Topical 5-aminolevulinic photodynamic therapy with red light vs intense pulsed light for the treatment of acne vulgaris: A split face, randomized, prospective study

Linglin Zhang, MDa,#, Yun Wu, MDa,#, Yunfeng Zhang, MDa, Xiaojing Liu, PhDa, Bo Wang, MD, PhDb, Peiru Wang, MDa, Guolong Zhang, MDa, and Xiuli Wang, MD, PhDa

aShanghai Skin Disease Hospital, Institute of Photomedicine, Tongji University School of Medicine, Shanghai, China; bDepartment of Dermatology, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

ABSTRACT
5-Aminolevulinic acid photodynamic therapy (ALA-PDT) has been an effective method for treating acne vulgaris. Red light is the most widely used light source while Intense pulsed lights (IPL) is reported effective and well-tolerated. The purpose of this study was to evaluate the efficacy and adverse reactions of ALA-PDT with red light on acne compared with ALA-PDT with IPL. 12 patients were recruited in the randomized, prospective and split-face study. 5% ALA cream were applied on the whole face with 2 hours' incubation before narrow band LED (633 ± 10 nm, 36 ~ 108 J/cm²) on one side of face and IPL (590 ~ 1200 nm, 15 ~ 17 J/cm²) on the other side. Three treatment sessions were administered with 2-week interval each time and 8 weeks' follow up. The number of the total acne lesions and inflammatory lesions of the side treated by red light-PDT showed a relatively higher reduction rate that that by IPL-PDT (P < 0.05). Significant PpIX fluorescence decrease was observed only for the group of red light (P < 0.05). Lower pain intensity numeric rating scale values and Investigator’s Global Severity Assessment (IGA) grading for erythema of the IPL side were observed (P < 0.05). The results suggested that both red light and IPL are effective for ALA-PDT on acne vulgaris. ALA-PDT with red light may achieve better efficacy by more effective photobleaching of protoporphyrin IX (PpIX), whereas IPL may accomplish less adverse reactions and better tolerance.

Introduction
Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous follicle, mostly found in young adults aged between 18 to 40. Its clinical features include comedones, papules, pustules and nodules/cysts. Severe acne may leave disfiguring scars, which possibly bring physical and psychological morbidity such as poor self-image, depression and anxiety. Systemic antibiotic or isotretinoin with topical therapies are recommended for severe acne, but there are limitations of these therapies such as bacterial resistances, teratogenicities and other side effects.

In recent decades, Photodynamic therapy (PDT) with the prodrug 5-aminolevulinic acid (ALA) or its ester derivative (eg, methyl ester of ALA or MAL) as a porphyrin precursor have been gaining increasing popularity and it is regarded as the most evidential treatment of all laser and light devices for acne by the U.S guidelines. Our previous study reported that ALA is able to be absorbed and accumulated in sebaceous glands and then intracellularly converted to photosensitizer protoporphyrin IX (PpIX). When irradiated with special wavelength light, PpIX can produce reactive oxygen species (ROS) such as singlet oxygen and leads to a series of reactions. What’s more, photodynamic photorejuvenation has also been reported for this treating method.

There is a variety of light sources for PDT of acne. Red LED arrays (~ 635 nm) have the advantage of accuracy, intensity, robustness and it has been sufficiently the wide-area sources for facial acne PDT. We previously reported that 89.61% (69/77) patients...
showed excellent improvement (>90% clearance of acne lesions) after three or fewer treatment sessions of ALA-PDT conducted by red light (633 ± 6 nm). However, under the circumstance of low doses, low fluency and short exposure time, lots of cases of adverse reactions such as pain, hyperpigmentation and acute inflammatory reactions were still reported. Therefore, a method which can balance the efficacy and adverse events is urgently needed.

Intense pulsed lights (IPL) are filtered, noncoherent, nonlaser broadband light and are reported effective and well-tolerated for PDT of acne. Studies on ALA-IPL-PDT for the treatment of acne reported a reduction of lesion counts of 71.8%—87.7% after 12 weeks and side effects were mild and reversible. However, there are no studies comparing the efficacy of ALA-PDT with red light and IPL as light sources by split-face analysis. The aim of this prospective study is to evaluate and compare the effect and adverse reactions of 5-Aminolevulinic acid-mediated photodynamic therapy (ALA-PDT) irradiated with red light and IPL as light sources on Acne vulgaris.

**Results**

**PpIX generation and photobleaching of acne lesions**

There’s no difference of PpIX fluorescence intensity between the two sides (P = 0.147, t = -1.499) and PpIX fluorescence intensity decreased immediately after red light irradiation (P = 0.000, t = 24.407) while there’s no significant decrease immediately after IPL irradiation (P = 0.921, t = 0.101). (Fig. 1-2)

**Clinical outcomes**

Clinical response was showed in Fig. 3. The mean reduction rate of total acne lesions on the side after red light-PDT was 41.48 ± 12.49%, 59.71 ± 12.98%, 73.36 ± 10.29%, 85.50 ± 5.39% at 2 weeks after each treatment and 4, 8 weeks after the last treatment. On the IPL-PDT side, the mean reduction rate was 33.06 ± 18.27%, 51.06 ± 14.22%, 63.14 ± 11.21%, 75.55 ± 8.09% respectively. There was a significant difference in the reduction rate at 2 weeks after the second treatment (P = 0.033, t = 2.430) and 4 (P = 0.010, t = 3.130), 8 weeks (P = 0.002, t = 4.178) after the last treatment but no difference in the reduction rate at 2 weeks after the first treatment session (P = 0.192, t = 1.389). (Fig. 3-4)

To compare the efficacy of different types of acne lesions, the number of comedones and inflammatory lesions including inflammatory papules, pustules and nodules/cysts were counted and the reduction rate was showed in Fig. 6. Compared with the counts before treatments, the number of comedones at 2 weeks after each treatment and 4, 8 weeks after the last treatment of red light-PDT were reduced with a mean reduction rate of 0, 19.25 ± 13.91%, 37.30 ± 18.79%, 52.58 ± 21.84% while that of IPL-PDT were 0, 20.27 ± 12.21%, 43.97 ± 15.29%, 57.62 ± 14.40%. There’s no significant difference between the two sides in the reduction rate of comedones (P = 0.516, Z = -0.649; P = 0.847, t = -0.198; P = 0.349, P = -0.977; P = 0.514, t = -0.675). The mean reduction rate of inflammatory lesions of the side treated by red light-PDT were separately 56.75 ± 17.14%, 77.74 ± 16.07%, 85.96 ± 14.15%, 95.73 ± 5.61% at 2 weeks after each treatment and 4, 8 weeks after the last treatment and that of the side treated by IPL-PDT were 49.25 ± 25.81%, 67.37 ± 24.62%, 72.64 ± 17.83%, 84.02 ± 7.18%. The count of the side treated by red light-PDT showed higher reduction with significant difference at 4, 8 weeks after the last treatment (P = 0.034, t = 2.419; P = 0.005, t = 3.527) (Fig. 5)

**Adverse reactions**

In terms of adverse reactions, Pain was a major complaint during light irradiation but could relieve within the treatment day. The maximal painful sensation was evaluated for 12 patients in total. The PI-NRS value was 5.0 for the side treated by red light-PDT and 2.5 (2.3) for the side treated by IPL-PDT respectively. There was a significant difference between the two sides (P = 0.002, Z = -3.017). In addition, Immediately after red light irradiation, the treated site showed various degrees of erythema, edema and exudation which could be alleviated by ice-cold bags and subsided within 8 weeks. However after IPL, only mild erythema and edema were seen and could subside within 1 to 3 days. Statistical differences in the IGA grading scores for the erythema between the two sides were observed 2 (P = 0.005, Z = -2.798), 4 (P = 0.002, Z = -3.135), 8 (P = 0.014, Z = -2.451) weeks after the last treatment session (P = 0.002, Z = -3.315). (Table 2) Transient exacerbation of acne lesions were seen in treated site by both light sources of 4 patients
and subsided within 2 weeks. Mild transient pigmentation occurred in treated site by red light-PDT of 2 patients and disappeared within 4 weeks. No patient developed a scar, or other significant adverse effects.

**Discussion**

Photosensitizer, incubation time and light source are critical factors that can influence the efficacy of PDT. ALA has been used as photosensitizer for PDT to treat acne in China since 2004. In 2012, our prospective study proved that similar PpIX levels and lesion

---

**Figure 1.** Fluorescence images of left and right side face of one patient. Acne lesions on the right side were treated by red light-PDT and acne lesions on the left side were treated by IPL-PDT. (A)(B) Fluorescence images immediately before light irradiation. (C) Fluorescence image immediately after red light irradiation.(D) Fluorescence image immediately after IPL irradiation. The intensity of brick-red colour was decreased after red light irradiation.

**Figure 2.** Protoporphyrin IX (PpIX) fluorescence intensity before and immediately after light irradiation at the acne lesions on both sides of face. The fluorescence intensity was significantly decreased after red light irradiation (*P < 0.05).
clearance rate were seen in areas receiving 3, 5, and 10% ALA. Besides, the average PpIX level increased with the increase in incubation time between 1 and 5 hours simultaneously. One year later, a self-controlled multicenter clinical trial stated a low-dose topical ALA-PDT regimen using 5% ALA, 1 hour incubation and red light source of 3 treatment sessions is suggested as optimal scheme for the treatment of different severity of acne vulgaris in Chinese patients.

Various light sources have been used in the process of ALA-PDT for the treatment of acne, which include light-emitting diodes (LEDs), filtered incandescent or arc lamps, slide projectors, fluorescent lamps, IPLs, lasers and sunlight. Red light and blue light are widely used in PDT for the treatment of acne as well as pulsed sources such as IPLs and pulsed dye lasers (PDLs). The scattering and absorption of photons are closely related to the penetration of light into skin. With the increase of wave length, the ability of the scattering and absorption of photons decease. In contrast, the longer the wave length is, the deeper the light penetrates. Facial sebaceous glands are located...
approximately 0.5 to 1.0 mm from the cutaneous surface.\textsuperscript{16} However, ALA has a maximum absorption band in the blue light spectrum (405–415 nm) and weaker absorption bands, which are located in the green (506 nm to 540 nm), yellow (572–582 nm) and red spectra (628–635 nm).\textsuperscript{8} In order to achieve optimal efficacy, red light is the optimal choice not only because it has deep penetrating wavelength region but also it has relatively higher absorption of the Porphyrin that can lead the PDT reaction efficiently to the follicular units and sebaceous glands. However, possibly because of the intensity of the Red Light that different degrees of pain were reported after red light-PDT. When irradiated with higher irradiances, patients would feel further painful and suffer more from the severity of erythema.\textsuperscript{17} Hence, we need to seek other light sources to balance the efficacy and adverse reactions.

IPLs, with a broad spectrum of 500–1200nm, include ALA absorption bands of green, red and yellow. ROS such as singlet oxygen generated during a high fluence light pulse can drive a series of oxygen-dependent and non-oxygen-dependent reactions through the Oxygen depletion.\textsuperscript{18} For one thing, ROS can damage blood vessels and leads to vascular coagulation. For another, the reduction of cytokines such as Interleukin 1 alpha (IL-1\textalpha) and the increase of transforming growth factor-\(\beta\) (TGF-\(\beta\)) may contribute to IPL’s role of anti-inflammation and rejuvenation effect.\textsuperscript{19} Histological changes showed decreased elastic fibers in the dermis deformation, increased collagen fibers after IPL treatment.\textsuperscript{20} Barakat et al reported the significant decrease of neutrophils after the treatment of IPL for acne.\textsuperscript{21}

| Table 1. Characteristics of the patients. |
|------------------------------------------|
| Gender                                   |
| Male                                     | 9  |
| Female                                   | 3  |
| Age(years)                               | 18–27 |
| Mean                                     | 21.75±2.989 |
| Acne grade                               | 6  |
| Grade III                                | 6  |
| Grade IV                                 | 6  |
| Mean Acne Lesions                        | 22.75±5.119 |
| left                                     | 22.33±4.599 |
| Right                                    | 22.75±5.119 |
| P                                        | 0.836 |

There’s not enough studies compared and contrast different light sources for ALA-PDT for the treatment of acne, especially for red light and IPL. Hong et al compared the effect and tolerability of MAL-PDT using red light and IPL for treating acne vulgaris through split-face analysis. The improvement in lesion count was a reduction of 48.7% on the red light side and 52.5% on the IPL side at 8 weeks after the last treatment. Red light showed a faster response time than IPL.\textsuperscript{22} In this study, both light sources were effective for ALA-PDT on acne lesions but a relatively lower reduction both at 4 weeks and 8 weeks after IPL-PDT, which indicated a better efficacy of red light-PDT than IPL-PDT for the treatment of acne. Although IPL-PDT has been claimed effective for the treatment of acne and ALA photobleaching and ROS production probably occurs during the initial minutes of light irradiation,\textsuperscript{23} a millisecond-domain light pulse is sufficient for PDT remains uncertain. Togsverd-Bo reported LED (632 nm, 18 and 37 J/cm\(^2\)) produced significantly higher photobleaching percentages compared with IPL and LPDL.\textsuperscript{24} In this study, higher PpIX photobleaching of red light-PDT was also observed. Whether the characteristic of IPL of anti-inflammation and other effects combined with a relatively weaker photodynamic effect contribute to this outcome, which needs to study further.

The reduction rate of inflammatory lesions including inflammatory papules, pustules and nodules/cysts showed significant difference for the two different light sources but no difference of comedones were observed, which implied that red light-PDT was more effective for inflammatory lesions. Whether IPL-PDT is more effective to certain type of acne lesions is still under controversial debate. Mei et al reported lower reduction of non-inflammatory than inflammatory lesion counts\textsuperscript{10} In contrast, Yeung et al stated a higher reduction rate of non-inflammatory acne 4 weeks after the treatment.\textsuperscript{25} Further studies may focus on the indication and parameters of IPL-PDT.
Pain, acute inflammatory skin reactions, pigmentation are the most common side effects of photodynamic therapy for the treatment of acne. Ulceration and scarring are rare thanks to relatively low dose and short incubation time. Although pain can be reduced by cold spray and ice bags, the painful treatment course can still affect the compliance of patients in clinical practice. Researches have proved that pain was slighter with pulsed light than continuous sources because of short pulse duration.26 Besides, erythema severity was slighter on the side treated by IPL during the whole treatment sessions and follow up sessions. Transient pigmentation can be observed on the red light side of some patients as well. What’s more, it is quite interesting to found that some patients claimed that they prefer to choose IPL as light source during the treatment sessions and they would choose IPL repeatedly for the future treatment even the cost of IPL is much higher.

Patients and methods

Study design

This is a randomized and controlled prospective study. Inclusion criteria: Patients of both sexes with an age between 18 and 40, who presented with acne lesions on the forehead and on both sides of the faces and were clinically diagnosed with acne vulgaris and grade 3–4 according to clinical classification by European Guidelines group13 were enrolled in the study. Exclusion criteria: pregnant, lactating, or planning to become pregnant during the study; a history of cutaneous photosensitization, porphyria, or photodermatitis; any ongoing skin conditions (eg, psoriasis, seborrheic dermatitis or allergic dermatitis) that could interfere with the evaluations; a severe systemic condition and unsafe for subjects to participate; a history of systemic retinoids within 6 months or history of systemic steroids and antibiotics within 1 month or history of any topical treatment of acne within 2 weeks. The study protocol conformed to the ethical guideline of the 1975 Declaration of Helsinki approved by the research ethics committee of Shanghai Skin Diseases Hospital.

Patients and lesions

12 patients (9 men and 3 women) who visited our hospital dating from September 2014 to April 2016 have been recruited and signed written informed consents. The baseline characteristics of all patients and lesions were listed in Table. 1. Patients were provided with full face PDT treatment with 5-Aminolevulinic acid (ALA) plus red light on one side of the face and with ALA plus IPL on the other side. The application side of the two different methods were randomized before the first treatment according to the random sequence produced by computer programs. There was no statistical difference between the two sides in terms of acne lesions (p = 0.836, t = −0.210).

Treatment protocol

Fresh ALA cream (5%, wt/wt) was prepared using ALA powder (Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co. Ltd., Shanghai, China) and was applied evenly to acne lesions after the face was cleaned with mild soap. The ALA-applied area was occluded with cling film and covered with a black cloth for light. After 2 hours’ incubation, the lesion surface was rinsed with clean water to remove the excess ALA and was prepared for light irradiation.

The side treated by red light: The lesions were then exposed to a LED light source (633 ± 6 nm) (Omnilux Revive, Photo Therapeutics Ltd., Manchester, UK) in the red light spectrum. The distance between the LED device and the face was adjusted to deliver a power density of 66 mW/cm² to the surface of the face. During the first and second course, a suboptimal light dose (36 J/cm² and 72 J/cm²) was delivered and a full dose (108 J/cm²) was delivered during the third course.

The side treated by IPL: The lesions were exposed to an IPL device (M22 Universal IPL, Lumenis, San Jose, CA, USA). The treatment influence was 15~17 J/cm² (15J/cm² for the first course and an add of 1 J/cm² was delivered with the increase of treatments) with a spot size of 15 × 35 mm. The filter emitted light with the wavelength between 590 and 1200 nm. A single pass without overlapping was performed, and double pulses of 5.0 ms duration which interspaced with a 30 ms delay were used.

During one side for light irradiation, the other side of the face was protected from light. The similar PDT protocol was repeated for 3 sessions at 2-week interval each time.

Examination of protoporphyrin IX (PpIX) fluorescence

To examine the generation and photobleaching of PpIX, 5-ALA-applied area was exposed to a wood's
lamp (SW-12, Sigma, Shanghai, China) light (320~400 nm). Fluorescence images were captured by a digital camera equipped with a 420-nm long-pass filter. To measure the amount of PpIX, PpIX fluorescence intensity was detected in the acne lesions of comedones, inflammatory papules, pustules and nodules/cysts (3 lesions for each type) before and immediately after light irradiation in the 1st session of ALA-PDT using fluorescence spectroscopy (Curalux;Munich, Germany, excitation wavelength 405 nm, emission wavelength 440–800 nm). The measurement was repeated three times at each spot.

Evaluation of clinical outcomes

Patients were examined carefully and the numbers of acne lesions of both sides of face including comedones, inflammatory papules, pustules and nodules/cysts were recorded by two dermatologists at the baseline, the recording time schedule was before each treatment and at 4 and 8 weeks after the last treatment. Images of both sides of face were taken for comparisons. The clearance rate of skin lesions (%) = (the total number of skin lesions before treatment – the total number of skin lesions after treatment)/ the total number of skin lesions before treatment × 100%.

Evaluation of adverse reactions

To examine and evaluate possible adverse reactions, patients were asked to report the severity of pain during the first treatment session, which was evaluated with an 11-point pain intensity numeric rating scale (PI-NRS) (0 = no pain, 10 = worst possible pain). Post treatment reactions such as erythema, edema, exudation, hyperpigmentation and scarring were evaluated immediately after each treatment and during the follow-up. Evaluation of erythema severity was performed by Investigator’s Global Severity Assessment (IGA) grading at 4,8 weeks after the last treatment session and the evaluation was based on the following criteria:

0: No erythema.
1: Reddish, mild erythema
2: Red, moderate erythema
3: Dark red, edematous and severe erythema or hyperpigmentation.

Statistics

Results were analyzed using statistics software (PASW Statistics 19, IBM SPSS Statistics, Armork, NY, USA). Graphs were completed using GraphPad Prism version 6.00(GraphPad Software, Inc., San Diego, CA). PI-NRS values and IGA grading between the 2 groups were compared by Mann-Whitney U test. Paired t-test were used to compare the PpIX fluorescence intensity of 2 groups and lesion count. All P values were two-tailed, and a P value <0.05 was considered to be statistically significant. Data were expressed as the means ± standard deviation unless otherwise specified.

Conclusion

This is the first prospective and split face study which compares red light with IPL for ALA-PDT on acne vulgaris. Our data indicated that both light sources were safe and effective for clinical practices and have their own advantages. Red light may achieve better efficacy by more effective photobleaching of PpIX but IPL showed less adverse reactions and better tolerance. Therefore we believe IPL-PDT has the potential to become an alternative light source for ALA-PDT for the treatment of acne vulgaris in the future and further studies may focus on the indication and parameters of IPL-PDT.

Acknowledgments

This work was supported by Shanghai Municipal Commission of Health and Family Planning (201540273) and Guide support project in western medicine of Shanghai Municipal Science and Technology Commission (16411961700).

References

1. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. The Lancet. 2012;379(9813):361–72. doi: 10.1016/S0140-6736 (11)60321-8.
2. Ramli R, Malik AS, Hani AF, Jamil A. Acne analysis, grading and computational assessment methods: an overview. Skin Res Technol. 2012;18(1):1–14. doi: 10.1111/j.1600-0846.2011.00542.x. doi:10.1111/j.1600-0846.2011.00542.x. PMID:21605170
3. Zaenglein AL, Pathy AL, Schlosser BJ, Alkhan A, Baldwin HE, Berson DS, Bowe WP, Graber EM, Harper JC, Kang S, et al. Guidelines of care for the management of acne vulgaris.J Am Acad Dermatol. 2016;74(5):945–73.e33. doi: 10.1016/j.jaad.2015.12.037.
4. Ding HL, Wang XL, Wang HW, Huang Z. Successful treatment of refractory facial acne using repeat short-cycle ALA-PDT: Case study. Photodiagnostics Photodyn Ther. 2011;8(4):343–6. doi: 10.1016/j.pdpdt.2011.07.003. PMID:22122923

5. Sakamoto FH, Lopes JD, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice: part I. Acne vulgaris: when and why consider photodynamic therapy? J Am Acad Dermatol. 2010;63(2):183–93; quiz 93–4. doi: 10.1016/j.jaad.2009.09.056 10.1016/j.jaad.2009.09.056 PMID:20633796

6. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S. Photodynamic photorejuvenation. Dermatol Surg. 2002;28(8):742–4; discussion 744. doi:10.1097/00042728-200208000-00019 10.1046/j.1524-4725.2002.02018.x PMID:12174070

7. Zhang HY, Ji J, Tan YM, Zhang LL, Wang XJ, Wang PR, Yang DG, Shi L, Huang Z, Chen SY, Wang XL. Evaluation of 5-aminolevulinic acid-mediated photorejuvenation of neck skin. Photodiagnostics Photodyn Ther. 2014;11(4):498–509. doi: 10.1016/j.pdpdt.2014.10.003. doi:10.1016/j.pdpdt.2014.10.003. PMID:25461963

8. Sakamoto FH, Torezan L, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice: part II. Understanding parameters for acne treatment with photodynamic therapy. J Am Acad Dermatol. 2010;63(2):195–211; quiz -2. doi: 10.1016/j.jaad.2009.09.057 10.1016/j.jaad.2009.09.056 PMID:20633797

9. Wang XL, Wang HW, Zhang LL, Guo MX, Huang Z. Topical ALA PDT for the treatment of severe acne vulgaris. Photodiagnostics Photodyn Ther. 2010;7(1):33–6. doi:10.1016/j.pdpdt.2010.01.003. PMID:20230991

10. Mei X, Shi W, Piao Y. Effectiveness of photodynamic therapy with topical 5-aminolevulinic acid and intense pulsed light in Chinese acne vulgaris patients. Photodermatol Photoimmunol Photomed. 2013;29(2):90–6. doi:10.1111/php.12031. PMID:23458393

11. Gold MH, Bradshaw VL, Boring MM, Bridges TM, Biron JA, Carter LN. The use of a novel intense pulsed light and heat source and ALA-PDT in the treatment of moderate to severe inflammatory acne vulgaris. J Drugs Dermatol. 2004;3(6 Suppl):S15–9. PMID:15624737

12. Rojanamatin J, Choawawanich P. Treatment of inflammatory facial acne vulgaris with intense pulsed light and short contact of topical 5-aminolevulinic acid: a pilot study. Dermatol Surg. 2006;32(8):991–6; discussion 996–7. doi:10.1111/j.1524-4725.2006.32221.x 10.1097/00042728-200608000-00003. PMID:16918560

13. Nast A, Dréno B, Bettoli V, Degitz K, Erdmann R, Finlay A, Ganceviciene R, Haedersdal M, Layton M, Esteban K, et al. Guideline on the Treatment of Acne. European Dermatology Forum [accessed on 30 Oct 2013]. http://www.isplad.org/data/efea2ac 91d7a63c211a093f3012a888.pdf . [accessed on 30 Oct 2013].
sources. Exp Dermatol. 2012;21(10):745–50. doi:10.1111/j.1600-0625.2012.01557.x. PMID:22882358

25. Yeung CK, Shek SY, Bjerring P, Yu CS, Kono T, Chan HH. A comparative study of intense pulsed light alone and its combination with photodynamic therapy for the treatment of facial acne in Asian skin. Lasers Surg Med. 2007;39(1):1–6. doi:10.1002/lsm.20469. PMID:17252567

26. Babilas P, Knobler R, Hummel S, Gottschaller C, Maisch T, Koller M, Landthaler M, Szeimies RM. Variable pulsed light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratosis: a prospective randomized controlled trial. Br J Dermatol. 2007;157(1):111–7. doi:10.1111/j.1365-2133.2007.07959.x. PMID:17542980