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Letter to the Editor

Painless and efficient ALA-PDT and MAL-PDT of Actinic Keratosis can be achieved by drastically reducing the Drug-Light Interval (DLI)

Serge Mordon

University of Lille, INSERM, CHU Lille, U1189 – ONCO-THAI – Assisted Laser Therapy and Immunotherapy for Oncology, F-59000 Lille, France

Email: serge.mordon@inserm.fr - ORCID: 0000-0002-1208-7153

During Photodynamic Therapy (PDT) of Actinic Keratosis, either 5-ALA (Amino-Levulinic Acid) or MAL (Methyl Amino Levulinate) is utilized as precursor that preferentially accumulates in dysplastic cells. The precursor then converts to PpIX via the heme pathway and causes apoptosis of the cells when illuminated. The major drawback of PDT is the pain experienced during the illumination. In fact, though ALA or MAL are not taken up into the nerve endings, reactive oxygen species (ROS) produced during light exposure may cause cell degranulation of mast cells leading to release of inflammatory mediators. Among them, bradykinin and histamine are known to directly stimulate sensory nerve endings.

PDT was originally operated at sufficiently long drug–light interval (DLI) so that the PpIX distribution is already in equilibrium. Recommendation was 14-18 hours (1). The hypothesis that ALA-PDT and MAL-PDT can work with a reduced or even without any DLI seems counter-intuitive. This letter aims to review three clinical studies demonstrating that short DLI is associated to low pain and high efficacy.

In 2008 by Wiegell et al performed a randomized controlled study to compare conventional red light-emitting diode (LED) light vs. daylight (2). One area was illuminated by red LED light (37J/cm²) after 3-h incubation with MAL under occlusive dressing; the other area was treated with daylight for 2.5 h after the MAL cream had been under occlusion for only half an hour. A reduction of 79% in the daylight area of AK lesions and 71% in the LED area were observed. However, daylight was significantly less painful than LED light with a mean maximal pain score during daylight exposure of 2.0 (SD ± 1.9) compared with 6.7 (SD ± 2.2) during red LED exposure (p< 0.0001)

Gandy et al. have also proposed a novel protocol to effectively treat AKs with PDT that eliminates the pre-illumination incubation period in order to reduce the pain (3). The clinical evaluation consisted in a conventional preparation of the lesion by scrubbing the face and scalp with warm soapy water and descaling hypertrophic AKs with a 4 mm non-disposable curette. ALA was then applied to the patient's face and scalp just before placing him under the blue light for 33 minutes and 20 seconds (two cycles of 16m and 40s). With this protocol, the patient tolerated the complete course of treatment and reported no pain (0 out of 10). At one week, the treated areas revealed resolving erythema and desquamation, indicating a good response to therapy.

Mordon et al. performed, on 47 patients, a randomized, controlled, multicenter, intra-individual clinical study (4). One area was illuminated by red LED light ($37\text{J}/\text{cm}^2$) after 3-h incubation with MAL under occlusive dressing; the other with a new device for 2.5 h after the MAL cream had been applied for only half an hour. The clearance rate was similar for the 2 sides (94.2% vs. 94.9%). However, the pain score was significantly lower for the 30 minutes DLI compared to the 3 hours DLI respectively 0.3 vs 7.4 ($p < 0.001$).

At last, Maire et al performed MAL-PDT of 38 male patients with AK lesions of the scalp (5). Artificial Daylight (White LED) illumination was performed, almost immediately (3 to 5 minutes) after MAL cream application, for 2.5 hours (light dose: $26.1\text{ J}/\text{cm}^2$). 33 of the 38 patients (87%) of patients experienced no pain and the remaining five patients (13%) rated their pain level as one.

When using ALA or MAL, it is important to avoid the confusion between incubation time and DLI. When performing ALA-PDT or MAL-PDT, DLI is the period of time between first PpIX production by dysplastic cell and its activation by light. Studies of intracellular PpIX formation kinetics have demonstrated that PpIX formation by dysplastic cells is quasi-instantaneous after 5-ALA administration (6). Since ALA or MAL is not removed, formation of PpIX will continue as long as the dysplastic cell is alive. Short DLI are associated with reduced PpIX buildup in target tissue due to absence of PpIX diffusion into surrounding tissues containing intact sensory nerve fibers. Short DLI should be used since it is a very simple way to reduce pain.

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