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Low-irradiance red light compared to conventional red light in photodynamic therapy of actinic keratosis: a way to reduce pain during treatment

Serge Mordon, PhD. (<https://orcid.org/0000-0002-1208-7153>)

Anne Sophie Vignion-Dewalle, PhD. (<https://orcid.org/0000-0003-0979-3310>)

Address: INSERM, Univ. Lille, CHU Lille, U1189-OncoThAI-Image Assisted Laser Therapy for Oncology, Lille, F-59000, France.

Electronic address: serge.mordon@inserm.fr.

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Conventional photodynamic therapy (C-PDT), which requires an irradiation with 37 J/cm^2 of red light after 3 hours of Methyl aminolevulinate incubation is an effective protocol, approved in Europe, for thin and non-pigmented AK on the face and scalp (Pariser et al., 2008; Szeimies et al., 2009). However C-PDT is associated with high pain scores (Morton et al., 2006; Rubel et al., 2014; Wiegell et al., 2008). This letter aims to review and discuss clinical studies (Table 1) dealing with PDT involving irradiation with low-irradiance (lower than 20 mW/cm^2) red light (Li-PDT).

In 2012, Ibbotson et al evaluated the Ambulight® device emitting 7 mW/cm^2 red light (Ibbotson & Ferguson, 2012). Twenty three patients received both C-PDT and Ambulight which was programmed to remain switched off for three hours and then to switch on automatically and remain on for a further three hours. The mean pain score for was 1 (minimum: 0; maximum: 7) for PDT using the Ambulight® device and 5 (minimum: 1.5; maximum: 9) for C-PDT. At one year, lesion clearance rate was 84 %.

Gholam et al have also evaluated Li-PDT using the BF-RhodoLED® lamp system with an irradiance of 15.4 mW/cm^2 for 40 minutes in order to achieve a light dose of 37 J/cm^2 . Thirty-one patients were enrolled (Gholam, Bosselmann, Enk, & Dick, 2018). Li-PDT resulted in significant less pain scores than C-PDT (2.8 for Li-PDT vs 7.6 for C-PDT) while maintaining a similar efficacy four weeks after treatment: percentage reduction of 69.9% for Li-PDT vs 74.3% for C-PDT.

Vicentini et al performed a study evaluating PDT using a light-emitting fabric device delivering fractionated red light at a low irradiance of 12 mW/cm^2 (Li-PDT) (Vicentini et al., 2018). After 30 minutes of MAL incubation, the Li-PDT device was switched on and illumination was performed for 2h30 giving a light dose of 37 J/cm^2 . With a mean pain score of 0.4, Li-PDT was found to be almost pain free compared to C-PDT (5.0). Efficacy was 84 % for Li-PDT and 76.8% for C-PDT at 6 month-follow up.

The 3 studies found a significant and clinically relevant reduction in pain for Li-PDT compared to C-PDT at the same light dose. The data reported by these three studies were pooled in order to evaluate the relationship between irradiance (mW/cm^2) and pain (Figure 2). A linear relationship was observed with a coefficient of determination (R-squared) of 0.726.

It is usually admitted that pain is correlated with PpIX production. Regarding daylight-PDT, it is presumed that continuous production and photoactivation of small amounts of PpIX instead of fast photo activation of large amounts decreases pain (Wiegell et al., 2008). This explains that pain score

reported in Study #3 where pain (0.4) is lower than those reported in Studies #1 (7 mW/cm² ; pain: 1.0) and #2 (15 mW/cm² ; pain: 2.8) . In Study #3, illumination was performed after 30minutes of incubation whereas the two others studies uses an incubation time of 3 hours. Martin found that a 15minutes incubation resulted in significantly less pain than a 75minutes incubation time (Martin, 2016).Comparatively, Daylight PDT is associated to pain scores, typically around 2.0(Wiegell et al., 2012).

In conclusion, since pain is always reported as the main drawback of C-PDT, irradiation with low irradiance red light should be considered by dermatologists. The controlled light delivery of Li-PDT is an advantage over daylight-PDT, which has also been explored as a less painful means to deliver PDT. However, the limitation of continuous low irradiance is prolonged treatment times.

Compared to daylight-PDT, Li-PDT consistently delivers the same light dose and can be conducted in all weather conditions, in all geographic locations, all year round.

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Table

Author	Comparative study	Number of patients	Duration illumination	Light dose	Pain	Efficacy (% reduction)
Gholam(Gholam et al., 2018)	RhodoLED 15.4 mW/cm ² vs Aktilite (66.2 mW/cm ²)	31 Actinic Keratoses Grade I - III	40 minutes vs 9min and 19 s	37 J/cm ² vs 37 J/cm ²	2.8 ± 1.5 vs 7.6 ± 1.5	At 1 month FU 67.9 ± 11.8 vs 69.9 ± 2.1
Vicentini (Vicentini et al., 2018)	Flexitheralight 12 mW/cm ² vs Aktilite (65 mW/cm ²)	25 Actinic Keratoses Grade I - II	50 minutes vs 9min and 50 s	37 J/cm ² vs 37 J/cm ²	0.4 ± 0.6 vs. 5.0 ± 2.6	At 6 month FU 84.0% vs 76.8 %
Ibbotson(Ibbotson & Ferguson, 2012)	Ambulight (7 mW/cm ²) Vs Aktilite® (80–90 mW/cm ²)	23 small lesions of Bowen's disease and superficial BCC	180 minutes vs 20 minutes	75 J/cm ² vs 75 J/cm ²	1.0 (0-7) vs 5.0 (1.5-9)	At 1 year FU 84 % vs ?

Table 1: Data reported for the clinical studies included in the review: from refs: (Vicentini et al., 2018)(Ibbotson & Ferguson, 2012)(Gholam et al., 2018). *Grade I Actinic Keratosis are slightly palpable, grade II are moderately thick, and grade III AK are very thick and/or obvious*

Figures

Figure 1: Light-emitting fabric device (from ref (Vicentini et al., 2018))

Figure 2: Pain scores (0-10) vs Irradiance (mW/cm²). Data were obtained from refs: (Vicentini et al., 2018)(Ibbotson & Ferguson, 2012)(Gholam et al., 2018)