complete response rate for DL-PDT was 42.9%. To our knowledge, the patient complete response for DL-PDT has not been reported earlier. As patient complete response is a major indicator of the need of further treatments and further costs, future research should focus more attention on this subject.

The majority of PDT studies report lesion clearance rates ranging from 71% to 92% for LED-PDT, and from 75.9% to 79.5% for DL-PDT (10, 13, 14, 22, 23). Our results show equal clearance rates for LED-PDT (89.2%), but slightly lower clearance rates for DL-PDT (72.4%). The slightly lower efficacy rates for DL-PDT could be explained by a longer follow-up period (6 months) than in the previous studies reporting 3-month clearance rates.

A few facts might have affected our DL-PDT effectiveness results[2].

Despite its higher efficacy, LED-PDT might not be an attractive option for patients, as the use of DL-PDT results in significantly less pain and time spent at the clinic. Thus, we still prefer the use of DL-PDT over the conventional treatment during the summer months. With its short visit time, DL-PDT can be implemented in private practices, which could reduce the burden on public clinics. A further CEA analysis of DL-PDT should be conducted including QALYs and patient preference. Furthermore, the cost-effectiveness of newer

[2]Meteorological studies have shown that DL-PDT can be implemented in Reykjavik (located in the same latitude (64°N) with Finland) until the middle of September (24). In the first 2 years we continued treatments until early October, which influenced the response rates. Of the 14 patients treated in late September to early October only 16.7% (1/6) in the DL-PDT group and 87.5% (7/8) in the LED-PDT group were completely cleared. Thus, the treatment should be limited to the summer months in northern countries. However, the most effective light-dose needed for DL-PDT remains unclear. We did not use light-dosimeters for DL-PDT and thus accurate light doses are not available. We used a different sunscreen (ACO Sun Kids High Protection Sun Spray® SPF 30, ACO) from that used in previous studies (14). However, the absorption spectrum only minimally overlapped the blue light region and thus was assumed not to affect treatment outcome. A 0.25-mm thick layer of MAL cream has been approved as sufficient for DL-PDT, resulting in 74% lesion complete clearance (25). To our knowledge the efficacy of <1-mm layer photosensitizer has not been studied for LED-PDT. Thus, in our study, the DL-PDT group received a thinner layer of MAL cream (0.25 mm) than the LED-PDT group (1 mm), which reduced the costs for DL-PDT, but also may have affected the response rate. In LED-PDT we used the standardized protocol of a 1-mm thick layer of the photosensitizer under 3 h occlusion, while no occlusion was used in DL-PDT. This results in higher amounts of protoporphyrin IX (PpIX) in the tissues of the LED-group than in the DL-group; in the latter PpIX is activated while developing (13). A larger trial evaluating different thicknesses of MAL cream in LED-PDT is warranted. The present study found DL-PDT to be significantly less painful compared with LED-PDT. A limitation is that this finding and patient preference were not included in assessment of QALYs and the CEA analysis. LED-PDT might not be an attractive option for patients, as the use of DL-PDT significantly lowers pain and time spent at the clinic. An earlier split-face study comparing LED-PDT and DL-PDT reported higher patient preference for DL-PDT (13). Further limitations to our study include the lack of investigator-blinded outcome evaluation and assessment of adverse reactions. We did not perform skin biopsies to verify AK diagnoses, and despite the high accuracy of clinical diagnoses this should be considered a limitation (26). To simplify the treatment process for cost evaluation we used a treatment method targeted to lesions. Had we targeted the whole field, the cost of the treatment would have been higher and this may have affected the CEA analysis. The results may not be easily generalized to the working age population as it focused on pensioners.

low-concentration photosensitizers in DL-PDT needs to be studied (25, 27).

In conclusion, this study assessing the detailed costs of DL-PDT and LED-PDT for treatment of AKs found that, in terms of CEA, DL-PDT provides a lower value for money compared with LED-PDT.

ACKNOWLEDGEMENTS

We would like to thank research nurse Ulla Oesch-Lääveri from Päijät-Häme Central Hospital for her dedication to this study. The corresponding author received a research grant from Orion Pharmos Foundation (not involved in any of the products used in the study) and from Foundation for Clinical Chemistry Research.

The authors declare no conflicts of interest.

REFERENCES

1. Tessari G, Girolomoni G. Nonmelanoma skin cancer in solid organ transplant recipients: update on epidemiology, risk factors and management. Dermatol Surg 2012; 38: 1622–1630.
2. Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a Queensland Community. J Invest Dermatol 2000; 115: 273–277.
3. Schaefer I, Augustin M, Spehr C, Reusch M, Kornek T. Prevalence and risk factors of actinic keratoses in Germany-analysis of multisource data. J Eur Acad Dermatol Venereol 2014; 28: 309–313.
4. Memon AA, Tomenson JA, Bothwell J, Friedmann PS. Prevalence of solar damage and actinic keratosis in a Merseyside population. Br J Dermatol 2000; 142: 1154–1159.
5. Neidecker MV, Davis-Ajami ML, Balkrishnan R, Feldman SR. Pharmacoeconomic considerations in treating actinic keratosis. Pharmacoeconomics 2009; 27: 451–464.
6. Eriksson T, Tinghög G. Societal cost of skin cancer in Sweden in 2011. Acta Derm Venereol 2015; 95: 347–348.
7. Ceilley RI, Jorizzo JL. Current issues in the management of actinic keratosis. J Am Acad Dermatol 2013; 68: 28–38.
8. Samrao A, Cockerell CJ. Pharmacotherapeutic management of actinic keratosis: focus on newer topical agents. Am J Clin Dermatol 2013; 14: 273–277.
9. Braathen LR, Morton CA, Basset-Seguin N, Bissonnette R, Gerritsen MJ, Gilaberte Y, et al. Photodynamic therapy for skin field cancerization: an international consensus. J Eur Acad Dermatol Venereol 2012; 26: 1063–1066.
10. Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guideline for topical photodynamic therapy part 1: treatment delivery and current indications – actinic keratosis, Bowen's disease, basal cell carcinoma. J Eur Acad Dermatol Venereol 2013; 27: 536–544.
11. Babilas P, Schreml S, Landthaler M, Szeimies RM. Photodynamic therapy in dermatology: state-of-the-art. Photodermatol Photoimmunol Photomed 2010; 26: 118–132.
12. Rubel DM, Spelman L, Murrell DF, See JA, Hewitt D, Foley P, et al. Daylight PDT with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional PDT in actinic keratosis treatment: a randomised controlled trial. Br J Dermatol 2014; 171: 1164–1171.
13. Wiegell SR, Haedersdal M, Philipsen PA, Eriksen P, Enk CD, Wulf HC. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study. Br J Dermatol 2008; 158: 740–746.
14. Wiegell SR, Wulf HC, Szeimies RM, Basset-Seguin N, Bissonnette R, Gerritsen MJ, et al. Daylight photodynamic therapy for actinic keratosis: an international consensus: International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venereol 2012; 26: 673–679.
15. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988; 124: 869–871.
16. Olsen EA, Abernethy ML, Kulp-Shorten C, Callen JP, Glazer SD, Huntley A, et al. A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. J Am Acad Dermatol 1991; 24: 738–743.
17. Moseley H. Light distribution and calibration of commercial PDT LED arrays. Photochem Photobiol Sci 2005; 4: 911–914.
18. Caekelbergh K, Annemans L, Lambert J, Roelandts R. Economic evaluation of methyl aminolaevulinate-based photodynamic therapy in the management of actinic keratosis and basal cell carcinoma. Br J Dermatol 2006; 155: 784–790.
19. Wilson EC. Cost effectiveness of imiquimod 5% cream compared with methyl aminolevulinate-based photodynamic therapy in the treatment of non-hyperkeratotic, non-hypertrophic actinic (solar) keratoses: a decision tree model. Pharmacoeconomics 2010; 28: 1055–1064.
20. Zane C, Facchinetti E, Rossi MT, Specchia C, Calzavara-Pinton PG. A randomized clinical trial of photodynamic therapy with methyl aminolaevulinate vs. diclofenac 3% plus hyaluronic acid gel for the treatment of multiple actinic keratoses of the face and scalp. Br J Dermatol 2014; 170: 1143–1150.
21. Pariser D, Loss R, Jarratt M, Abramovits W, Spencer J, Geronemus R, et al. Topical methyl-aminolevulinate photodynamic therapy using red light-emitting diode light for treatment of multiple actinic keratoses: a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol 2008; 59: 569–576.
22. Wiegell SR, Haederstal M, Eriksen P, Wulf HC. Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolevulinate and home-based daylight exposure: a double-blinded randomized clinical trial. Br J Dermatol 2009; 160: 1308–1314.
23. Wiegell SR, Fabricius S, Gniadecka M, Stender IM, Berne B, Kroon S, et al. Daylight mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicenter study. Br J Dermatol 2012; 166: 1327–1332.
24. Wiegell SR, Fabricius S, Heydenreich J, Enk CD, Rosso S, Bäumler W, et al. Weather conditions and daylight-mediated photodynamic therapy: protoporphyrin IX-weighted daylight doses measured in six geographic locations. Br J Dermatol 2013; 168: 186–191.
25. Neittaanmäki-Perttu N, Karppinen TT, Grönroos M, Tani TT, Snellman E. Daylight photodynamic therapy for actinic keratoses: a randomized double-blinded non-sponsored prospective study comparing BF-200 aminolevulinic acid with methyl-5-aminolaevulinate. Br J Dermatol 2014; 171: 1172–1180.
26. Holmes C, Foley P, Freeman M, Chong AH. Solar keratosis: epidemiology, pathogenesis, presentation and treatment. Australas J Dermatol 2007; 48: 67–74.
27. Neittaanmäki-Perttu N, Grönroos M, Karppinen TT, Taneli T, Snellman E. Hexyl-5-aminolaevulinate 0.2% versus methyl-5-aminolaevulinate 16% daylight PDT for treatment of AKs: results of a randomized double-blinded pilot trial. Br J Dermatol 2015 May 24. [Epub ahead of print].