Original Article

Efficacy of Intense-pulsed Light Therapy with Topical Benzoyl Peroxide 5% versus Benzoyl Peroxide 5% Alone in Mild-to-moderate Acne Vulgaris: A Randomized Controlled Trial

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ABSTRACT

Objective: Acne vulgaris is a disease of pilosebaceous unit with multifactorial pathogenesis and threats patients' social functioning. There is a growing research to find faster, more effective, and easy to use treatments. The aim of this study is to evaluate the efficacy of benzoyl peroxide 5% (BP) with and without concomitant intense-pulsed light (IPL) therapy in mild-to-moderate acne vulgaris. **Methods:** In this controlled trial, 58 eligible patients with mild-to-moderate acne and Fitzpatrick skin phototype III and IV were randomly allocated to two groups. All patients were asked to use a thin layer of BP every night. The IPL therapy was administered at the end of first, 2nd, and 3rd months. Acne Global Severity Scale (AGSS), Acne Severity Index (ASI), and total lesion counting (TLC) along with patient satisfaction were recorded. Patients were also examined 1 month after the final therapeutic visit. **Findings:** The IPL group showed greater reduction in AGSS ($P < 0.001$) and TLC ($P = 0.005$) than the control group. However, the difference in ASI was not significant ($P = 0.12$). Patients in IPL groups were more satisfied than control group ($P < 0.001$). **Conclusion:** Adding IPL to BP can result better response to BP alone. In acne treatment, combination therapy such as IPL and other topical agents should be kept in mind.

Keywords: *Acne, Benzoyl peroxide, intense-pulsed light therapy, trial*

Introduction

Acne vulgaris is a common adolescence disorder, affecting almost 80% of people mostly in their teens, with the most severity in females aged 14–17 and

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males aged 16–19.[1,2] The prevalence is almost same for both sexes with a higher severity in males. Major factors in acne are hyperactivity of sebaceous glands and the involvement of acne proprium bacterium. Acne entails clinical manifestations and leaves scars in untreated cases and this makes it important mainly due to adverse effects on the patient's self-confidence, social communication, and psychological functions that result in psychosocial and clinical disorders and even suicide.[1-5] Even though various single and combinational treatments have been introduced, the best method is still controversial and this necessitates the search for less invasive, fast, more tolerable and efficient, and long-lasting options.[6,7] Topical antibacterial agents are preferred to systemic treatments and benzoyl peroxide (BP) has distinct advantages among these topical options. BP is a nonantibiotic antibacterial agent and its keratolytic property reduces the sebaceous glands activity. BP is more effective than topical antibacterials, especially in inflamed lesions.[8]

Lasers have clinical applications for about 50 years while the very different technology of intense-pulsed light (IPL) therapy has drawn great attention during the last two decades.[4,9,10] This method has been used alone or in combination with other topical and systemic treatments in various skin conditions and compared to alternatives.[6,9,11,12] Effectiveness of IPL to the case of adding topical 5-aminolevulinic acid (ALA) has been compared where using IPL was not successful and patients returned to the baseline status at the end of study.[12] IPL has been used in the treatment of inflammatory facial acne vulgaris in a semiexperimental setting.[9] IPL and ALA combinational treatment showed better results than single IPL. Another study on patients with facial acne has compared the effect of IPL against IPL and photodynamic therapy.[13] None of these treatments were better than control group in moderate inflammatory acne. However, both treatments had delayed effects on noninflammatory lesions. In a comparative study, the efficacy of IPL was compared to other light-based therapies in acne vulgaris.[14] Efficacy of topical erythromycin against the using concomitant IPL therapy has been evaluated where the combinational therapy showed better effects on erythematous macules.[11] In a more recent clinical trial, the efficacy of IPL and BP has been compared.[6] The results of this study indicate comparable results from both treatments with better effects from BP at the midpoint of the study period.

Due to multifactorial pathogenesis of acne, more desirable results, in general, are expected from combinational therapies.[15] Due to well-known advantages of nonantibiotic antibacterial agent BP over the other topical alternatives in the treatment of acne and growing evidence on the efficacy of IPL, the current study aimed to evaluate the efficacy of their combination over commonly prescribed topical alone option in a clinical trial framework. This is the first time to use this combinational therapy that covers almost all aspects of acne pathogenesis and may result in more desirable results.

Methods

This randomized controlled trial was conducted from January 2015 to September 2015 in a large academic institute in the central Iran. The study protocol was approved by the Ethics Committee of the Isfahan University of Medical Sciences. Eligible patients were referred to the study by clinicians and were asked to participate in the study and written informed consent was obtained after clear description of the trial to the participants.

In this controlled trial, 58 eligible patients with mild-to-moderate acne and Fitzpatrick skin phototype III and IV were randomly allocated to two groups by generating random blocks of size 2. The first patient in each block was randomly allocated to treatment or control group and the second to the other group. Since there was a laser intervention, the study was unblended. The following were the major inclusion criteria: afflicted with mild-to-moderate acne vulgaris, patient preference to experience laser therapy, having no acne scar, no pregnancy or breast feeding, not receiving topical or systemic antibiotic in the last 2 weeks, not receiving systemic steroid and retinoid in the last 6 months, photosensitivity, no tendency to developing hypertrophic and keloid scars, and volition to participate. Exclusion criteria included sensitivity to BP, using intervening treatments at the same time, and irregular visits or loss to follow up. We considered persons with following conditions as mild-to-moderate acne patients: (1) almost clear skin with rare noninflammatory lesions and rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red), (2) Some noninflammatory lesions with few inflammatory lesions (papules/pustules only; no nodulo-cystic lesions), and (3) Noninflammatory lesions predominate, with multiple inflammatory lesions evident, several to many comedones and papules/pustules, and there may or may not be one small nodulo-cystic lesion.[15]

After entering the study, all patients, in both groups, received BP 5% (Pangel™, Belgium) regularly for 3 months. They were asked to use a thin layer of BP gel over each night on his/her face avoiding areas around lips and nose and wash it at the following morning. This

process was continued in both groups over the study period, except for those who experienced complications from BP. Patients with complication were asked to cut using BP for a few nights and restart in lower doses again. After a month from the start of using the gel, each patient at the treatment IPL group received IPL therapy with wavelength of 570 nm filter, 15 j/cm^2 energy fluence, and 40 ms pulse duration in a single pulse mode. SOLARI™ (Lutronic Corporation, Ilsan, Korea) system was used for IPL administration. The IPL therapy was also repeated 2 and 3 months after the beginning of gel. Hence, there were three IPL sessions starting after a month from topical gel with a month interval between sessions. Interval between IPL sessions has been taken from 1 week to 1 month in previous reports. Since our patients received BP and IPL simultaneously, we chose maximum interval of 1 month to avoid the increase of complications such as skin dryness and redness.

All patients in both groups were visited at the end of each month and 1 month after the trial termination as follow-up. At each visit, the patient's skin was examined for papules, pustules, and comedones and the number of each type of lesions was recorded. These records were used to measure major outcomes of Acne Global Severity Scale (AGSS),[16] Acne Severity Index (ASI),[17] and total lesion counting (TLC). These measures include both qualitative and quantitative assessments and cover various aspects of disease status. Previous works usually use one of these measures, and therefore, we chose all of them to facilitate comparison to other studies. Each patient was also asked to point his/her satisfaction at each visit on a straight line without midpoints ranging from 0: dissatisfied to 10: very satisfied. Then, the length from 0 to the marked point was measured using a ruler and recorded as the patient satisfaction score. Expected complications of pain, burning, postinflammation pigmentation, erythema, scaling, redness, and dryness were also of interest.

Required sample size was calculated by PASS software (NCSS, Kaysville, Utah). We considered type I error of 0.05 and type II error of 0.17 and standard error of mean of 0.3 and 0.7 for between and within group factors of main outcome, AGSS. This led to 29 samples in each group. Descriptive statistics of percent and mean ± standard deviation were reported for categorical and continuous variables. We used *t*-test and Chi-squared tests to ensure the groups be balanced with respect to major demographic factors. Outcomes were also compared at each visit by Mann–Whitney test. Repeated-measures analysis of variance was used to compare the outcomes collected in the study period. Significance level was set at 0.05. Normality of data was assessed by Kolmogorov–Smirnov test. All analyses were implemented using SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0., Armonk, NY, USA: IBM Corp.). This study was registered in Iranian Registry of Clinical Trials (IRCT2016051727947N1).

Results

Figure 1 shows the study design of the trial. All excluded patients were replaced with new ones. Hence, the total number of 29 patients with complete information in both groups was entered in the final analysis.

Baseline characteristics of the groups are shown and compared in Table 1. As comparisons indicate, the randomization was successful and two groups were well-balanced. Data were also normally distributed ($P > 0.05$).

Table 2 shows comparisons of measures between two groups at each visit. For all outcomes, the differences

Table 1: Baseline characteristics for study groups

Baseline characteristics	BP and IPL group (*n*=29)	BP-alone group (*n*=29)	*P*
Sex:female	23 (79.3)	20 (69.0)	0.36
Age	25.41±5.85	25.83±6.34	0.79
AGSS	3.34±0.67	3.38±0.68	0.84
ASI	37.47±16.67	42.95±41.08	0.50
TLC	41.86±14.17	44.83±25.36	0.58

Data described as *n* (%) or mean±SD, BP=Benzoyl peroxide 5%, AGSS=Acne global severity scale, ASI=Acne severity scale, IPL=Intense-pulsed light, TLC=Total lesion counting, SD=Standard deviation

Table 2: Comparisons of various measures of acne between two groups at different visits

Baseline characteristics	BP and IPL group (*n*=29)	BP-alone group (*n*=29)	*P*
AGSS			
Month 1	3.17 (0.88)	3.34 (0.72)	0.46
Month 2	2.37 (0.77)	2.93 (0.96)	0.02
Month 3	1.68 (0.81)	2.31 (0.80)	0.002
Follow up	0.93 (0.84)	2.17 (0.83)	<0.0001
ASI			
Month 1	31.61 (15.44)	31.09 (14.67)	0.80
Month 2	21.31 (11.63)	24.81 (12.56)	0.30
Month 3	12.26 (8.61)	19.08 (10.61)	0.008
Follow up	5.43 (6.16)	17.98 (11.02)	<0.0001
TLC			
Month 1	35.06 (13.52)	35.17 (12.86)	0.89
Month 2	24.34 (10.71)	27.93 (10.92)	0.21
Month 3	14.03 (8.49)	21.03 (8.92)	0.001
Follow up	6.95 (6.81)	19.65 (9.11)	<0.0001

Data described as mean (SD), BP=Benzoyl peroxide 5%, AGSS=Acne global severity scale, ASI=Acne severity scale, IPL=Intense-pulsed light, TLC=Total lesion counting, SD=Standard deviation

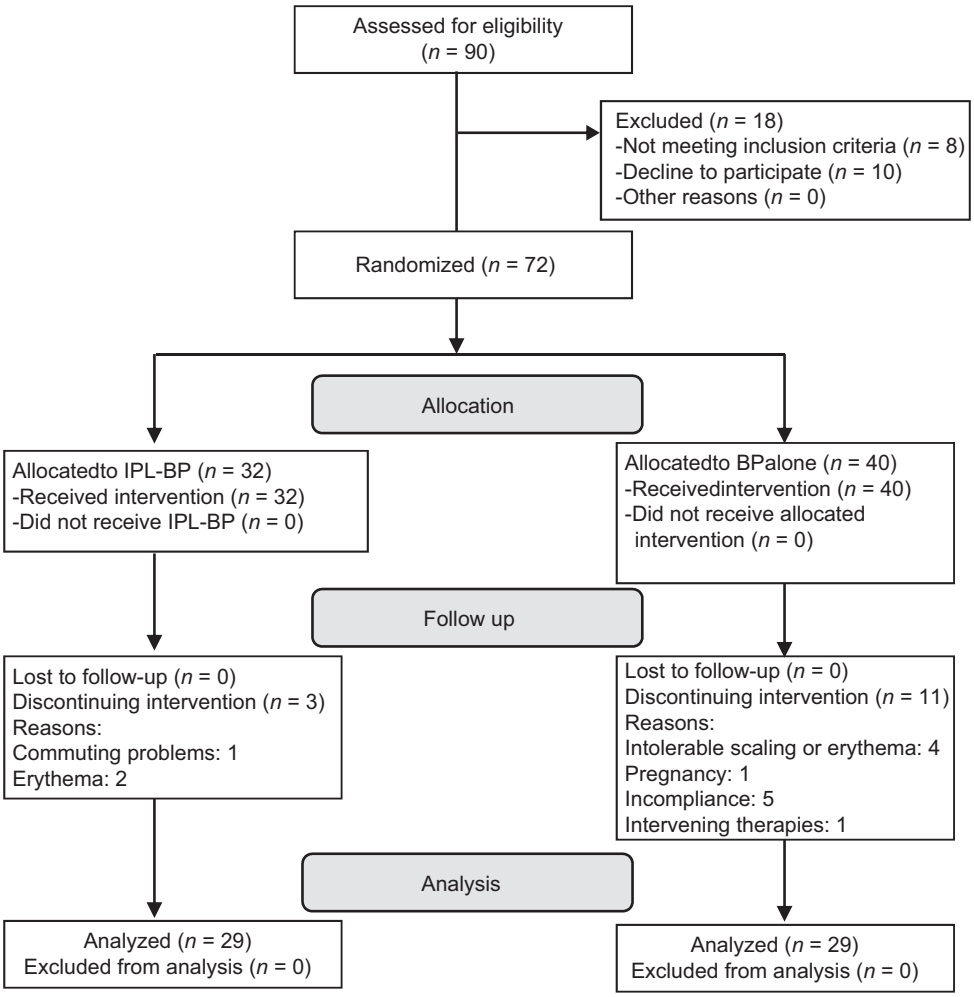

Figure 1: CONSORT flow chart of the study

between groups are subtle at earlier visits. However, the differences are noticeable in final therapy visit and follow-up as well ($P < 0.05$). Mean and corresponding 95% confidence interval of each index at each visit are displayed in Figure 2. Both groups showed decreasing pattern in the AGSS as shown in Figure 2a. However, significant difference between two groups ($P = 0.007$) and the interaction between time and group ($P < 0.001$) indicate the superiority of using IPL along with topical cream compared to single therapy. Figure 3 shows photos of a patient at different stages of the study.

Even though ASI had decreasing pattern [Figure 2b] for both groups ($P < 0.001$), there was no evidence that the difference between groups was statistically significant ($P = 0.12$). Decreasing pattern was also present for TLC [Figure 2c] in both groups ($P < 0.001$) with a steeper reduction in the group receiving concomitant IPL therapy ($P = 0.005$). As shown in Figure 2d, patient satisfaction in treatment group increases more rapidly than control group ($P < 0.001$).

In control group, 4 patients experienced erythema, 6 patients with dryness, 2 patients with scaling, 1 patient with erythema and scaling, and 1 patient with dryness and scaling. In treatment group, following complication were reported due to topical treatment: 9 with erythema, 3 with dryness, 4 with scaling, 3 with erythema and dryness, and 2 with dryness and scaling. Also following complications were reported due to IPL, 6 patients with erythema and 4 with pain. Patients who were sensitive to BP were asked to stop using it for a few nights and then restart with lower doses to let their skin get adopted. They were advised to use moisturizing lotions if needed. All symptoms were removed after almost a week. All the complications were present during treatment period and no symptoms were reported at the follow-up visit.

Discussion

Using concomitant IPL therapy with topical BP, 5% significantly improved the various severity indices of acne in this trial. Furthermore, patients with IPL therapy reported more satisfaction from the treatment. The results

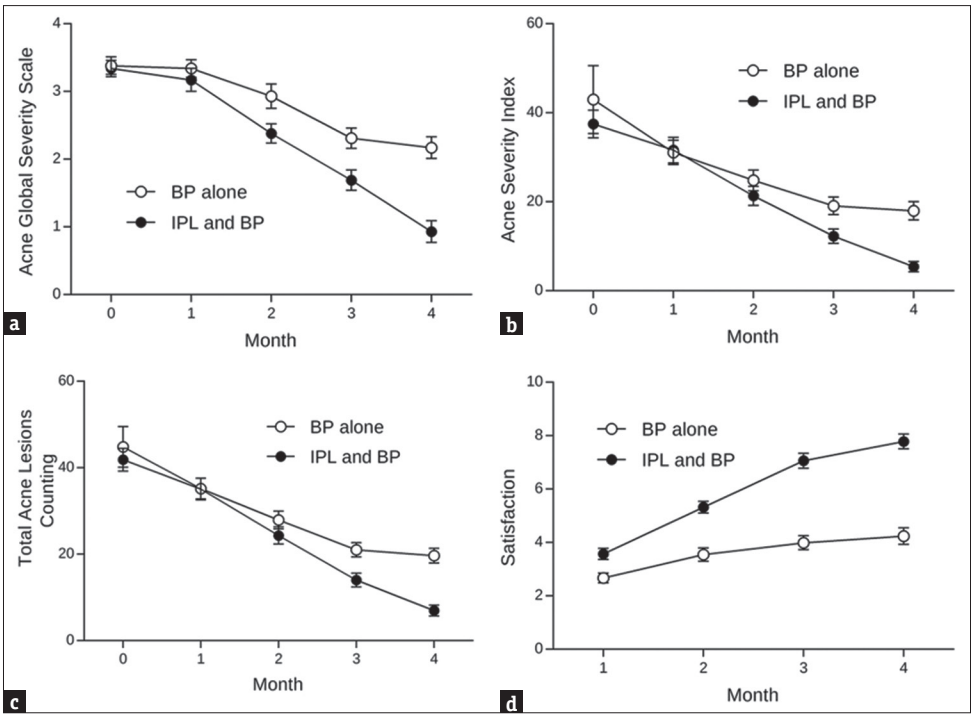

Figure 2: Mean and 95% confidence interval for (a) Acne Global Severity Scale; (b) Acne Severity Index; (c) Total lesions counting; (d) Patient satisfaction, in the IPL and benzoyl peroxide group versus the benzoyl peroxide-alone group

Figure 3: Photographs of a patient at entering the study (left), after 2 IPL sessions (the middle), and 1 month after treatment termination (right)

also suggested accelerated improvement pattern in this group.

Among the other topical antibacterial agents, BP is commonly used in mild-to-moderate acne treatments, especially for patients who cannot take systemic antibacterials.[2,8] It has a strong bactericidal effect and reduces propionibacterium acne in follicles. Unlike other antibiotic alternatives, no resistance has been detected against BP and due to its keratolytic and comedolytic properties, especially in combination with other therapies; it is commonly used in mild-to-moderate cases.[8]

The lower prevalence of acne in summer sunny days has motivated the use of ultraviolet and laser in the acne treatment. This happens through killing acne microorganism and destroying acne producing glands of pilosebaceous. Intense-pulsed light therapy eradicates acne using heat and light and also alleviates redness after the acne treatment.[11] IPL and other light-based therapies are attractive as they have no complications such as antibiotic resistance and teratogen side effect profiles.[4] No adverse effects of systemic treatments, safety, and ease of use have increased the IPL popularity.[9]

Usefulness of IPL in acne is controversial, especially as a single treatment. IPL has shown no superiority over BP in some previous reports.[6] However, IPL could have merits over topical options in some conditions.[11] Despite the single or combinational therapies with IPL in previous studies, to our knowledge, no study has addressed the efficacy of IPL and BP in the acne treatment. This combinational choice could reduce the treatment period and increase patient compliance. As results suggest, all severity indices, patient satisfaction, and complications patterns are clearly steeper for treatment group and the effect of combined therapy becomes much distinct by passing the time. The difference 1 month after the last therapeutic visit is remarkable and indicates more long-term benefit could be expected from IPL.

In IPL therapy, patients need to refer to clinic several times and this may be a disadvantage. IPL could result in

postinflammatory hyperpigmentation (PIH) in dark skin patients. It also costs more than conventional treatments. Free visits in our study and lower amounts of prescribed drugs may be an explanation for patient adherence and satisfaction and this could be different in public practice.

Generally, complications following laser and light-based therapies are more frequent than topical treatments.[4] In our study, although the complication frequency was higher in the IPL group, patient satisfaction has increased by time.

Topical treatments with BP component have been shown more effective than BP alone. Erythromycin 3%/BP 5% combination has been shown to be effective in treating mild-to-moderate inflammatory acne by affecting the antioxidant defense enzymes.[8,18] This combination gives more reduction in levels of superoxide dismutase, glutathione peroxidase, and catalase in leukocytes than BP alone.[19] It also has *in vivo* anti-propionibacterial activity greater than erythromycin 3% alone.[8,20] Although BP has a greater and more rapid suppressive effect on follicular population of *Propionibacterium acnes* than clindamycin, their combinational gel has proven clinical efficacy through both antibacterial and anti-inflammatory superior to single treatments.[8,21,22] Using these combinational alternatives along with IPL could be promising areas of the future work. Efficacy and safety of single IPL therapy in acne treatments could be assessed in a trial framework. Increasing the number of visits and/or reducing the visit interval could give an optimal therapy policy.

IPL affects other normal structures of the skin and may result in local hair loss and depigmentation in treated areas. Each filter has its own features. No tangible hair loss or depigmentation was present by the filter we used here. Even though pain is common during IPL session, patients tolerated it well because of its positive effects. One patient had PIH after first IPL session that recovered before the next IPL session.

Our study has some limitations. Sample size was relatively small and conducting a similar study on a larger sample with diverse demographic and pretreatment conditions could shed light on unknown aspects of the treatment. The sample was matched in two arms and this limited further subgroup analysis. Studies with shorter intervals between IPL sessions, for example, one week, and longer on-trial periods are recommended.

IPL could help improve results from topical agents such as BP in treating mild-to-moderate acne vulgaris. Higher frequencies of complication are common in laser and light-based therapies. However, they could be ignored in comparison to gained benefits. Future research is warranted to assess the effect of IPL and combinational topical agents such as erythromycin/BP and clindamycin/BP.

Authors' Contribution

Fatemeh Mokhtari, Gita Faghihi, Amir Hossein Siadat and Maryam Gholami referred patients to the study and collected data. Fatemeh Mokhtari, Maryam Gholami and Bahareh Abtahi-Naeini designed the study. Maryam Gholami examined patients and applied laser. Tohid Jafari-Koshki and Sayed Mohsen Hosseini analyzed the data. Mohammad Ali Nilforoushzadeh assisted in study design. Maryam Gholami and Tohid Jafari-Koshki drafted the manuscript. All authors read and approved the final draft.

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Conflicts of interest

There are no conflicts of interest.

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