

Cold Air Analgesia in Photodynamic Therapy of Basal Cell Carcinomas and Bowen's Syndrome: An Effective Addition to Treatment: A Pilot Study

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BACKGROUND. There is considerable interpatient variability in pain tolerance during and after treatment of skin cancer with photodynamic therapy (PDT). Additionally, erythema and edema are common, with mild crusting and healing over 1 to 2 weeks. **OBJECTIVE.** To determine whether concurrent cold air analgesia improves the tolerability of PDT.

METHOD. Twenty-six patients with two similar superficial skin cancers were treated with PDT. One lesion was treated with cold air analgesia and the other without. Patients rated their pain during treatment using the Wong Baker Faces Pain Scale

and detailed duration of posttreatment pain. At week 2, the inflammatory response was assessed.

RESULT. A statistically significant difference in the analgesia group was shown with respect to the mean duration of pain and the level of erythema after the first treatment as well as pain scores during the second treatment.

CONCLUSION. Patient acceptance of PDT for treatment of nonmelanoma skin cancer is improved with lessened morbidity assessed with concurrent use of cold air analgesia to the treatment field.

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TOPICAL PHOTODYNAMIC THERAPY (PDT) is gaining acceptance as an effective treatment option for nonmelanoma skin cancer. A systematic review of the published evidence indicates that topical PDT is effective in treatment of actinic keratoses of the face and scalp, Bowen's disease, and superficial basal cell carcinomas.¹

Topical PDT involves photoactivation in the presence of oxygen of a topically applied photosensitizer localized to target neoplastic or dysplastic tissue. The resultant production of reactive oxygen intermediates such as singlet oxygen leads to apoptosis and vascular damage, which promote tumor destruction.²

The most commonly used topical photosensitizer is 5-aminolevulinic acid (ALA), a precursor in the heme biosynthetic pathway. Various formulations of ALA have been tried with the addition of penetration enhancers such as dimethylsulfoxide and ethylenediamine tetra-acetic acid and even deferoxamine. A more recent development has been the availability of esters of ALA, notably the methyl ester.^{1,3}

As an evolving treatment, there has been no consensus on the method for topical PDT. Variables include the photosensitizer used and the formulation, the time of application, the light source and spectrum, lesion preparation, and a number of treatments. The method chosen for use in this study conformed to that in several recent clinical trials.^{1,4,5}

Early reports have indicated that most patients treated with PDT require no analgesia. However, pain occurs both during and after treatment and on occasion can be intolerable in certain individuals.⁶⁻¹⁰

Pain during PDT most likely results from a combination of intense nerve stimulation by reactive oxygen species and hyperthermia. Treatment of large and/or ulcerated lesions and those on the face and scalp is more likely to induce pain, but there is considerable interpatient variability in pain tolerance of PDT. Immediately after illumination, erythema and edema are common, with mild crusting and healing over 1 to 2 weeks.¹

Previous attempts to control the pain of PDT have included topical or injectable local anesthetic, concurrent use of cryogen sprays, and use of hand-held ventilator fans and water sprays.¹

The use of cold air analgesia (CAG) during treatment is described in the laser literature as being

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very effective.¹¹ The objective of this pilot study was to determine whether there is any benefit during and after treatment from concurrent use of CAG to the treatment field during PDT.

Method

Twenty-six patients with either superficial basal cell carcinomas or in situ squamous cell carcinomas were recruited. Informed written consent was obtained from all patients. Each patient recruited had two similar lesions with respect to type and site. One lesion was randomly allocated to have PDT without analgesia (NAG) and the other to treatment with a combination of PDT and CAG.

The treatment technique consisted of the surface of the lesion being prepared by very gentle curettage without local anesthetic. The aim was to remove scales and surface crusts and to roughen the surface of the lesion in order to aid penetration of the photosensitizer. At no stage was vigorous curettage carried out in an effort to debulk the tumor significantly, as this would be too painful and would potentially result in a significant scar. Subsequently, 20% ALA cream was applied in a layer approximately 1mm thick to the lesion and the surrounding 5mm of normal skin. The area was then covered with an occlusive plastic film dressing (Tegaderm). Four hours later, after removing the dressing and cleaning the area with saline, the site was immediately treated with 37 J/cm² of red light. The light source consisted of a lamp with 128 lightemitting diodes with a peak wave length of 636 ± 5 nm (PhotoCure Light Emitting Diode PDT Lamp CureLight 128). The light is held between 50 and 80mm from the skin. CAG was delivered using a device that produces air at a temperature of -35°C when held at a distance of between 10 and 20 cm from the skin (Zimmer cold air blower) (Figures 1 and 2). This process was repeated a second time 1 week later.

Immediately after treatment to each lesion, patients were asked to rate their pain during their treatment, according to the Wong-Baker Faces Pain Rating Scale. The Wong-Baker Pain Scale contains six faces depicting graduated levels of distress.¹² A comparison of pain levels between the two lesions in each patient treated either with or without CAG was thereby undertaken. A questionnaire was also filled out after the first treatment to assess the duration of posttreatment pain for each lesion. The duration was categorized as either nil, less than 1 hour, 1 to 3 hours, or greater than 6 hours. Before the second treatment, lesional sites were assessed for inflammatory response (erythema). During the second treatment, pain was again assessed using the Wong-Baker Pain Faces Rating Scale.



Figure 1. The Zimmer Cold Air Blower



Figure 2. A patient undergoing PDT with simultaneous application of cold air using the Zimmer Cold Air Blower.

Because of a comparison was being made between the effects of PDT on two lesions in the same study subject, a paired t-test was used. Average pain ratings and standard deviations are reported. The distribution of

pain score was approximately normal. A similar comparison was made for duration of pain and erythema.

Duration of pain was also dichotomized as 0 (no pain) and 1 (any pain). The two treatments for lesions were compared using a McNemar's chi-squared test. Erythema was dichotomized as 0 (nil or mild erythema) and 1 (moderate or severe erythema). Again, the two treatments were compared using a McNemar's chi-squared test. All statistical analyses were performed using SAS version 8 statistical software.

Results

Figure 3 shows the box plot of the Wong-Baker Faces Pain rating scale between the lesion treated with NAG (mean \pm SE, 2.7 ± 1.57 ; median of 2) and the lesion treated with CAG (mean \pm SD, 2.2 ± 1.41 , median of 2) for week 1. There was no significant difference ($p = 0.136$) between these two treatments at week 1; however, the average pain score at week 2 for the NAG (mean \pm SD, 3 ± 1.47 , median of 3)-treated lesion was significantly higher ($p = 0.025$) compared to the CAG (mean \pm SD, 2.4 ± 1.47 , median \pm 2)-treated lesion. The mean duration of pain for the NAG (mean \pm SD, 1.8 ± 0.91)-treated lesion was significantly ($p = 0.0001$) higher compared with the CAG (mean \pm SD, 0.7 ± 0.72)-treated lesion. The average redness score in the NAG (mean \pm SD, 1.8 ± 0.67)-treated lesion was significantly ($p = 0.0005$) higher compared with the CAG (mean \pm SD, 1.2 ± 0.67)-treated lesion.

Discussion

There was a statistically significant reduction in pain scores in the CAG group during the second treatment.

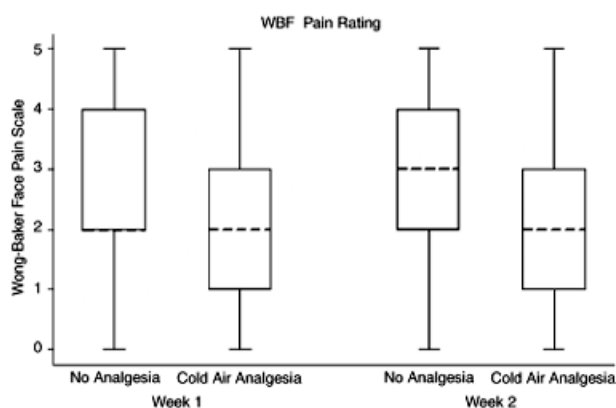


Figure 3. Box Plot for Wong-Baker face pain scale; the dashed line is the median. The box is the upper and lower quartiles, and the whiskers are the largest and smallest values.

The duration of pain after the first treatment and the degree of erythema as assessed at the second treatment also showed a statistically significant benefit for CAG. The use of CAG results in greater tolerability of the second PDT treatment and decreased duration of posttreatment pain and erythema. The morbidity of the treatment is therefore significantly lessened, and patient acceptance is greater as a result. This relatively simple and inexpensive addition to PDT has many advantages over other described alternatives, such as topical and injectable local anesthetics, cryogen sprays, and water spray systems. The shortcomings of these alternatives include the pain associated with local anesthetic injections and the restriction in total dose in the setting of large or multiple lesions. Topical anesthetics are generally relatively ineffective and as with injectable local anesthetics do not have the benefit of reducing the duration of pain after treatment or the degree of erythema as a marker of inflammation. Normal ventilator fans and water spray systems are unable to produce the low temperatures resulting from CAG used in this study, and cryogen spray systems are unable to cover large areas when large lesions require treatment.

Follow-up 6 months after treatment has shown no early recurrences in either the NAG- or CAG-treated groups. Whether the reduction in erythema and inflammation in the CAG-treated group reduces clinical effectiveness and cure rate is undetermined but unlikely considering the photochemical rather than photothermal nature of the photodynamic effect. Long-term follow-up is planned to assess whether there is an impact of CAG on cure rates.

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