



University of Dundee

Factors influencing pain and efficacy of topical photodynamic therapy

Lydon, E.; Dawe, R. S.; Ibbotson, S. H.

Published in:
British Journal of Dermatology

DOI:
[10.1111/bjd.17204](https://doi.org/10.1111/bjd.17204)

Publication date:
2019

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Lydon, E., Dawe, R. S., & Ibbotson, S. H. (2019). Factors influencing pain and efficacy of topical photodynamic therapy: a retrospective study. *British Journal of Dermatology*, *180*(1), 205-206.
<https://doi.org/10.1111/bjd.17204>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

DR ROBERT S. DAWE (Orcid ID : 0000-0002-4732-071X)

PROFESSOR SALLY H IBBOTSON (Orcid ID : 0000-0001-5685-752X)

Article type : Research Letter

Factors influencing pain and efficacy of topical photodynamic therapy: a retrospective study

E. Lydon*, R. Dawe, S. Ibbotson

Photobiology Unit, Dermatology Department, University of Dundee, Ninewells Hospital & Medical School, Dundee, DD1 9SY, UK

*Emma Lydon was a 4th year medical student when doing this study

Corresponding author: Sally Ibbotson

E-mail: s.h.ibbotson@dundee.ac.uk

Funding sources: none.

Conflicts of interest: S.H.I. has previously received honoraria and travel expenses from Galderma for presentations at meetings. E.L. received travel expenses from the Photobiology Unit in Dundee for her attendance at the European Society for Photodermatology Symposium at the European Academy of Dermatology and Venereology in Vienna.

Photodynamic therapy (PDT) is widely used to treat superficial non-melanoma skin cancers and dysplasia.¹ Pain may be experienced during irradiation, with one study showing pain intervention was required in 44% of PDT treatments.² Other retrospective studies indicated that large treatment areas on head and neck sites, actinic keratoses and strong protoporphyrin IX fluorescence may be predictors of more severe PDT-induced pain, but data were not conclusive.^{3,4} Excepting nerve blockade or reduction in irradiance, other pain relief methods are relatively ineffective. It is therefore important to identify predictors of PDT-

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.17204

This article is protected by copyright. All rights reserved.

induced pain to better inform patients and practitioners. We aimed to identify patient or lesion characteristics or aspects of treatment that were associated with PDT-induced pain and treatment outcomes at one year, in patients with superficial basal cell carcinomas (sBCC) and Bowen's disease (BD).

The study was undertaken in the Scottish PDT Centre. Caldicott Guardian Approval was granted. Data relating to patient, lesion, treatment parameters and outcomes were retrieved from the dedicated in-house PDT database and, when necessary, from PDT case notes. Patients included in the study were those who commenced topical methyl aminolevulinate (Metvix[®]) PDT between 01.01.11 and 31.12.13 for a diagnosis of sBCC and/or BD. The treatment regimen that was used employed gentle surface preparation and a three hour Metvix[®] application time, followed by red LED irradiation (predominantly Aktelite; approximately 85 mW/cm²; 75 J/cm²). Treatment was repeated at one week to complete the treatment cycle and clinical assessment and follow-up was undertaken at three months, with a repeat treatment cycle at that stage if there was evidence of residual disease. Follow-up to one year after last PDT treatment was undertaken. Endpoints were assessed as per our routine PDT clinic practice.

Pain was assessed using VAS scores immediately after PDT irradiation (0-10cm). Fluorescence was graded visually using a standard Wood's light examination (0-3 for none, weak, moderate, strong fluorescence) and erythema was also graded visually by naked eye examination (0-3 for none, mild, moderate, severe erythema) using these semi-quantitative scales and clinical outcome (no response, partial or complete clearance) was assessed at follow-up >10 months after treatment completion (defined as one-year outcome). Data from the first treatment for pain, fluorescence and erythema were used and were assessed by linear regression models for the continuous outcome variable of pain and logistic regression for the binary outcome of clear or not clear at one year. In these models "clustering" by patient was taken into account, recognising that lesions within an individual should not be considered to be independent. Various exploratory multivariate analyses were conducted: the final models for pain included all factors significant at p<0.1 on univariate analyses, including fluorescence, erythema, gender and an interaction term for fluorescence and erythema. The assumptions for the models used (for example, normal distribution of residuals and constant variance of residuals for linear regression) were checked. Stata (Stata Corp., Texas, 2015) was used.

Data relating to 173 lesions in 74 patients were included. The median (range) age was 75 (40-100) years and 63% of lesions were in women. Of the lesions, 46% were sBCC, with a median diameter of 1.4 (0.3-10) cm and 95% one-year clearance. The remaining 54% were

BD, with a median diameter of 1.3 (0.2-10) cm and 93% one-year clearance. Most lesions in women were on lower limbs, with 61% more (95% confidence interval 50% to 72%) lower limb lesions in women than men. The overall median pain score was 4.6 (0-10cm). Women recorded higher pain scores than men (Figure 1A), $p=0.009$. Although highly significant, the difference in pain by gender was moderate with women reporting a median of 1 cm (95% confidence interval 0.2 to 1.9) more pain than men, $p=0.021$, on univariate analysis.

Pain increased as fluorescence increased (Figure 1B), $p<0.0001$. Fluorescence was however not a good predictor of pain, explaining only 3.6% of pain experienced (R-squared 0.036).

As with fluorescence, pain increased as erythema increased (Figure 1C), $p=0.017$. Although significantly (a finding unlikely to be chance) associated with pain erythema only accounted for 3.3% of pain experienced (R-squared 0.033).

Patient age, skin phototype, diagnosis, lesion site and size were not significantly associated with reported PDT-induced pain. Most lesions were clear following PDT. However, smaller lesions were more likely to clear (Figure 1D), $p=0.002$. No association was found between any of the other variables examined and one-year clearance.

Thus, female gender, strong fluorescence and erythema were associated with higher levels of reported PDT-induced pain. However, these did not explain most of the pain experienced, highlighting that there are other factors involved. This emphasises the heterogeneous nature of PDT-induced pain and reinforces the diversity of factors involved and subjectivity of pain reporting. High clearance rates were achieved, particularly for smaller lesions. Limitations of this study included its retrospective design and that data analysed were for each lesion's first treatment, and analysis of all treatments may have been helpful to see if continued high rates of erythema/fluorescence were associated with increased pain during subsequent PDT treatments. Furthermore, assessments of fluorescence and erythema were semi-quantitative and based on visual grading, as opposed to more detailed objective measurements, which may have been more discriminating, but are not undertaken in routine practice. As clearance rates in this sample were so high it was difficult to analyse predictors of clearance as the number of lesions not cleared was small. However, multivariate analysis used to minimise confounding variables' impact in this retrospective study helped to differentiate which variables were most associated with pain and outcome.

This analysis differentiates this study from others.^{3,5} For example, Grapengiesser and colleagues reported on PDT-induced pain in 60 patients (69 lesions) and showed, using univariate analyses that pain scores were higher in males, head and larger treatment sites

and actinic keratoses, but the authors also commented on the limitation that it tends to be males who have large areas of actinic keratosis on head and neck treated by PDT and thus it was not possible to define which factor was most influential because of these confounding influences.³ Furthermore, Virgili and colleagues investigated factors that may be implicated in PDT-induced pain in 121 Italian patients and whilst they too demonstrated higher pain scores at head and neck sites and for actinic keratosis, they did not show any clear overall impact of gender and again highlighted the limitations of their study, which involved univariate analysis of data.⁵

Thus, in summary, we have attempted to minimise the impact of confounding factors through the use of multivariate analysis of data and to provide useful information for PDT practitioners and patients regarding possible predictors of PDT-induced pain and efficacy that may help to inform optimisation of treatment regimens.

References

- 1 Morton CA, McKenna KE, Rhodes LE. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; **159**: 1245-66.
- 2 Miller IM, Nielsen JS, Lophaven S *et al.* Factors related to pain during routine photodynamic therapy: a descriptive study of 301 patients. *J. Eur. Acad. Dermatol. Venereol.* 2011; **25**: 1275-81.
- 3 Grapengiesser S, Gudmundsson O, Larkö O *et al.* Pain caused by photodynamic therapy of skin cancer. *Clin Exp Dermatol* 2002; **27**: 493-7.
- 4 Gholam P, Denk K, Sehr T *et al.* Factors influencing pain intensity during topical photodynamic therapy of complete cosmetic units for actinic keratoses. *J. Am. Acad. Dermatol.* 2010; **63**: 213-8.
- 5 Virgili A, Osti F, Maranini C *et al.* Photodynamic therapy: parameters predictive of pain. *Br J Dermatol* 2010; **162**: 460-1.

