# Safety of Large Field (>20cm$^2$) Photodynamic Therapy Using 10% Aminolevulinic Acid Hydrochloride Nanoemulsion Gel Comparing Blue to Red Light Illumination

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## INTRODUCTION

- Actinic keratoses (AKs) are precursor lesions that may progress to squamous cell carcinomas.[1,2]
- Treatment of AKs has traditionally involved cryotherapy, 5-fluorouracil, and other topical therapies. With a growing desire for U.S. dermatologists to treat field cancerization and to increase patient compliance, photodynamic therapy (PDT) has become an important treatment modality.[3]
- Photodynamic therapy with 10% aminolevulinic acid hydrochloride nanoemulsion gel (10% ALA gel; Biofrontera) followed by red light illumination was approved in the U.S. for the treatment of AKs and healthy surrounding skin up to 20 cm$^2$ in May, 2016.
- Photodynamic therapy with 10% ALA gel has been shown to have fewer local skin reactions compared to the use of 20% ALA solution on treatment areas 25 cm$^2$.[4]
- In the clinical setting, U.S. dermatologists routinely use PDT to treat cancerous fields >25cm$^2$ with blue or red light. However, it is unclear in regions >25cm$^2$ if the light source used correlates to observed local skin reactions.
- This study compares local skin reactions after 10 J/cm$^2$ blue light or 37 J/cm$^2$ red light illumination following PDT with 10% ALA gel on treatment areas >20 cm$^2$.

## METHODS

- This is a retrospective, descriptive case series in Texas from January 1-December 31, 2018 that compared the safety data on 190 patients with AK treatment areas >20cm$^2$ with blue light compared to red light illumination.
- After debridement, one tube (2 grams) of 10% ALA gel was utilized in each treatment area >20cm$^2$ for all 279 PDT treatments and incubated on full face and ears (Face) for 60 minutes prior to illumination but incubated for 90 minutes with plastic wrap occlusion on the bilateral dorsal hands (Hands), bilateral dorsal wrists to elbows (Arms), scalps (Scalp), decolletés (Chest), anterior or posterior necks (Neck), bilateral shins or calves (Legs), and upper backs (Back) prior to illumination.
- Incubation was followed by illumination by either narrowband blue light [DUSA, 417nm] or narrowband red light [Galderma, 630nm].
- A specific PDT post-care regimen was recommended to expedite healing and decrease irritation by applying physical sunblock zinc oxide 10% (sunblock) and topical restorative skin cream with zinc and copper [Avene] and/or post-procedure laser gel [Elta] (healing creams) simultaneously every 2 hours during waking hours for 48-96 hours after PDT treatment.
- Data is reported by treatment area for irritation (stinging/burning, dryness, scaling, and erythema), post-PDT care, extent of irritation (level 5-strong burning and scaling; level 4-persistent mild burning, scaling, redness; level 3-persistent redness with minimal scaling; level 2-temporary redness and scaling; level 1-mild temporary redness without scaling) and month of irritation. Irritation was reported from 1-28 days post PDT.

## RESULTS

- Of the 190 patients, 64.7% (123/190) were males and 35.3% (67/190) were females. Ages ranged from 40-95, with a mean age of 74 (Table 1).
- Fitzpatrick skin types included 45.3% (86/190) type 2, 54.2% (103/190) type 3, and 0.5% (1/190) type 4 (Table 1).
- Of the 103 sessions with blue light, PDT treatments included 72.8% (75/103) on Face, 2.9% (3/103) on Hands, 2.9% (3/103) on Arms, 12.6% (13/103) on Scalp, 4.9% (5/103) on Chest, 1.9% (2/103) on Neck, 1.0% (1/103) on Legs, and 1.0% (1/103) on Back (Table 1).
- Overall irritation incidence in was 4.7% (13/279). Of the 176 sessions with red light, PDT treatments included 74.4% (131/176) on full face and ears (Face), 7.4% (13/176) on bilateral dorsal hands (Hands), 4.0% (7/176) on bilateral dorsal wrists to elbows (Arms), 10.2% (18/176) on scalps (Scalp), 1.7% (3/176) on decolletés (Chest), 0.0% (0/176) on anterior or posterior necks (Neck), 2.3% (4/176) on bilateral shins or calves (Legs), and 0.0% (0/176) on upper backs (Back) (Table 1).

## RESULTS

**Table 1: Patient Demographics**

| | Red Light | | | Blue Light | | |
|---|---|---|---|---|---|---|
| **Age** | | | | | | |
| **Average** | 74 | 74 | 73 | 74 | 74 | 76 |
| **Age Range** | 40-95 | N/A | 40-83 | 46-92 | N/A | 68-81 |
| | **Sessions (n=176)** | **Patients (n=114)** | **Sessions With Irritation (n=9)** | **Sessions (n=103)** | **Patients (n=76)** | **Sessions With Irritation (n=4)** |
| **Sex** | | | | | | |
| **Male** | 114 | 74 | 5 | 69 | 49 | 4 |
| **Female** | 62 | 40 | 4 | 34 | 27 | 0 |
| **Location** | | | | | | |
| **Arms** | 7 | N/A | 1 | 3 | N/A | 0 |
| **Hands** | 13 | N/A | 1 | 3 | N/A | 0 |
| **Face** | 131 | N/A | 7 | 75 | N/A | 4 |
| **Legs** | 4 | N/A | 0 | 1 | N/A | 0 |
| **Neck** | 0 | N/A | 0 | 2 | N/A | 0 |
| **Chest** | 3 | N/A | 0 | 5 | N/A | 0 |
| **Scalp** | 18 | N/A | 0 | 13 | N/A | 0 |
| **Back** | 0 | N/A | 0 | 1 | N/A | 0 |
| **Fitzpatrick Skin Type** | | | | | | |
| **1** | 0 | 0 | 0 | 0 | 0 | 0 |
| **2** | 70 | 46 | 3 | 53 | 40 | 2 |
| **3** | 105 | 67 | 6 | 50 | 36 | 2 |
| **4** | 1 | 1 | 0 | 0 | 0 | 0 |
| **5** | 0 | 0 | 0 | 0 | 0 | 0 |

Figure 1: Irritation by Light Source (n=279)

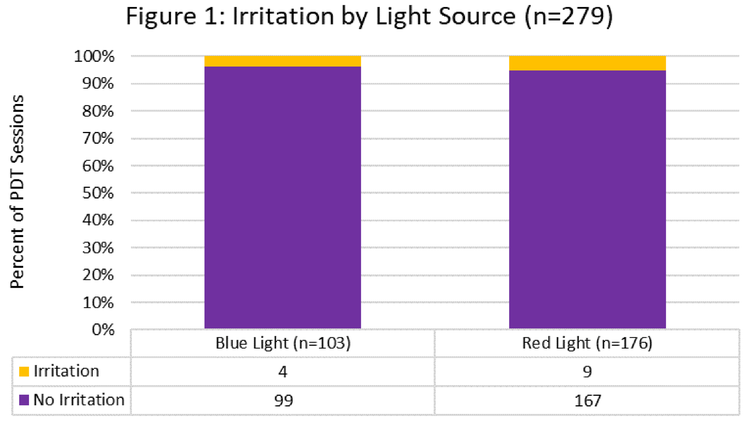
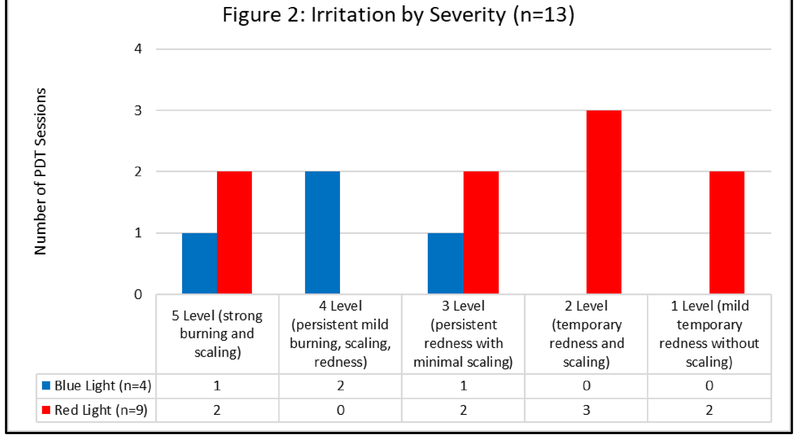
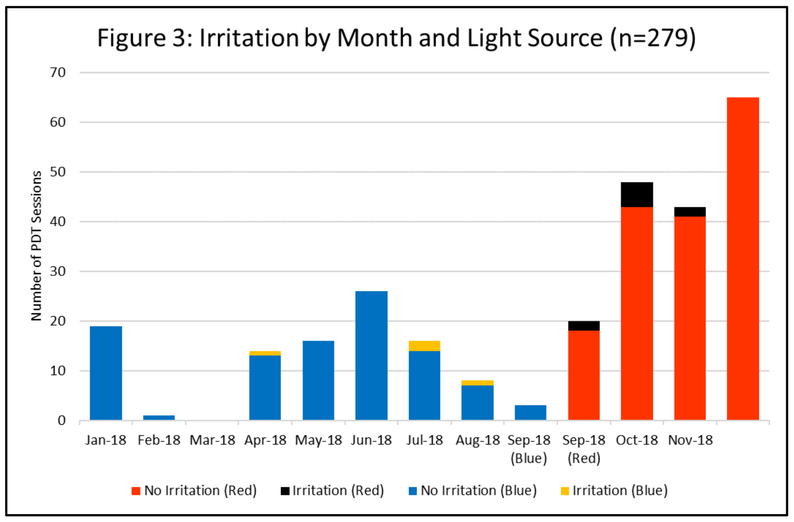



Figure 2: Irritation by Severity (n=13)




- Irritation after sessions was observed (from greatest to least) in 8.4% (11/131) full face and ears (Face), 6.3% (1/16) bilateral dorsal hands and fingers (Hands), 3.2% (1/31) scalps (Scalp), 0% (0/10) bilateral dorsal wrists to elbows (Arms), 0% (0/8) decolletés (Chest), 0% (0/2) anterior/posterior necks (Neck), 0% (0/5) on bilateral shins or calves (Legs), and 0% (0/1) upper back (Back) (Table 1).
- Greatest incidence of the 4.7% (13/279) of patients with irritation after PDT occurred on the Face in 84.6% (11/13), followed by Hands in 7.7% (1/13) Scalp in 7.7% (1/13), and none on Arms, Neck, Legs, Chest, and Back (Table 1).
- No statistical difference in irritation with PDT treatments existed between red light and blue light illumination (p=0.68) (Figure 1).
- After PDT with blue light illumination, 5% (4/76) of patients experienced irritation in 4% (4/103) of PDT treatments (Figure 1).
- After PDT with red light illumination, 8% (9/114) of patients experienced irritation in 5% (9/176) of PDT treatments (Figure 1).

Figure 3: Irritation by Month and Light Source (n=279)




- Irritation after PDT with blue light illumination was graded level 5 (strong burning and scaling) in 1 session, level 4 (persistent mild burning, scaling, redness) in 2 sessions, and level 3 (persistent redness with minimal scaling) in 1 session (Figure 2).
- Irritation after PDT with red light illumination was graded level 5 (strong burning and scaling) in 2 sessions, level 3 (persistent redness with minimal scaling) in 2 sessions, level 2 (temporary redness and scaling) in 3 sessions, and level 1 (temporary redness without scaling) in 2 sessions (Figure 2).
- 1 of the 15 sessions in April, 2 out of the 18 sessions in July, 1 out of the 9 sessions in August, 2 out of the 25 sessions in September, 5 out of the 53 sessions in October, and 2 out of the 45 sessions in November had irritation after PDT. None of the other months had any irritation after PDT (Figure 3).
- Of the 95.3% (266/279) PDT sessions without irritation, subjects were compliant with a specific PDT post-care regimen to apply physical sunblock zinc oxide 10% [Elta] (sunblock) and topical restorative skin cream with zinc and copper [Avene] and/or post-procedure laser gel [Elta] (healing creams) simultaneously every 2 hours during waking hours for 48-96 hours after PDT treatment.

## CONCLUSIONS

- This investigation finds no difference in local skin reactions in treatment areas >20 cm$^2$ after incubation with 10% ALA gel followed by 10 J/cm$^2$ blue light compared to 37 J/cm$^2$ red light illumination.
- PDT with 10% ALA gel in regions larger than 20cm$^2$ illuminated by either red light or blue light report fewer local skin reactions compared to the Phase III clinical trials.
- We hypothesize that shorter incubation or full-face PDT treatment may produce less PPIX, less PPIX-induced cell necrosis, increased PPIX-induced cell apoptosis, and decreased irritation.[5]
- No irritation was observed in winter months of December-February, and in late spring months of May and June; further studies are needed to determine the significance.
- Efficacy was not examined in this study, so it is unknown whether decreased irritation suggests decreased efficacy.
- Irritation may be mitigated by stringent adherence to a specific PDT post-care regimen using sunblock and healing creams every 2 hours during waking hours for 48 hours after PDT treatment.

## REFERENCES

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