Pilot study utilizing short contact protocols for treatment of actinic keratoses (AK) with ALA gel-red light photodynamic therapy (PDT)

Jessica Johnson, BS [1], Jackson Hanna, BS [2], Amy S. Nowacki, PhD [3], Edward Maytin, MD, PhD [1,2,4,(*)]

[1] Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, U.S.A.
[2] Department of Dermatology, Cleveland Clinic, Cleveland, OH, U.S.A.
[3] Quantitative Health Science, Cleveland Clinic, Cleveland, OH, U.S.A.
[4] Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH, U.S.A.; (*) Principal Investigator
Disclosures & Commercial Support: NIH Grant P01 CA084203; IIT grant from Biofrontera Inc.

Background

PDT uses a photosensitizing drug, 5-aminovelunic acid (ALA) and an artificial light source to target neoplastic lesions in an entire skin field. The downside of most current PDT treatment protocols (conventional, or c-PDT), are the photosensitizer's long incubation times (~3-4 hours) and the stinging pain during illumination. However, recent studies suggest that shorter incubation times during blue light PDT (m-PDT) can reduce pain and have efficacy similar to c-PDT. We sought to translate the blue light m-PDT protocol to red light PDT (635 nm). We hypothesize that a shorter incubation with a 10% ALA nano-formulation gel will result in reduced patient reported pain levels, yet will maintain similar clinical efficacy (lesion clearance) as c-PDT; the latter is modelled in our study as Group C.

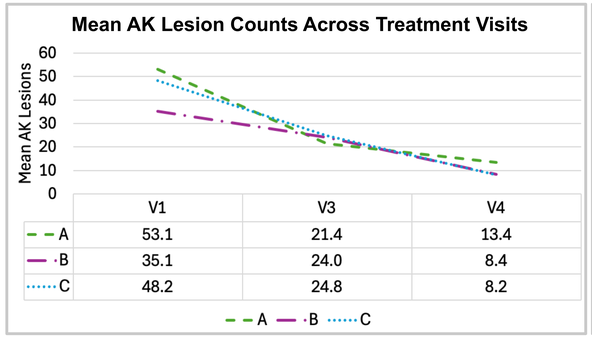
Methods

- Randomized clinical trial (n = 30)
- Enrollment Criteria: A minimum of 10 AK lesions on the face
- Block randomization scheme
- Topical Ameluz to entire face; no occlusion

Group: *Incubation*, *Illumination*
Group A (n = 10): *10 min, 20 min* (74 J/cm^2)
Group B (n = 10): *20 min, 10 min* (37 J/cm^2)
Group C (n = 10): *1 hour, 10 min* (37 J/cm^2)

Outcomes Measures:
- AK Lesions – counted and photographed
- Pain – reported on an 11-point VAS scale (0 = no pain, 10 = intolerable pain)
  - After treatment starts, pain reported at 1 min, 5 min, and end of treatment

Statistical Measures:
- For evaluating AK lesion clearance, a non-inferiority model was utilized with a non-inferiority margin of -15%
- For comparing pain across the three groups, a linear regression model and ANOVA was utilized



	V1	V3	V4
A	53.1	21.4	13.4
B	35.1	24.0	8.4
C	48.2	24.8	8.2

Figure 1. AK lesions were counted at Baseline (V1), 8 weeks post 1st PDT (V3) and 3-6 months after 2nd PDT (V4).

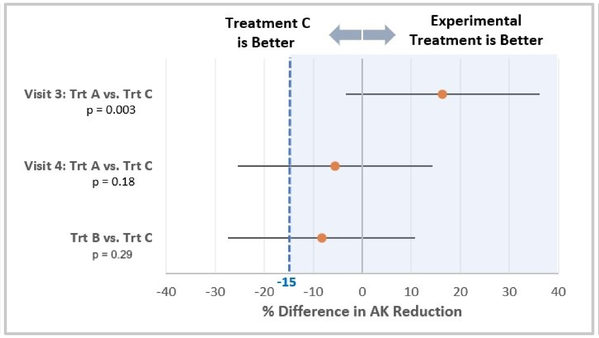


Figure 2. Forest plot demonstrating the comparison of reduction of AK lesions between different treatment groups at a clinical efficacy margin of -15% and a 90% CI interval.

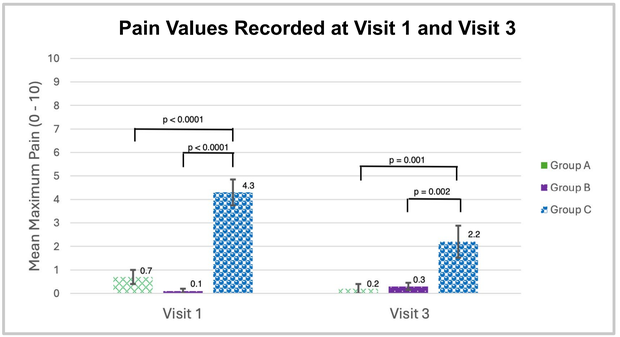


Figure 3. Maximum pain values recorded during each PDT treatment, averaged for each group. Patient who dopped out was excluded from the analysis. Error bars represent the standard error.

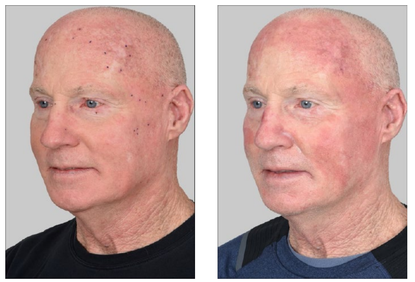
Visit Schedule

0 d	3 d	8 wk	3-6 m
Visit 1 (V1) PDT Treatment Lesion Count Photographs	**Visit 2 (V2)** Photographs	**Visit 3 (V3)** PDT Treatment Lesion Count	**Visit 4 (V4)** Lesion Count

Results

After 2 PDT treatments, the reduction in AK lesions from baseline were 76% (Group A), 74% (Group B), and 82% (Group C). The reduction in AK lesions from PDT Treatment #1 (V1 to V3) was non-inferior between Group A and C (p = 0.003). However, Group B did not meet the -15% non-inferiority margin when compared to Group C (p = 0.29). At either of the two visits, pain in Groups A and B was significantly lower than for Group C (V1: A, p < 0.001, B, p < 0.0001; V3: A, p = 0.001, B = 0.002).


Before PDT | 3 Days After PDT
Group A


Before PDT | 3 Days After PDT
Group B


Before PDT | 3 Days After PDT
Group C

Future Directions

The results support the use of a shortened red light PDT incubation protocol for the treatment of AK lesions on the face.

Our protocol is a more tolerable treatment for patients, as evidenced by the minimum pain levels reported, and easier for physicians and patients because of the shorter times required.

References

1. Kaw U, Ilyas M, Bullock T, et al. A regimen to minimize pain during blue light photodynamic therapy of actinic keratoses: Bilaterally controlled, randomized trial of simultaneous versus conventional illumination. *J Am Acad Dermatol*. 2020;82(4):862-868. doi:10.1016/J.JAAD.2019.09.010
2. Pariser DM, Houlihan A, Ferdon MB, Berg JE. Randomized Vehicle-Controlled Study of Short Drug Incubation Aminolevulinic Acid Photodynamic Therapy for Actinic Keratoses of the Face or Scalp. *Dermatologic Surg*. 2016;42(3):296. doi:10.1097/DSS.0000000000000630
3. Gandy J, Labadie B, Farshidi DB, Zachary C. Photodynamic Therapy Effectively Treats Actinic Keratoses Without Pre-Illumination Incubation Time. *J Drugs Dermatol*. 2017;16(3):275. Accessed September 26, 2023. /pmc/articles/PMC6241219/
4. Martin GM, Martin G. In-office Painless Aminolevulinic Acid Photodynamic Therapy: A Proof of Concept Study and Clinical Experience in More Than 100 Patients. *J Clin Aesthet Dermatol*. 2016;9(2):19. Accessed September 26, 2023. /pmc/articles/PMC4771386/
5. Anvery N, Christensen RE, Dirr MA, et al. Comparative effectiveness of 5-aminolevulinic acid photodynamic therapy with no incubation versus one-hour incubation for the treatment of actinic keratosis: A randomized controlled trial. *J Am Acad Dermatol*. 2023;89(2):401-403. doi:10.1016/J.JAAD.2023.03.056
6. Li J, Zhang Y, Zhang G, et al. Modified painless photodynamic therapy for facial multiple actinic keratosis in China: A prospective split-face control study. *Lasers Surg Med*. 2023;55(10). doi:10.1002/LSM.23728
7. Mordon S, Vignion-Dewalle AS, Abi-Rached H, et al. The conventional protocol vs. a protocol including illumination with a fabric-based biophotonic device (the Phosistos protocol) in photodynamic therapy for actinic keratosis: a randomized, controlled, noninferiority clinical study. *Br J Dermatol*. 2020;182(1):76-84. doi:10.1111/BJD.18048