

## Photodynamic Therapy of Non-melanoma Skin Cancer with Methyl Aminolaevulinate is Associated with Less Pain than with Aminolaevulinic Acid

Magdolna Gaál, Sylwia Otrósinka, Eszter Baltás, Henriette Ócsai, Judit Oláh, Lajos Kemény and Rolland Gyulai

Department of Dermatology and Allergology, University of Szeged, Albert Szent-Györgyi Clinical Center, Korányi fasor 6, HU-6720, Szeged, Hungary.

E-mail: gaalmagdolna@yahoo.com

Accepted June 17, 2011.

During photodynamic therapy (PDT), illumination of the skin surface leads to the excitation of protoporphyrin IX (PpIX). As PpIX returns to its basic energetic state, reactive oxygen radicals are generated, inducing the apoptosis of tumour cells (1). PDT is currently regarded as the first-line treatment for actinic keratosis (AK), superficial basal cell carcinoma (BCC) and Bowen's disease (BD) (2). Therapy-related pain is the most frequent side-effect. Patients usually report a cumulative burning sensation during illumination, which becomes intense within a few minutes of the start of the procedure. In some cases, pain can be so severe that the illumination must be stopped prematurely, resulting in insufficient PpIX formation and inadequate therapeutic result. The aim of our study was to evaluate the degree of treatment-associated pain during PDT with two different photosensitizers, 5-aminolaevulinic acid (ALA) and methyl aminolaevulinate (MAL), in different anatomical regions.

### PATIENTS AND METHODS

PDT was performed on 182 occasions to treat non-melanoma skin cancer (80 occasions for AK, 97 for BCC and 5 for BD). Eighty-seven patients were involved (32 females, 55 males, mean age 72 years, age range 43–92 years). The locations of the tumours were as follows: head and neck region: 111 (cheeks: 22, forehead: 31, temporal area: 12, nose: 18, auricular region: 12, lip: 1, scalp: 11, neck: 4), trunk: 45 (back: 29, chest: 15, abdomen: 1), and extremities: 26 (shoulders: 13, arms: 6, hands: 5, shin: 1, thigh: 1). Patients were randomly assigned to receive either 20% ALA or 16% MAL ointment for 4 h in an occlusive dressing. ALA was used for 103 treatments (48 patients, 18 females, 30 males, age range 46–92 years, mean age 72 years) and MAL for 79 treatments (39 patients, 14 females, 25 males, age range 43–87 years, mean age 70.4 years). After 4 h of photosensitizing, the dressing was removed. Thirty minutes prior to illumination, patients were offered, and if requested, administered 500 mg paracetamol orally for pain relief. Illumination was performed with 630-nm visible red light at a dose of 37 J/cm<sup>2</sup>, using a monochromatic diode lamp (Aktilite®, PhotoCure ASA, Oslo, Norway). The degree of patient-reported pain was assessed immediately after PDT on a 0–10 numeric rating scale (NRS), where 0 = no pain, and 10 = unbearable pain. One and two-way analysis of variance (ANOVA), Student's *t*-test and the Scheffé test (*post hoc*), were applied for statistical analysis with Statistica 8.0 software (StatSoft Inc.). Differences were considered statistically significant at  $p < 0.05$ . Four weeks after the first treatment, a follow-up examination was performed. Therapeutic results were characterized as one of the three categories: complete remission, incomplete remission, or no response.

### RESULTS

Ten patients with a total of 24 treatments experienced intolerable pain, necessitating premature discontinuation of the treatment. In 21 of these incomplete treatments, the photosensitizer used was ALA.

The levels of pain in the regions of the head, trunk and extremities during PDT were compared between the groups receiving the different photosensitizers, ALA and MAL. In the head region, MAL-PDT caused significantly less pain than did ALA-PDT (two-way ANOVA, Scheffé *post hoc* test,  $p_1 = 0.00068$ ). The level of pain during PDT of AKs was significantly greater than that in the case of BCCs (two-way *t*-test,  $p = 0.0025$ ). In the BCC and AK groups, significant differences were detected between MAL and ALA (Fig. 1).

There was no significant difference in the degree of pain between the genders (two-way *t*-test,  $p = 0.19$ ). In-

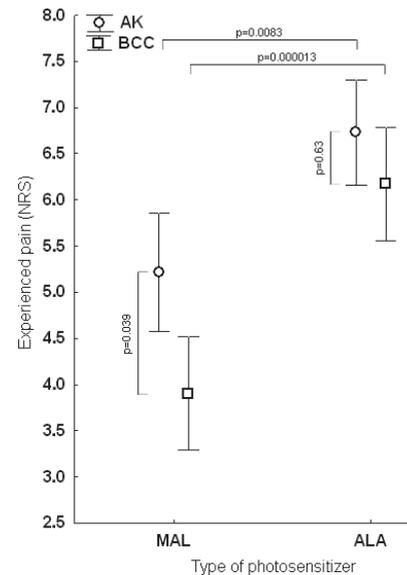


Fig. 1. Comparison methyl aminolaevulinate (MAL)- and 5-aminolaevulinic acid (ALA)-photodynamic therapy (PDT)-associated pain in patients with actinic keratosis (AK) and basal cell carcinoma (BCC) (mean numeric rating scale (NRS) values with standard deviation (SD) bars). Pain during BCC treatment was lower in both the ALA and MAL groups; however, only reached statistical significance in the MAL group (two-way analysis of variance (ANOVA),  $p = 0.0025$ , Scheffé *post hoc* test,  $p_1/\text{MAL-AK}:\text{MAL-BCC}/ = 0.039$ ;  $p_2/\text{ALA-AK}:\text{ALA-BCC}/ = 0.63$ ). MAL-PDT caused significantly less pain than ALA-PDT in both diagnosis groups ( $p_3/\text{MAL-AK}:\text{ALA-AK}/ = 0.0083$ ;  $p_4/\text{MAL-BCC}:\text{ALA-BCC}/ = 0.000013$ ).

creasing age was associated with more pain sensation: significant difference was found between the 40–59 years and the > 80 years groups (one-way ANOVA,  $p=0.008$ , Scheffe *post hoc* test,  $p_{40-59: > 80}=0.014$ ).

No significant difference was observed between the different methods of pain relief: cooling the skin with wet gauze during treatment, oral analgesia, or both (one-way ANOVA,  $p=0.77$ ).

The two photosensitizers, ALA and MAL, were equally efficient (Table SI; available from <http://www.medical-journals.se/acta/content/?doi=10.2340/00015555-1223>).

## DISCUSSION

PDT-associated pain is influenced by several intrinsic (patient-related) and extrinsic (treatment-related) factors. The anatomical region, the diagnosis and the size of the lesion, as well as the degree of photo-ageing, are significant intrinsic determinants of treatment-related pain (3). Lesions on the scalp or forehead are more sensitive than those on the trunk and the extremities (4). Patients with AK seem to experience more intense pain than those with BCC (possibly due to more advanced photo-ageing), and, in general, pain increases with lesion size (4).

Extrinsic PDT factors, such as the use of analgesics, type of photosensitizer, light source, wavelength and dose, at least theoretically, provide the possibility to influence treatment-related pain. Several studies have reported attempts to moderate PDT-induced pain, but comparative investigations have not yet been performed. Cooling with wet gauze, thermal water spraying, and pre-treatment with capsaicin have also been tried, but with either no or limited effect (4). Pain of the most sensitive anatomical regions was successfully controlled by conduction anaesthesia (5). Cold air analgesia and subcutaneous local infiltrative anaesthesia, also proved valuable (6, 7). Nerve blocks provided effective pain relief during topical PDT (8). Pain can also be modulated through the choice of different light sources and wavelengths (9).

MAL and ALA are the most widely used topical photosensitizers in the treatment of non-melanoma skin cancer. However, relatively few data are available concerning treatment-associated pain using the different photosensitizers. Kasche et al. (10) found that MAL-PDT caused significantly less pain than did ALA-PDT in patients with multiple AKs on the scalp. The reason is probably the greater tumour selectivity of MAL or the fact that ALA, but not MAL, is actively transported to the peripheral nerve endings, triggering nerve stimulation during its excitation (10). Steinbauer et al. (11) also considered the use of ALA, in contrast with MAL, as a factor predictive of higher PDT-associated pain.

In the present study, we evaluated treatment-associated pain during PDT of non-melanoma skin cancer in different anatomical regions, using the two photosensitizers, MAL and ALA. We found that, in the sensitive head

region, MAL-PDT was more tolerable and caused significantly less pain than ALA-PDT. There was a tendency for ALA-PDT to be more painful in all anatomical regions, but, in the case of the trunk and the extremities, the differences were not significant. PDT of AK was significantly more painful than treatment of BCCs. Our findings are in accordance with previous studies as concerns the connection between the diagnosis and the therapy-induced pain. Moreover, the observed significant difference between MAL- and ALA-PDT associated pain in the BCC and AK groups, is in line with the previous observation that MAL-PDT causes less pain.

Providing adequate pain relief during PDT presents difficulty. Our data confirm that, while ALA- and MAL-PDT are similarly highly effective for the treatment of non-melanoma skin cancer, MAL-PDT is better tolerated. The lower level of treatment-associated pain suggests better suitability of MAL-PDT for the treatment of sensitive anatomical regions or for patients at risk of more pain (e.g. those with larger lesions, diagnosis of AK, photo-ageing or field cancerization).

## ACKNOWLEDGEMENTS

This study was supported by TÁMOP 4.2.2-08/1 and TÁMOP-4.2.1/B-09/1/KONV-2010-0005 grants and DEAK Kooperációs Kutatói Zrt. GOP-I.I.2-07/1-2008-0007 Projekt.

*The authors declare no conflicts of interest.*

## REFERENCES

1. Fritsch C, Goerz G, Ruzicka T. Photodynamic therapy in dermatology. *Arch Dermatol* 1998; 134: 207–214.
2. Braathen LR, Szeimies RM, Basset-Seguín N, Bissonnette R, Foley P, Pariser D, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. *International Society for Photodynamic Therapy in Dermatology*, 2005. *J Am Acad Dermatol* 2007; 56: 125–143.
3. Sandberg C, Stenquist B, Rosdahl I, Ros AM, Synnerstad I, Karlsson M, et al. Important factors for pain during photodynamic therapy for actinic keratosis. *Acta Derm Venereol* 2006; 86: 404–408.
4. Grapengiesser S, Ericson M, Gudmundsson F, Larko O, Rosen A, Wennberg AM. Pain caused by photodynamic therapy of skin cancer. *Clin Exp Dermatol* 2002; 27: 493–497.
5. Wennberg AM. Pain, pain relief and other practical issues in photodynamic therapy. *Australas J Dermatol* 2005; 46 Suppl: S3–S4.
6. Pagliaro J, Elliott T, Bulsara M, King C, Vinciullo C. Cold air analgesia in photodynamic therapy of basal cell carcinomas and Bowen's disease: an effective addition to treatment: a pilot study. *Dermatol Surg* 2004; 30: 63–66.
7. Borelli C, Herzinger T, Merk K, Berking C, Kunte C, Plewig G, et al. Effect of subcutaneous infiltration anesthesia on pain in photodynamic therapy: a controlled open pilot trial. *Dermatol Surg* 2007; 33: 314–318.
8. Halldin CB, Paoli J, Sandberg C, Gonzalez H, Wennberg AM. Nerve blocks enable adequate pain relief during topical photodynamic therapy of field cancerization on the forehead and scalp. *Br J Dermatol* 2009; 160: 795–800.

9. Babilas P, Knobler R, Hummel S, Gottschaller C, Maisch T, Koller M, et al. Variable pulsed light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratosis: a prospective randomized controlled trial. *Br J Dermatol* 2007; 157: 111–117.
10. Kasche A, Luderschmidt S, Ring J, Hein R. Photodynamic therapy induces less pain in patients treated with methyl aminolevulinate compared to aminolevulinic acid. *J Drugs Dermatol* 2006; 5: 353–356.
11. Steinbauer JM, Schreml S, Babilas P, Zeman F, Karrer S, Landthaler M, et al. Topical photodynamic therapy with porphyrin precursors-assessment of treatment-associated pain in a retrospective study. *Photochem Photobiol Sci* 2009; 8: 1111–1116.