BJD
British Journal of Dermatology

The pulsed-dye laser as an adjuvant treatment modality in acne vulgaris: a randomized controlled single-blinded trial

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Accepted for publication
25 March 2010

Key words
acne vulgaris, benzoyl peroxide, clindamycin, laser surgery, pulsed-dye lasers, randomized controlled trial

Conflicts of interest
None declared.

DOI 10.1111/j.1365-2133.2010.09806.x

Summary

Background Acne vulgaris is the most common skin disease and can pose a substantial therapeutic challenge. Recently, several phototherapeutic modalities, most notably pulsed-dye laser (PDL) treatment, have been introduced, but the published results – albeit promising – are controversial.

Objectives To assess the efficacy of an adjuvant PDL treatment when combined with a proven topical treatment [fixed-combination clindamycin 1%–benzoyl peroxide 5% hydrating gel (C/BPO)].

Methods Eighty patients (38 males and 42 females, mean ± SD age 19·7 ± 5·9 years) were randomized in a 1 : 2 ratio to receive C/BPO alone or in combination with PDL treatment (wavelength 585 nm, energy fluence 3 J cm^{-2}, pulse duration 0·35 ms, spot size 7 mm). Patients were evaluated at baseline and at 2 and 4 weeks after initial treatment. The primary end points were the Investigator's Static Global Assessment (ISGA) score and lesion count; the secondary end point was the Dermatology Life Quality Index (DLQI).

Results Both groups showed a significant improvement during observation [ISGA 27·1% (C/BPO) and 24·6% (C/BPO + laser), total lesion count 9·2% and 9·0%, inflammatory lesion count 36·3% and 36·9%, DLQI 54·5% and 42·5%], but there was no significant or otherwise appreciable difference between treatment modalities as far as the extent of improvement was concerned. Patients with more severe findings at baseline had a greater benefit from either therapy regimen.

Conclusions Our findings do not support the concept of a substantial benefit of PDL treatment in acne vulgaris.

Acne vulgaris is the most common skin disease, affecting approximately 85% of teenagers and roughly half of young adults between the ages of 20 and 30 years.[1,2]

Acne is not a life-threatening disease, and thus treatment is elective; however, active acne lesions and their residual, sometimes permanent, scars can cause substantial and persistent social, psychological or emotional harm, rendering treatment a necessity. The mainstays of acne therapy today are topical anticomedonic/keratolytic agents (retinoids, azelaic acid, salicylic acid) and/or antimicrobial agents [antibiotics, benzoyl peroxide (BPO), azelaic acid, zinc] depending on the severity and chronicity of disease.[3–6] The current German treatment guidelines[4] stipulate monotherapy only in mild cases (acne comedonica with fewer than 10 pustules or papules); the method of choice in moderate or severe acne vulgaris is a combination approach of an antibiotic (usually erythromycin, clindamycin or tetracycline) with either isotretinoin or BPO. Presently, BPO-containing formulations are internationally considered to be important first-line treatments for mild-to-moderate acne vulgaris.[7]

Systemic treatment with antibiotics, isotretinoin and/or antiandrogens is recommended only when topical therapy proves ineffective or in very severe cases with a strong tendency towards scarring.[3–6]

Novel and promising treatments with laser/light devices [such as blue light, red light, pulsed-dye lasers (PDLs), infrared lasers, light-emitting diodes] have been reported to have varying degrees of efficacy in treating acne vulgaris.[6–9] While beneficial effects have been attributed to many of these modalities, methodological constraints have made evidence-based efficacy assessment impossible.[8] Only very few studies (i) were conducted in patients with severe acne, (ii) compared laser therapy with conventional modalities, or (iii) examined long-term benefits of treatment; this limits the conclusive nature of an assessment.[8–10] Currently, national and international treatment guidelines do not recommend laser treatment.[3,4]

The results of PDL treatment of acne vulgaris published so far are controversial. Whereas Seaton *et al.*[11] described a marked improvement of mild-to-moderate acne after low-fluence PDL therapy, Orringer *et al.*[12] were unable to replicate said results in a similar, albeit not identical, study design. More recently published studies failed to resolve the controversy, and they varied in terms of treatment procedure(s) as well as results.[13–15]

While published results are certainly promising enough to warrant further independent research, they are insufficient to justify abandoning methods with proven efficacy. While planning the adjuvant application of PDL in the present study, we also took into account patient treatment ethics and the short 'window of opportunity' for scar prevention when active inflammatory lesions are present. This meant that we provided all patients with the well-established and evidentially effective modality of a fixed-combination clindamycin 1%–BPO 5% hydrating gel (C/BPO).[16–24] The goal of the study was to assess the efficacy and safety of a low-fluence PDL treatment in addition to C/BPO in patients with facial inflammatory acne.

Table 1 Investigator's Static Global Assessment score

Score	Definition
Grade 0	Normal, clear skin with no evidence of acne vulgaris
Grade 1	Skin almost clear: rare noninflammatory lesions present, with occasional noninflamed papules (papules must be resolving and may be hyperpigmented, although not pink) requiring no further treatment in the Investigator's opinion
Grade 2	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulocystic lesions)
Grade 3	Noninflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules; there may or may not be one small nodulocystic lesion
Grade 4	Inflammatory lesions are more apparent; many comedones and papules/pustules; there may or may not be a few nodulocystic lesions
Grade 5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulocystic lesions

Patients and methods

Patients

Patients were recruited consecutively on a 'first come – first served' basis at a regional treatment centre for aesthetic laser surgery (Laserklinik Karlsruhe) between October 2008 and April 2009. The required sample size was calculated in adherence to U.S. Food and Drug Administration (FDA) guidelines[25] as 29 patients per group [based on a 70/30 success/failure ratio as set forth by the Investigator's Static Global Assessment (ISGA) score].

Patients eligible for participation were selected according to the following inclusion and exclusion criteria. Inclusion criteria were: (i) adolescents and adults with mild-to-moderate inflammatory acne vulgaris (ISGA grades 2–4, Table 1); (ii) Fitzpatrick skin phototype I–III; and (iii) the ability and willingness to comply with the requirements of the protocol. Exclusion criteria were: (i) atopic dermatitis (because of the irritating potential of BPO[26]); (ii) a history of regional enteritis, Crohn's disease or antibiotics-associated colitis; (iii) oral antibiotics during the last 4 weeks prior to enrolment; (iv) oral isotretinoin during the last 52 weeks prior to enrolment; (v) oral contraceptives during the last 26 weeks prior to enrolment; (vi) topical acne treatment during the last 4 weeks prior to enrolment (including artificial or natural ultraviolet therapy); (vii) laser surgery interventions within the treatment region during the last 12 weeks prior to enrolment; (viii) coagulation disorders or anticoagulant treatment; (ix) photosensitizing medication (e.g. tetracycline, gold); and (x) pregnancy.

Prior to study enrolment, written informed consent was obtained from all patients (or from the parents or guardians of the patients who were under age). The study met Good Clinical Practice criteria and the principles of the Declaration of Helsinki. The protocol was approved by the institution's human research review committee and registered with ClinicalTrials.gov (identifier: NCT01052246).

During the observation period, 134 patients with acne vulgaris were screened for eligibility. Eighty-nine patients fulfilled the inclusion and exclusion criteria and agreed to participate. Seven patients failed to complete the follow-up examinations (four without stating reasons and one each due to side-effects of C/BPO, vocational reasons, and unrelated disease, respectively) and were thus excluded from the study. Two patients had to be excluded due to noncompliance (discontinuation of C/BPO or sunbathing).

Overall, 80 patients eventually completed the trial. Patients were aged between 13·3 and 43·8 years (mean ± SD 19·7 ± 5·9, median 17·8), and the cohort was almost evenly divided among males (n = 38; 48%) and females (n = 42; 52%).

Study design

To achieve meaningful results that are internationally comparable, the study was planned in strict adherence to FDA guidelines[25] as a prospective randomized controlled single-blinded trial. It was not possible to blind either the patient or the therapist, but the examiners were blinded as far as group assignment and examination time were concerned.

Patients were randomly assigned to one of two treatment regimens: (i) C/BPO, and (ii) C/BPO in combination with PDL treatment (C/BPO + laser). Because of the well-proven effect of C/BPO and the much less established efficacy of PDL treatment, patients were assigned to treatment groups in a 1 : 2 ratio using a computer-generated randomization schedule.

Interventions

All patients received topical monotherapy with C/BPO (Duac® Akne Gel; Stiefel Laboratorium GmbH, Offenbach, Germany). To provide standardized conditions within the sample, the gel was applied to the entire face regardless of the location of the lesions. It was applied once per day in the evening throughout the observation period and left on overnight. The facial skin first had to be thoroughly washed, rinsed with warm water and gently patted dry.

In addition, patients randomized to the C/BPO + laser group received two nonpurpuric treatments (at baseline and after 2 weeks) with a PDL (NLite™ V; Medical Bio Care, Berlin, Germany) set to the following parameters: wavelength 585 nm; energy fluence 3 J cm^{-2}; pulse duration 0·35 ms; spot size 7 mm.

Laser irradiation was applied to the whole of each respective anatomical facial region (e.g. the entire cheek or the entire forehead) that contained lesions regardless of the distribution of lesions within the location. Laser pulses were placed closely adjacent with minimal overlap. An average of 300 pulses per session was applied in a single pass (treatment duration approximately 10 min). During the treatment, patients' eyes were covered with protective goggles. To ensure consistency, all laser treatments were performed by the same therapist (S.K.) who did not participate in the evaluation.

Evaluation

The primary end points were the ISGA score (Table 1) and the lesion count (total number of lesions and number of inflammatory lesions); the Dermatology Life Quality Index (DLQI[27]) served as a secondary end point.

Patients were evaluated at baseline and at 2 and 4 weeks after the initial treatment. The evaluation instruments were as follows:

1 The ISGA, a commonly applied outcome measure in acne vulgaris treatment studies,[24,28–30] was based on standardized photographs and was performed by three independent investigators blinded to time of imaging and group assignment at baseline, 2 and 4 weeks. The lighting and imaging conditions were strictly standardized by ensuring a constant distance and angle between camera and subject. Photographs were taken with a Canon Digital Camera (EOS 350 D with Macro Lens EF-S 60 mm f/2·8 USM; Canon Inc., Tokyo, Japan) equipped with a lens-mounted ring flash (Macro Ring Lite MR-14EX; Canon Inc.). Standardized views (frontal, 45° oblique, and lateral) were used, and a single laboratory processed all photographs. Images taken before and after treatment, respectively, were mixed intraindividually prior to evaluation.

2 The number of inflammatory lesions (papules and pustules) and the total number of lesions (including open and closed comedones) on the whole face (except the nose) were counted on site by a fourth independent investigator who was blinded with regard to group assignment and time point. All lesion counts were performed at baseline and at 4 weeks.

3 The DLQI is an intensively utilized and validated instrument for assessing skin-related quality of life (QoL).[27] It assesses the QoL within the last 7 days in various dimensions (activities of daily living, leisure/sport, work/school, personal relationships, therapy) using a simple and time-saving set of 10 questions to be answered on a four-point scale (0–3 points, total maximum of 30); higher point scores indicate more pronounced QoL impairment. An improvement of ≥ 5 points is considered clinically relevant. The DLQI was recorded at baseline, 2 and 4 weeks.

4 Active questions about side-effects (erythema, oedema, purpura, blisters, crusts, bleeding, hyper- or hypopigmentation, scars, atrophy, pain, paraesthesia) were recorded by a medical assistant not otherwise involved in the trial at 2 and 4 weeks.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS/PC+) program version 12.0 for Windows (SPSS, Chicago, IL, U.S.A.), employing the Wilcoxon signed rank test, Mann–Whitney U-test and χ^2 test. The mean of the three investigators was used for the analysis of the ISGA, and the instrument's interobserver reliability was assessed with Cohen's κ statistic. The significance level was set to $P < 0{\cdot}05$. Descriptive statistics were also calculated (mean, SD, median, minimum, maximum, numbers, percentage rate).

Results

Sample description

The main localizations of acne lesions were the forehead and cheek, which were affected in roughly three-quarters of the sample. In 40%, lesions were present in the chin region; involvement of the neck or temples was comparatively rare with approximately 10% each (Table 2). Both treatment groups were similar in terms of lesion localization, sex distribution and age (Table 2).

Investigator's Static Global Assessment

Both groups showed a significant reduction in ISGA point scores after treatment, and the amount of reduction was roughly equivalent: C/BPO treatment alone resulted in an improvement from 3·17 ± 0·76 to 2·31 ± 0·54 (mean ± SD) points (equalling 0·86 points or 27·1%), whereas after C/BPO + laser the score declined from 3·37 ± 0·60 to 2·54 ± 0·72 points (equalling 0·83 points or 24·6%). Throughout observation, the ISGA point score was somewhat higher in the C/BPO + laser group, and the difference was statistically significant 4 weeks after treatment (Fig. 1).

The interobserver reliability of the ISGA was excellent. Prior to treatment, the three observers agreed without exception (Cohen's $\kappa = 1{\cdot}00$), and both 2 and 4 weeks after treatment

Table 2 Sample description and P-values for comparisons between fixed-combination clindamycin 1%–benzoyl peroxide 5% hydrating gel (C/BPO) and C/BPO + laser group, respectively

		Group		
	Entire sample	C/BPO	C/BPO + laser	P-value
Sex, n (%)				
Male	38 (48)	14 (48)	24 (47)	1·000[a]
Female	42 (52)	15 (52)	27 (53)	
Age (years)				
Range	13·3–43·8	13·3–35·4	14·0–43·8	0·169[b]
Mean ± SD	19·7 ± 5·9	18·5 ± 4·8	20·4 ± 6·4	
Median	17·8	17·3	17·9	
Localization, n (%)				
Forehead	63 (79)	22 (76)	41 (80)	0·777[a]
Cheek	66 (82)	22 (76)	44 (86)	0·359[a]
Chin	32 (40)	10 (34)	22 (43)	0·486[a]
Neck	9 (11)	4 (14)	5 (10)	0·716[a]
Temple	6 (8)	1 (3)	5 (10)	0·409[a]
No. of localizations				
Range	1–4	1–4	1–4	0·126[b]
Mean ± SD	2·2 ± 0·8	2·0 ± 0·8	2·3 ± 0·8	
Median	2	2	2	

[a]χ^2 test. [b]Mann–Whitney U-test.

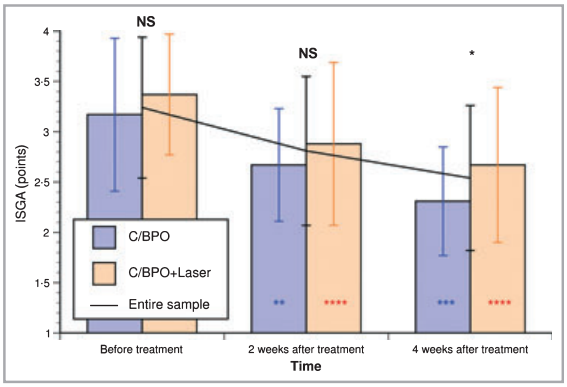

Fig 1. Investigator's Static Global Assessment (ISGA) score (mean ± SD) before and after treatment. C/BPO, fixed-combination clindamycin 1%–benzoyl peroxide 5% hydrating gel. NS, not significant, *P < 0·05, **P < 0·01, ***P < 0·001, ****P < 0·0001. Coloured asterisks within bars: significance of difference from baseline; black asterisk above bars: group difference at that time.

there were only sporadic cases of disagreement [Cohen's κ = 0·97 (2 weeks) and 0·95 (4 weeks), respectively].

Total lesion counts

The lesion counts yielded a similar result to the ISGA: both the total number of lesions and the number of inflammatory lesions declined significantly during observation in both groups. The C/BPO + laser group started with a somewhat more severe finding from the outset which remained more or less consistent throughout (Fig. 2). The relative improvement was almost exactly equivalent between groups: the total lesion count was reduced by 9·2% (C/BPO) and 9·0% (C/BPO + laser); the number of inflammatory lesions by 36·3% (C/BPO) and 36·9% (C/BPO + laser), respectively.

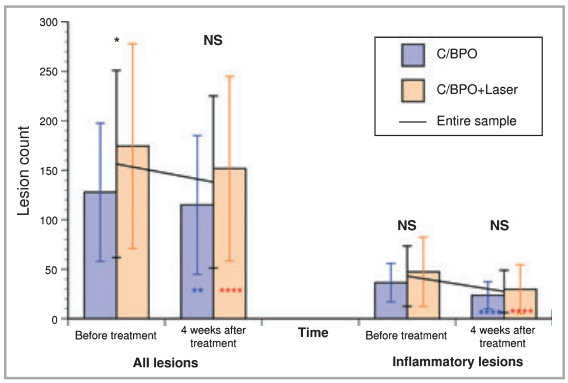

Fig 2. Lesion count (mean ± SD) before and after treatment. C/BPO, fixed-combination clindamycin 1%–benzoyl peroxide 5% hydrating gel. NS, not significant, *P < 0·05, **P < 0·01, ****P < 0·0001. Coloured asterisks within bars: significance of difference from baseline; black asterisk above bars: group difference at that time.

Dermatology Life Quality Index

In accordance with the aforementioned variables, the effect of treatment modalities on the DLQI was largely equivalent; the laser-treated group had less favourable findings from the outset and maintained this difference throughout observation. The DLQI was significantly reduced in both groups by 2·31 points (54·5%) in the C/BPO and 3·06 points (42·5%) in the C/BPO + laser group, respectively (Fig. 3).

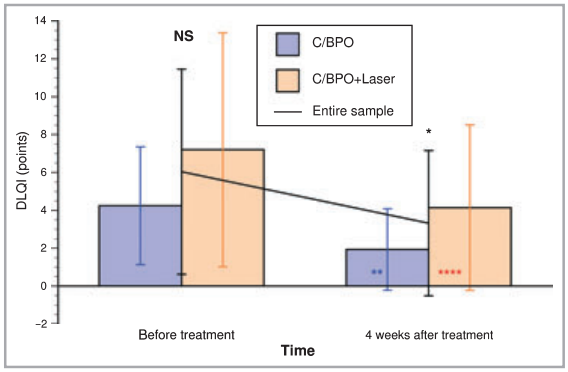

Fig 3. Dermatology Life Quality Index (DLQI) score (mean ± SD) before and after treatment. C/BPO, fixed-combination clindamycin 1%–benzoyl peroxide 5% hydrating gel. NS, not significant, *P < 0·05, **P < 0·01, ****P < 0·0001. Coloured asterisks within bars: significance of difference from baseline; black asterisk above bars: group difference at that time.

While this difference appears to be clinically insignificant, the strong positive correlation between DLQI at baseline and improvement ($P < 0{\cdot}00001$) indicated that subjects with more severe QoL impairment at baseline had a greater benefit from therapy. Indeed, the mean ± SD improvement was clinically significant in patients with more than 10 points ($-6{\cdot}2 \pm 1{\cdot}4$ points) and especially in those with more than 20 points ($-19{\cdot}0 \pm 1{\cdot}0$) at baseline. However, after group stratification for DLQI at baseline [≤ 10 points ($n = 64$), 11–20 points ($n = 12$), > 20 points ($n = 2$)] there was still no treatment-related difference in terms of improvement within strata. The two patients with more than 20 points both received PDL treatment, so strictly speaking no statement concerning this specific group is warranted.

Side-effects

The only observed side-effect was one case of mild purpura lasting 3 days in the C/BPO + laser group (incidence 2%); no further side-effects were reported.

Discussion

First and foremost, the present study confirms the rapid and profound effect of C/BPO on mild-to-moderate acne vulgaris and its excellent tolerability.[16–24] The well-known side-effects of BPO – mainly skin dryness, scaling and pruritus – can be avoided by including a moisturizing gel, which helps ensure excellent treatment compliance.[19,23] The effect of C/BPO treatment was substantially greater in more severe and inflammatory cases, underlining the importance of the antimicrobial treatment modality constituted by BPO.

Administering PDL treatment in a fashion that has previously shown to be effective as compared with a 'sham' intervention,[11] on the other hand, yielded no additional effect in the present study. A similar finding has been reported by Orringer *et al.*,[12] albeit in comparison with nontreatment. Despite some differences in detail, the stark contrast in results cannot sufficiently be explained by the laser treatment parameters. All in all, the differences were marginal: Orringer *et al.*[12] used the exact same settings as applied in the present study and delivered 385 pulses in a split-face design. Seaton *et al.*[11] applied 500 pulses to the entire face ('from brow to jawline', although interestingly no mention is made of the frequently affected forehead) with a slightly smaller spot size of 5 mm. The total calculated treatment area was substantially smaller at 98·2 cm^2 (Seaton *et al.*[11]) as opposed to 148·2 cm^2 (Orringer *et al.*[12]), while in the present study only affected anatomical regions were treated, resulting in a treatment area (115·5 cm^2) that falls in between the two aforementioned studies.

A recent study by Choi *et al.*[15] also showed a marked improvement, but only after four sessions and with a slower onset of effect as compared with intense pulsed light (IPL). However, the fact that the acne worsened *during* the course of IPL treatment after an initial improvement raises scepticism about the evaluation methods and warrants further independent confirmation. Another concern here is the split-face design – which Orringer *et al.*[12] used as well – that has a major drawback when inflammatory conditions are targeted. As Chu[31] pointed out, the successful treatment of acne on one side of the face could influence the lesions on the opposite side, for instance if it is mediated by a soluble factor [such as transforming growth factor (TGF)-β] induced by laser treatment.

Moreover, Choi *et al.*[15] employed a higher energy fluence (8–10 J cm^{-2} as compared with 3 J cm^{-2} in the present and other published studies[11,12]). Therefore, it cannot be ruled out that the present study would have yielded differences after a longer duration of treatment and follow-up and/or higher fluence. According to Seaton *et al.*,[11] the effect was achieved with 3 J cm^{-2} and was most pronounced after 4 weeks. Consequently, our treatment parameters and follow-up period – which also considered a possible bias in results due to menstrual hormonal fluctuations – should have been sufficient.

The lack of significant side-effects of PDL treatment (which this study confirmed) is unanimous in the literature.[11,12,14,15,32,33]

An indisputable potential benefit of laser treatment over C/BPO could not be assessed here owing to the study design: PDL therapy is independent of patient compliance which – the benefits of fixed-combination regimens notwithstanding – is an ongoing issue in topical acne therapy.[34]

Another possible shortcoming of this study must be acknowledged: patients in the C/BPO + laser group had somewhat more severe disease than those in the C/BPO group. This occurred by chance, as the assignment to a given group was strictly randomized. However, this shortcoming can hardly explain the lack of a difference in improvement; on the contrary, as the extent of improvement was positively correlated to disease severity at baseline, the effect in the C/BPO + laser group should have been more marked if the baseline differences played any role at all.

The lack of effect of PDL in this study may be due to the similarity of the mechanisms of PDL and BPO. Whereas the effect of PDL on both inflammatory and noninflammatory lesions has been described,[11,32] it is generally accepted that the mode of PDL action is mainly anti-inflammatory,[14] as is that of BPO. Owing to the lack of additional efficacy over C/BPO, the present trial does not corroborate putative alternative mechanisms of PDL action, such as damage to sebaceous glands as proposed by Seaton *et al.*[35]

Regardless of the fact that different inflammation mediators are addressed – fibroblast growth factor receptor 2 by BPO[36] and TGF-β by PDL,[35] respectively – it is plausible that the beneficial potential of anti-inflammation is exhausted by either method. Conceivably, that would mean that an additional modality cannot improve the result any further. This hypothesis is challenged, however, by the findings of a split-face study which examined the effects of a high-energy IPL using minimal infrared (530–750 nm) in combination with adapalene (a third-generation anti-inflammatory retinoid). One month after the end of treatment, four sessions held at

3-week intervals (7–8 J cm^{-2}, 2 × 2·5 ms) had yielded a 58% reduction in inflammatory lesions vs. 33% on the side treated only with adapalene. It must be noted that 3 months post-treatment there was no difference between the treatment and the control group (personal correspondence quoted in Dierickx[37]).

This theory needs to be confirmed by an independent investigation, especially as the present study did not include an untreated or PDL-only group. In planning the trial, we considered such a design but rejected it because of ethical aspects: the controversial reports on the efficacy of PDL-only treatment currently do not consistently warrant the expectation of success. General evidence to date about the efficacy of light-based treatment modalities is scarce and focuses mainly on a combination of photosensitizers (such as 5-aminolaevulinic acid or methyl aminolaevulinate) and noncoherent light sources.[38] Therefore, we would have consciously risked the consequences of not providing treatment (i.e. mainly scar formation) for patients in the control group or asymmetrical scarring in the event of a split-face design. Not only is this problematic from an ethical perspective, but one is also likely to encounter compliance problems when fully informing patients about the possible consequences of group assignment.

Given the latter angle, future studies of PDL efficacy for acne treatment are not without their problems. The proven efficacy of topical treatment in most cases of mild-to-moderate acne vulgaris means that even the positive laser results published in the literature[11,14,15,31,32] are no better than equivalent to traditional treatment modalities, making cost-benefit assessments a necessity even when efficacy as such can be confirmed.

What's already known about this topic?

- Current evidence on the efficacy of pulsed-dye laser (PDL) treatment of acne vulgaris is scarce and controversial.

What does this study add?

- The present study examined PDL efficacy when combined with an established effective topical treatment in a randomized controlled setting.
- There were no significant group differences. Our findings do not support the concept of a substantial benefit of PDL treatment in acne vulgaris.

Acknowledgments

We thank G. Pfirrmann, L. Pohl, Y. Thiermann and D. Falk (Laserklinik Karlsruhe) for their assistance during the recruitment and evaluation phase of the trial. M. Jünger (Department of Dermatology, University Hospital Greifswald) critically revised the manuscript. The laser device under investigation was provided by the German distributor at no cost. No funding has been received in relation to the trial.

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