

Photodynamic Photorejuvenation: An 18-month Experience on Combination of ALA-IPL and a 630nm LED Continuous Light Source

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ABSTRACT

Photodynamic therapy (PDT) uses a photosensitiser, light and molecular oxygen to selectively kill cells. This new treatment has been used with a confluent light source to treat certain non-melanoma skin cancers and pre-cancerous lesions and is becoming increasingly popular in Australia. Intense pulsed light (IPL) has been used in the last 8 years to treat sun damaged skin and signs of photoageing as a non-ablative skin rejuvenation modality. Photodynamic photorejuvenation (PDPR) is a new form of treatment that combines the benefit of both treatments to give a superior therapeutic and cosmetic effect.

BACKGROUND

Photodynamic therapy (PDT) using topical photosensitisers such as 20% 5-aminolevulinic acid (5-ALA) solution or methylaminolevulinate has generated widespread interest for treatment of an increasing array of skin conditions by cosmetic skin physicians and dermatologists. Numerous dermatologic conditions such as actinic keratoses (AKs), basal cell carcinomas (BCCs), Bowen's disease and acne vulgaris are some of the more commonly encountered skin conditions that have been treated with photodynamic therapy.

HISTORY

Photodynamic therapy was first used clinically in 1900 when Rabb noted *Paramecium caudatum* cells died quickly when exposed to light in the presence of a photosensitiser acridine orange¹. Again, in 1903 Jesionek and Tappeiner treated skin cancer with light and eosin². In this case eosin was the photosensitiser. Physicians and scientists later focused on looking at haematoporphyrin² which when irradiated fluoresced red to reveal the location of tumours. In the United States a more purified haematoporphyrin derivative PHOTOFRIN® (porfimer sodium) was given intravenously in combination with an

ultraviolet light to locate tumours and then in combination with visible light to treat tumours³. In the 1970s Dougherty et al extensively explored the use of PDT in cutaneous and non-cutaneous malignancies^{4,7}. This has led to a plethora of applications of photodynamic therapy in various specialities of medicine including dermatology, oncology, urology and ophthalmology. Various photosensitisers were made and some were administered orally or intravenously for treatment of solid internal tumours while newer topical photosensitisers were made for cutaneous disorders. The newer photosensitisers such as 5-ALA and Methyl-ALA avoided the side effects of prolonged photosensitivity, gastrointestinal or hepatotoxic side effects of some oral or parenteral photosensitisers.

In dermatology, PDT's most exciting breakthrough has been for the treatment of skin malignancies and pre-malignant lesions. AKs, BCCs, and Bowen's disease are amongst the most successfully treated skin conditions. These conditions respond particularly well to PDT because of the presence of cells that undergo more rapid mitosis. Perhaps it is due to the lack of iron stores in these cells that there is an increased accumulation of protoporphyrin (PpIX) relative to the normal epidermal cells, rendering these cells more selective for the photodynamic reaction.

HAEM BIOSYNTHESIS PATHWAY AND PHARMACOLOGY OF PHOTODYNAMIC THERAPY

The haem biosynthetic pathway is reviewed here to aid the understanding of the pharmacology of ALA and porphyrin biosynthesis. ALA is produced in the mitochondria from glycine and succinyl-CoA via ALA synthetase (the rate limiting step). After a further series of condensation reactions, Protoporphyrin IX (a potent photosensitiser) is produced. This normally chelates with iron in

the presence of ferrochelatase to form haem. Increasing levels of haem form a negative feedback on ALA synthetase. When exogenous ALA (such as 5-ALA or Methyl-ALA) is applied to the skin, it is absorbed faster by the more rapidly dividing (abnormal) cells, such as malignant cells or sebaceous glands, forming a build up of PpIX. PpIX is formed at a rate faster than iron can be chelated by ferrochelatase into haem. The relative build up of PpIX may be due to an altered epidermal barrier in lesions such as basal cell carcinoma and actinic keratoses, thus facilitating a more rapid absorption of ALA compared to the normal epidermis. In addition, dysplastic and neoplastic cells have relatively depleted iron stores⁵ due to their rapid turnover limiting the transformation of PpIX into haem which in turn leads to an increased build up of PpIX in these cells. The preferential absorption of ALA in these cells forms the basis of photodynamic therapy in dermatology. When PpIX is exposed to a light source, it transforms into an excited state which then reacts with oxygen (diffused from nearby feeding capillaries) to form unstable, toxic singlet oxygen molecules resulting in death of the tumour cells.

ALA AND ITS INTERACTION WITH A LIGHT SOURCE

For a photodynamic reaction to be effective, a light source must emit the wavelength that lies within the absorption spectrum of the photosensitiser. Protoporphyrin IX is maximally activated by light sources emitting 409nm (Soret band of visible light). There are smaller absorption peaks at 544nm, 584nm and 635nm. The shorter wavelength 409nm (blue light) targets more superficial lesions while 635nm (red light) is used to penetrate deeper tissue, for instance in the treatment of skin malignancies where destruction of deeper cancer cells is desired. A photodynamic dose rate is directly proportional to the concentration of PpIX accumulated tissue and the number of photons of light delivered. Light sources used to activate PpIX can be in the form of low fluence continuous single wavelength light (such as LEDs) or higher fluence pulsed light sources (such as the Intense Pulsed Light, pulsed dye laser, argon lasers). In this article, the use of combined IPL and a 630nm red light will be used and results discussed.

AIMS

To investigate subjective and objective

improvement in skin condition after 1 PDPR treatment. Patients were followed up at day 3, day 7, 1 month and 3 months. Seventeen (17) patients were recruited for the study. The clinical effects, side effects and patient's perception were recorded at each stage of the procedure.

Patients selected had the following:

- photoaged skin
- Fitzpatrick type 1-3
- More than 10 facial actinic keratoses
- More than 1 facial skin malignancy in the past
- No recent sun tanning/solarium exposure on the face for at least one month
- No history of porphyria or photosensitivity

The average age of the patients treated was 59, with a range from 45 to 80. Photographs were taken before the treatment, day 3, 1 week and 1 month after the treatment to assess improvement. Patients were sent a questionnaire (Figure 1) to assess their subjective feedback on different aspects of the treatment side effects and patient satisfaction. Patients were evaluated for percentage improvement in actinic keratoses, hyperpigmentation, fine wrinkles, pore size, flushing, telangiectasias and skin tightening. Lastly, patient expectations and satisfaction with the procedure were also evaluated.

METHODS

Seventeen patients (9 men, 8 women) with varying degrees of photodamage and actinic keratoses on the face were treated with a single session of ALA-PDT using IPL (Quantum SR, Lumenis) as a pulsed light source followed immediately by exposure to a 630nm LED (Aktelite) confluent light source. The ALA was activated by 2 absorption peaks (584nm and 635nm) emitted by the IPL (560-1200nm) and further activated by the 630nm red LED light. The patient's face was first exfoliated with microdermabrasion and delipidated by an acetone scrub. ALA was then applied under occlusion for 1 hour prior to the IPL procedure. The face was then thoroughly washed to remove any non-absorbed ALA. The IPL was used with a 560nm cut off filter at a fluence of 23-28j/cm², double pulse of 3ms and 5ms with a 15ms delay. The patient's face was washed after the IPL procedure to remove the gel followed by exposure to the 630nm LED red light source for a maximum of 7 minutes 58 seconds delivering a total of 37j/cm². There was

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a variation in the duration of exposure to the LED depending on the tolerance of the individual patient to the light exposure. Patients were not pre-treated with any local anaesthetic or regional nerve blocks. Patients were given strict instructions to stay at home for 24 hours with minimal exposure to any strong lights and to keep indoors for 48 hours to prevent any delayed phototoxic reactions. SPF 30+ sunscreen was applied before the patients were discharged. Patients were instructed to wear a sun protective broad brimmed hat and a scarf to protect their face on the way out of the clinic.

SUMMARY OF RESULTS

Results were analysed according to the subjective patient responses on the questionnaire. After one treatment 86% of actinic keratoses resolved. There was 50% improvement in telangiectasia, 44% improvement in flushing, 57% improvement in hyperpigmentation, 37% improvement in pore size, 34% improvement in fine wrinkles, 52% improvement in skin texture, 48% improvement in skin's light reflection and 33% improvement in skin tightening. Side effects were mild in 13 out of the 17 patients which included erythema, skin flaking, oedema and mild crusting of AKs. Four (4) patients reported a moderate to severe phototoxic-like reaction with intense erythema and reactive folliculitis on the second day. These effects completely settled with 3 days of 20mg Prednisone daily and Keflex 500mg tds for one patient. The side effects of the other patients were also completely resolved without any drug intervention within 2 weeks. Two other subjects who feared having these reactions took Prednisone tablets as prophylaxis and reported little or no side effects to the procedure. Pain perception was variable. Average pain scale (out of 10) was 6.3 for IPL and 5.1 for the LED treatment. Four (4) patients could not tolerate the entire duration of treatment with 630nm light and had to stop after 3 minutes, 5 minutes, 5 minutes and 6 minutes respectively. Four (4) of the patients rated the procedure as "VERY GOOD/VERY SATISFIED", 13 rated the procedure as "GOOD/SATISFIED", no one rated the procedure as "BAD/NOT SATISFIED" or "VERY BAD/VERY DISSATISFIED". Two (2) patients rated the outcome of the procedure as

"NOT SURE/AWAITING FUTURE RESULTS"

The outcome for the 4 patients with a phototoxic-like reaction was complete resolution of crusting, pain, erythema and reactive folliculitis. Clinically, their skin had a better overall rejuvenation effect compared to the other subjects who had a milder reaction. The average time for complete resolution of these 4 patients was 3 weeks. There was one subject who had mild erythema lasting 6 weeks before complete resolution. There were no reported cases of scarring, hyperpigmentation or hypopigmentation. These subjects were of Fitzpatrick type 1 to 3 and thus in a lower risk group for pigmentary disturbance compared to patients of type 4 to 6.

DISCUSSION

Photodynamic photorejuvenation is an effective treatment for patients with multiple actinic keratoses who also desire to improve their photodamaged skin. This study confirms the effectiveness of ALA-IPL in the treatment of actinic keratoses found by David Avram and Mitchell Goldman⁸. In their study using ALA-IPL alone (without the use of LED light source) 68% of actinic keratoses resolved after 1 treatment, there was 55% improvement in telangiectasias and 48% improvement in pigmentary irregularities. Our results with actinic keratoses clearance (86%) may be attributed to the additional use of red light. Hyperkeratotic actinic keratoses were clearly more resistant to the treatment in our study confirming other investigators experience⁸. Our results with telangiectasias and hyperpigmentation are consistent with their study findings.

The treatment can be a stand alone treatment or incorporated as part of a series of normal IPL photorejuvenation procedures. The 560nm Intense Pulsed light source activates the ALA in the more superficial levels of the skin targeting the protoporphyrin-rich actinic keratoses cells and at the same time heating up the traditional chromophores of the skin (melanin and haemoglobin) to remove blemishes and capillaries. The 630nm red light is able to penetrate deeper into the skin and thus able to treat the deeper actinic keratoses and also to further treat areas missed by the IPL. The limiting factor, however, when using the red light is the pain associated with this

light treatment as its penetration is deeper compared to the 409nm Blue light. For this reason it was difficult to standardize the duration of red light exposure for all patients.

Other variables that affect the pain level of the red light treatment include; Fitzpatrick skin type, number of epidermal dysplastic lesions, quality of skin preparation by the operator, pre-existing skin quality of the patient and the patient's subjective pain threshold. The increased pain experienced by some patients with the red light could be explained by their cells manufacturing more Proporphyrin IX and this overflowing into nearby cutaneous nerves in the superficial dermis. When exposed to a longer wavelength and deeper penetration of red light, these photosensitized cells near the cutaneous nerves heat up causing pain due conduction of heat to adjacent nerve fibres. Pain in these circumstances can be minimized by lowering the intensity of red light exposure, using topical local anaesthesia after the IPL and before the red light treatment and using a cryospray from a distance or a cooling fan.

The four patients who developed a phototoxic-like reaction had younger and less hyperkeratotic skin enabling more drug penetration during the one hour occlusion phase. When more ALA is absorbed, more PpIX is made in the epidermal cells compared to other patients who were able to tolerate the full duration of the red light. As PDT dose is dependent on the amount of drug absorbed into the skin and the total amount of light delivered, a patient with more absorbed drug but less total light energy delivered would have similar treatment efficacy compared to other patients who have less drug absorbed into the skin but more light delivered.

Photodynamic photorejuvenation treatment is however not without possible significant side effects. It should be stressed to the patient that severe phototoxic reactions can sometimes occur (around 20%) with intense erythema, oedema, crusting and reactive folliculitis which can take 1 to 2 weeks to settle. They should also be aware that in rarer cases prolonged erythema can occur for up to 6 weeks (as seen with one patient). We have found that a 3-day course of Prednisone tablets was sufficient to settle the reaction.

There were no cases of post-inflammatory hyperpigmentation or hypopigmentation. All cases settled down completely within 3 weeks with excellent results.

CONCLUSION

This paper describes a new application of the IPL technology combined with LED technology that gives both a cosmetic and therapeutic dividend and a very high patient satisfaction rate. The clearance rate of actinic keratoses is increased by utilizing a 630nm red light after ALA-IPL compared to using ALA-IPL alone. This however can increase the discomfort of the treatment and increase the duration and severity of side effects including erythema, oedema, reactive folliculitis and crusting.



Phototoxic reaction day 3



Phototoxic reaction day 7

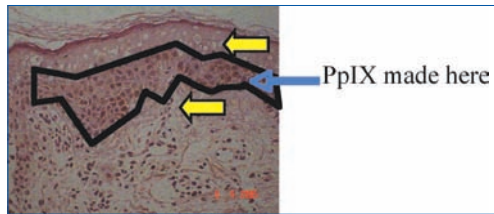


Phototoxic reaction 6 weeks post RX

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HISTOLOGY OF SKIN & LOCATION OF PPIX SYNTHESIS.



PHOTODYNAMIC THERAPY ALA-IPL: CLINICAL AUDIT PATIENTS QUESTIONNAIRE.

- 1) Why did you do photodynamic photorejuvenation?
 - a) treat actinic kercatoses
 - b) to rejuvenate my skin cosmetically (Hyperpigmentation & broken capillaries)
- 2) What area did you do ALA-IPL?
 - a) face
 - b) neck & chest
 - c) legs
 - d) arms/forearms/hands
- 3) What discomfort did you find in the Microdermabrasion part? Please rate severity scale 0-10 by putting an "X" on the line below

0 1 2 3 4 5 7 8 9 10
- 4) What discomfort did you find in the 1 hour of ALA application under occlusion? Please rate severity scale from 0-10.

0 1 2 3 4 5 7 8 9 10
- 5) What discomfort did you find in the IPL procedure? Please rate severity scale from 0-10.

0 1 2 3 4 5 7 8 9 10
- 6) What discomfort did you find in the 630nm LED light exposure? Please rate severity scale from 0-10.

0 1 2 3 4 5 7 8 9 10
- 7) What side effect did you experience in the first 48hrs? Please rate severity scale from 0-10.

0 1 2 3 4 5 7 8 9 10
- 8) What side effect did you experience in the first 1 week? Please rate severity scale from 0-10.

0 1 2 3 4 5 7 8 9 10
- 9) Did you find the procedure more or less uncomfortable than cryotherapy/Efudex cream/chemical peel? Please elaborate.
 - a) more
 - b) Less
- 10) At the end of 2 weeks after the procedure, what percentage of solar keratoses have been cleared?
 - a) 100%
 - a) 80-90%
 - b) 60-80%
 - c) 40-60%
 - d) 20-40%
 - e) 0-20%
- 11) At the end of 1 month after the procedure, what percentage of solar keratoses have been cleared?
 - a) 100%
 - e) 80-90%
 - f) 60-80%
 - g) 40-60%
 - h) 20-40%
 - 0-20%
- 12) At the end of 1 month after the procedure, what percentage of solar keratoses have been cleared?
 - i) 100%
 - j) 80-90%
 - k) 60-80%
 - l) 40-60%
 - m) 20-40%
 - n) 0-20%

13) What other improvements have you noticed after 1 session of ALA-IPL? By how much? Please put an "X" in appropriate area on the scale line.

a) broken capillaries

0%	50%	100%
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b) flushing

0%	50%	100%
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c) Abnormal pigmentation/blemishes

0%	50%	100%
----	-----	------

d) Pore size

0%	50%	100%
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e) Fine wrinkles

0%	50%	100%
----	-----	------

f) Skin texture

0%	50%	100%
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g) Light reflection on the skin

0%	50%	100%
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h) Skin tightening

0%	50%	100%
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14) Did you feel the treating physician's care was adequate? If not where can we improve on?

- a) Very Good/Very satisfied
- b) Good/satisfied
- c) Bad/not satisfied
- d) Very bad/very dissatisfied

15) Were you adequately informed about the procedure before having it done?

- a) Very Good/Very satisfied
- b) Good/satisfied
- c) Bad/not satisfied
- d) Very bad/very dissatisfied

16) Was your expectations about the procedure met?

- a) Very good/Very satisfied
- b) Good/satisfied
- c) Bad/not satisfied
- d) Very bad/very dissatisfied

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