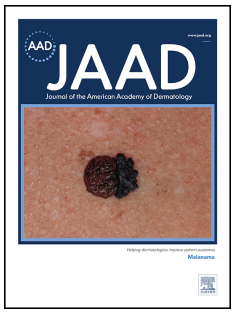
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Novel 1726 nm Laser Demonstrates Durable Therapeutic Outcomes and Tolerability for Moderate-to-Severe Acne Across Skin Types

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Novel 1726 nm Laser Demonstrates Durable Therapeutic Outcomes and Tolerability for Moderate-to-Severe Acne Across Skin Types

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Patient Consent: Subject consent is on file.
This was an IRB-approved study.

Key Words: acne, laser, isotretinoin, acne management, acne vulgaris, light therapies, acne guidelines, acne skin types, acne severity, hormone therapy, antibiotic therapy, sebaceous glands, selective photothermolysis, acne scarring, acne treatment alternatives

Checklist: the manuscript meets all the requirements for the article type being submitted.
The data from the study has not been previously published.

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Abstract

Background: Traditional acne management with topical therapy, systemic antibiotics, hormonal agents, or oral isotretinoin requires compliance and may produce significant side effects. However, alternative treatments with lasers had failed to demonstrate durable clearance.

Objective: To assess the tolerability and therapeutic outcomes of a novel 1726-nm laser treatment of moderate-to-severe acne across skin types.

Methods: A prospective, open-label, single-arm, IDE-approved, IRB-approved study of 104 subjects with moderate-to-severe facial acne and Fitzpatrick Skin Types ranging from II-to-VI was conducted. Subjects received three laser treatments at 3(-1/+2)-week intervals.

Results: Following final treatment, ≥50% reduction in active acne inflammatory lesions was 32.6% at 4-weeks follow-up, increasing further to 79.8% and 87.3% at 12 and 26-weeks, respectively. The percentage of subjects clear or almost clear increased from 0% at baseline to 9%, 36.0%, and 41.8% at 4-, 12- and 26-weeks follow-up. No serious adverse events were observed related to device or protocol; treatments were well tolerated, requiring no anesthetic. Therapeutic outcomes and discomfort were similar across all skin types.

Limitations: Lack of control group.

Conclusions: The study findings demonstrate the novel 1726 nm laser is well tolerated with durable progressive post-treatment improvement to at least 26 weeks for moderate-to-severe acne across skin types.

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INTRODUCTION

Acne is the most common skin condition nationally and eighth-most common disease worldwide, affecting 85% of teens and 50% of adults[1,2]. Predominantly facially distributed, acne causes poor self-image, anxiety, depression, negative psychosocial impact, and permanent scarring[3-5]. The financial burden of acne treatment is approximately $3 billion in the US annually[6].

Traditional acne management follows a well-established treatment algorithm of topical therapy with multiple pharmacologic classes, and progressive implementation of oral antibiotics, hormonal agents, or isotretinoin [5](Mendeley supplemental table 1). To date, durable outcomes in moderate-to-severe acne treatment have been attained by combining topical therapy with systemic antibiotics, hormonal agents, or oral isotretinoin. While lasers and energy-based devices have been tested, reproducible, durable outcomes in moderate-to-severe acne, has been lacking. The traditional pharmacologic algorithm endures, while lasers remain absent from the American Academy of Dermatology's first- and second-line acne treatment options.

The potential for device-based acne treatment alternatives was portended by early research with aminolevulinic acid red-light photodynamic therapy (PDT)[7]. Durable results were reported; however, adverse events (AEs) included peri-procedural discomfort, post-procedure pustular eruptions, blistering, and post-inflammatory hyperpigmentation in darker skin types[7, 8]. Alternative acne PDT protocols with variable success and photosensitivity are employed by some dermatologists, but not considered mainstream[9-11].

The current pharmacologic treatment algorithm imposes a burden, variable clearance rates, side effects, and complications. Topical treatments are often irritating and require high patient

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compliance. Oral antibiotics may cause drug allergy, gastrointestinal upset, and bacterial resistance. Hormonal agents, including oral contraceptives and spironolactone are associated with risks of hypercoagulability, and cardiac arrhythmia. Isotretinoin, while curative in approximately 60% of moderate-to-severe acne cases, entails high administrative burden and AEs–namely birth defects and depression[12]. Thus, researchers continued search for targeted and durably effective acne treatment alternatives.

As presaged by PDT, light may target sebaceous glands by selective photothermolysis, the principle of matching a wavelength and pulse duration to a specified skin target. While wavelengths 532, 585-595, and 1450 nm have been applied to acne, they were not preferentially absorbed by sebaceous glands over water, hemoglobin, or melanin. Selective sebaceous gland destruction was demonstrated using a free electron laser tuned from 1600-1800 nm[13]. The absorption spectra of sebum and water measured in near-infrared 800–2400 nm region demonstrated a narrow band (approximately 40 nm) of selective absorption in sebum over water peaking at 1726 nm[14, 15](Mendeley Supplemental Figure 1).

The laser with a tight bandwidth of the specific absorption ratio peak of 1726 nm achieves spectral selectivity for sebaceous glands. In this study, a novel 1726 nm laser was developed, optimized, and applied to determine tolerability, therapeutic outcomes, and durability of the responses in moderate-to-severe acne across skin types II-VI.

METHODS

Subjects

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104 subjects, 59 women, 45 men, ages 16-40, with Fitzpatrick Skin Types ranging from II to VI, were enrolled in this prospective, open-label, single-arm, IDE-approved, IRB-approved study conducted at seven sites (Mendeley supplemental table 2). None of the subjects were previously treated with isotretinoin.

Study Design

Following a 30-day washout from all acne medications, baseline standardized digital photographs were taken. Three independent expert dermatologist graders assessed and scored acne severity per subject using the Investigator's Global Assessment (IGA) scale(Mendeley supplemental table 3).

Three laser treatments were administered at 3(-1/+2) week intervals. Follow-up visits were at 4, 12, and 26 weeks after the third treatment. All enrolled subjects comprised the Intent to Treat cohort, and those completing three treatments and 12-week or 26-week follow-up without major protocol deviations comprised the Per-Protocol cohort.

Standardized digital photographs were taken from frontal, 45-and 90-degree angles at baseline, pre-treatment and follow-up using consistent camera settings (Canon EOS Rebel T7 Manual capture mode) and lighting conditions (camera brightness(ISO) ranges100-6400 based on skin type, shutter speed 20(1/20th of second), and aperture size f/20). Subjects completed a Subject Satisfaction Questionnaire(SSQ) to self-assess their acne and satisfaction with treatment outcome.

Laser Treatment

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Immediately pre-treatment, skin was cleansed and degreased using acetone with gauze wipe. No topical anesthetic was administered. During treatment, the handpiece was applied ensuring complete skin contact. The laser spot size used was 3.1 mm scanned over seven adjacent locations to form a hexagonal pattern. Following precooling 1-second delay, 1726 nm energy was delivered as single or double pulse with average fluence of 20.5 J/cm^2 and 22.8 J/cm^2, respectively. The maximum pulse duration is 50ms and a maximum fluence of 30 J/cm^2. After post-cooling 2-second delay with full contact, the handpiece was then moved to the next adjacent treatment area. Process was repeated until entire face treated in single pass with no overlap. The average treatment time ranged between 30 and 40 minutes.

Clinical Assessments

Lesion count reduction assessment

Clinical outcomes were assessed by a trained, blinded expert panel of three lesion count evaluators using a validated photography-based lesion count technique. Due to COVID-19 restrictions and regulatory agencies' concerns regarding blinding and bias of live assessments for single-arm studies, live in-person lesion counts were not performed. Photography-based lesion count methodology was designed, validated, and deployed for this study by blinding the evaluator(s) through randomization and label-masking of images taken at disparate study time points and remote assessments independent of other evaluators. Past criticisms of photographic assessments included difficulties visualizing small lesions, standardizing photographs, maintaining constant lighting and positioning, inconsistent photo-development procedure, and lack of palpation[16-18]. As a result, photographic advancements and standardization methods have since improved clarity,

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sharpness, depth visualization[17], and qualitative and quantitative consistency across sessions and raters[19].

Photographs at baseline, 4-week, and 12-week follow-up were randomized, label-masked, and presented to each expert evaluator for independent assessment. Each evaluator assessed, quantified, and recorded all active inflammatory lesions (papules, pustules, and nodules) and non-inflammatory (comedones) lesions within the defined facial treatment area with the jawline as the inferior boundary. The median of three counts per subject visit was utilized when summarizing the data. At 26-week follow-up, evaluators were presented with 45-degree angle photographs to assess improvement.

For lesion assessments, the following definitions and reference measurement scale were used to ensure consistency and minimize bias. Papules were defined as erythematous, raised lesions less than 5 mm in diameter. Pustules were defined as erythematous, raised lesions containing white exudate or pus, less than 5 mm in diameter. Nodules were defined as deep-seated, erythematous lesions greater than or equal to 5 mm in diameter.

Investigator acne severity assessments

The digital photographs, without randomization or label-masking, were reviewed and scored by the expert panel of three investigator dermatology graders to rate each subject's acne severity.

Endpoint reporting / statistical analysis

Primary

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Inflammatory Lesion Count Assessment

The primary study objective was to evaluate therapeutic outcomes, durability, and tolerability of laser treatment. The primary endpoint was percent reduction in active inflammatory lesions from baseline to 12 weeks after the 3rd and final laser treatment. Subjects with a ≥50% reduction in active inflammatory lesions at follow-up compared to baseline were defined as responders. The responder rate(RR) was the percentage of the responder population in the study.

Adverse Events Assessment

The tolerability of the laser treatment was assessed by review of all AEs reported by each subject immediately post-treatment and at follow-up visits.

Secondary

Secondary endpoints evaluated at 4, 12 and 26 weeks following final treatment included the percentage of subjects with IGA scores of 0 or 1(Clear/Almost Clear), and subject satisfaction assessment from the SSQ.

Other assessments

Nodule and Non-Inflammatory Lesion Analysis

The percentage reduction in nodules and non-inflammatory (comedonal) lesion count compared to the baseline was reported for the 4-, 12- and 26-week follow-ups.

Peri-Procedural Discomfort

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Immediately following each treatment, subjects were asked to rate the pain associated with the laser treatment by indicating a number that best represents the highest average pain level experienced during treatment using the 0-10 Visual Analog Mosby Pain Rating Scale(VAS).

Subgroup Analysis

Several subgroup analyses of the RRs and peri-procedural discomfort were conducted to further summarize the scalability of the procedure. The subgroups of interest were gender, age, Fitzpatrick skin type, and baseline acne severity.

Statistical Analysis

All statistical analyses were performed using a two-sided hypothesis test at the overall 5% level of significance. Continuous data were summarized using descriptive statistics: mean, standard deviation, median, minimum, and maximum, unless otherwise noted. In addition, Exact Binomial Confidence Intervals were presented for selected percentages.

RESULTS

104 subjects (59 Females/45 Males) were enrolled with a mean age of 22.2 (+/- 5.5) years. Almost all Fitzpatrick skin types were represented in the study population, with 67% Caucasian, 20% Asian, and 13% Darker skin types IV, V, and VI (African American, Hawaiian, Others)(Mendeley supplemental table 2). 89 of the 104 subjects completed 3 treatments and the 4- and 12-week follow-ups.

Primary Endpoints

Inflammatory Lesion Count Assessment

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Quantitative analysis of blinded assessments of inflammatory acne lesion counts demonstrated that the RR, as percentage of subjects with ≥ 50% reduction from baseline, increased following final treatment. The RR increased from 32.6% at 4-week follow-up to 79.8% at 12-weeks to 87.3% at 26-weeks following final treatment(Table I).

Adverse Events Assessments

During the study, 277 transient, mild AEs were observed: 104 transient erythema and 102 transient edema. Erythema resolved in 87% and 97% of subjects within 1 and 3 days, respectively; in 3%, within a week. Edema resolved in 81% and 96% of subjects within 1 and 3 days, respectively; in 4% within a week. 47 AEs consisted of a transient self-limited acneiform flare-up 2 days to 3 weeks post-laser treatment. No incidence of vesiculation, blistering, scarring, or hyperpigmentation was observed across skin phototypes(Table I).

Secondary Endpoints

Investigator Acne Severity Assessments

Baseline IGA

Each grader scored Independent Global Assessments (IGA) per subject, and medians of the three scores were used to summarize the data. Baseline IGA scores showed 99% of the pre-treatment population presented moderate-to-severe acne (Mendeley supplemental table 4).

Clear or Almost Clear Subjects

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Acne IGA severity following treatment demonstrated the percentage of subjects clear or almost clear increased from 0% at baseline to 9%, 36.0%, and 41.8% of subjects at 4-, 12- and 26-week follow-up intervals, respectively(Table I).

Mild, Moderate, or Severe Subjects

The percentage of subjects rated as mild, moderate, or severe acne decreased from 100% at baseline to 91%, 62.9%, and 58.2% at 4-, 12- and 26-week follow-up, respectively(Table I).

2-Point+ IGA Improvement

The percentage of subjects showing at least a 2-point improvement in their IGA scores improved progressively from 10.1% to 46% and 51.9% at the 4-week, 12-week, and 26-week follow-up intervals, respectively(Table I).

Subject Satisfaction Assessments

Subject satisfaction was high, with percentage of subjects reporting their skin looked better at 78.7%, 87.6%, and 79.7% at 4-week, 12-week, and 26-week follow-up intervals, respectively. (Table 2). The percentage of subjects reporting their skin looked smoother was 78.7%, 85.4% at and 82.3% at the 4-, 12- and 26-week follow-up visits(Table I).

Other assessments

Nodule and Non-Inflammatory Lesion Assessments

Nodule count reduction

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The mean nodule count reduction compared to baseline increased progressively from 45% at 4-weeks to 69% at 12-weeks and 93% at 26-weeks following final treatment(Table I). Nodule counts reduced further by at least 35% in successive follow-up visits.

Non-inflammatory lesion count reduction

The median non-inflammatory (comedonal) lesion count reduction compared to baseline increased from 22% at 4-week follow-up, to 31.7% at 12-weeks and 43.9% at 26-weeks following final treatment(Table I).

Peri-Procedural Discomfort

All subjects tolerated all treatments well. Topical or local anesthetics were not used. No sessions ended prematurely due to excessive discomfort. The mean and median VAS scores reported by subjects at each treatment visit are summarized(Table I).

Subgroup Analysis

RRs and peri-procedural discomfort were analyzed per skin type, gender, age group, and baseline acne severity. Age groups were subdivided into four groups: 16-19, 20-22, 23-25, and 26+ years. Since no patient with mild acne at baseline was enrolled, acne severity subgroup included moderate and severe acne subjects. Since no Fitzpatrick skin type I subjects were enrolled, the skin type subgroup included results for Type II-VI.

Responder Rates

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The RR was similar across all the subgroups analyzed, including skin phototypes, acne severity, gender, and age ranges(Table I).

Peri-Procedural Discomfort

Discomfort scores were similar across all the subgroups analyzed, including skin phototypes, acne severity, gender, and age ranges(Table I).

Clinical Outcomes

Before and after clinical photographs of severe acne in skin types II and VI are shown (Figures 1-4, Mendeley supplemental figures 2-3). For each subject, baseline(pre-treatment) and follow-up 4, 12, and 26-weeks post-final treatment demonstrate progressive and durable reduction in acne lesions and post-treatment cosmesis through successive post-treatment follow-up intervals in each representative skin type(Figures 1-4, Mendeley supplemental figures 2-3).

DISCUSSION

Based on the principles of selective photothermolysis, the 1726 nm wavelength is most preferentially absorbed by sebaceous glands making it an ideal choice for targeting acne lesions. Tuning the laser source and combining an efficient contact cooling system allows for a safe and efficacious treatment with durable outcomes without the need for pain mitigation.

In this study, we demonstrate a significant, durable reduction of moderate-to-severe acne across a broad range of skin types. Following three well-tolerated 1726 nm laser treatments, 79.8% of subjects demonstrated ≥50% improvement in inflammatory acne 3 months after the 3rd treatment. Six months post-treatment, this rose to 87.3% of subjects, indicating that the sebaceous gland effect

produced durable, progressive improvement. These findings of continued improvement over time without further treatment suggest a sebaceous gland modulating, mechanistic effect impacting the natural history of the disease(Mendeley supplemental table 5).

99 of 104 subjects remained enrolled at the 12-week follow-up visit, with 5 dropping out due to non-treatment-related issues. Treatment was remarkably well-tolerated, with an average pain score of 5.2 out of 10 despite no pain management. There was temporary perilesional erythema, but no residual erythema, edema, blistering, crusting hypo, or hyperpigmentation. An initial transient eruption between 2 days-to-3 weeks post-treatment was observed prior to clearing, which resembles our observations post-isotretinoin treatment. Subjects experiencing transient worsening were advised to increase topical administration of study physician-approved moisturizer to alleviate itchiness and/or dryness. Importantly, this is the first laser shown to be effective and with a favorable tolerability profile in all skin types II through VI.

The 1726 nm laser mechanism of action involves selective photothermolysis targeting of sebaceous glands. Histological assessments of skin samples excised five days post-treatment around the ear, ventrally between the fossa and tragus, demonstrated complete or almost complete sebaceous gland destruction(Mendeley supplemental figure 4). These findings are consistent with the report by Sakamoto et al. of a 1720 nm laser with contact cooling producing selective photothermolysis of sebaceous glands [13]. Furthermore, our findings provide an explanation for the durable, sustained, and progressive acne improvement observed for months following the final treatment. Thus, the 1726 nm laser may be the first treatment since isotretinoin that substantially

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reduces sebaceous gland activity in a durable manner but with a far more acceptable adverse event profile.

The 1726 nm laser is found to be safe and effective in a broad range of skin types studied here, yet controlled trials are needed with larger subject numbers and longer follow-up periods to reproduce treatment outcomes and response duration. The laser described here resulted in clinically meaningful progressive post-treatment improvement to at least 26-week follow-up and may alter the natural history of the disease, inducing a durable amelioration in moderate to severe acne across skin phototypes.

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TABLE I: Primary and Secondary Endpoints of Clinical Results for 1729 nm Laser Treatment of Acne. Primary endpoints include Responder Rates (overall and by subgroup), Summary of Adverse Events by relationship and severity. Secondary endpoints include Investigator's Global Assessment (IGA) and Nodule and Non-Inflammatory (Comedonal) Lesion counts, and Subject Satisfaction Assessment at baseline and follow-up visits.

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RESPONDER RATE PER-PROTOCOL		4-Week FU	12-Week FU	26-Week FU
Responder		29 (32.6%)	71 (79.8%)	69 (87.3%)
Non-responder		60 (67.4%)	18 (20.2%)	10 (12.7%)
95% Confidence Interval		(0.23, 0.43)	(0.70, 0.88)	(0.78, 0.94)
RESPONDER RATE SUBGROUP PER-PROTOCOL		4-Week FU	12-Week FU	26-Week FU
Female		25.6	80.9	88.4
Male		40.5	78.6	86.1
Skin Type				
II		25	83.3	100
III		29.6	74.1	81.8
IV		38.2	82.4	81.3
V		33.3	75	100
VI		25	100	100
Age Group				
16-19		37.8	81.1	96.8
20-22		35	85	79
23-25		21.4	71.4	76.9
26+		27.8	77.8	87.5
Baseline IGA				
Moderate		33.3	81.2	90.5
Severe		0.316	79	75
Investigator's Global Assessment (IGA) Per-Protocol Cohort				
Category	Baseline	4-Week FU	12-Week FU	26-Week FU
Individual IGA				
Clear Skin	0 (0.0%)	1 (1.1%)	2 (2.2%)	9 (11.4%)
Almost Clear	0 (0.0%)	7 (7.9%)	30 (33.7%)	24 (30.4%)
Mild	1 (1.1%)	39 (43.8%)	38 (42.7%)	33 (41.8%)
Moderate	69 (77.5%)	38 (42.7%)	17 (19.1%)	13 (16.5%)
Severe	19 (21.3%)	4 (4.5%)	1 (1.1%)	0 (0.0%)
IGA Subgroup				
Clear Skin or Almost Clear	0 (0.0%)	8 (9.0%)	32 (36.0%)	33 (41.8%)
Mild, Moderate or Severe	89 (100.0%)	81 (91.0%)	56 (62.9%)	46 (58.2%)
95% Confidence Interval		(3.96, 16.95)	(26.37, 47.31)	(30.77, 53.41)
Nodule and Non-Inflammatory Lesion Counts Per-Protocol Cohort				
Nodule Lesion Count	Baseline	4-Week FU	12-Week FU	26-Week FU
Mean (SD)	0.55 (1.08)	0.30 (0.87)	0.17 (0.53)	0.04 (0.19)
Range (min, max)	0, 6	0, 6	0, 3	0, 1
Comedonal Lesion Count				
Median	41	32	28	23
Range (min, max)	6, 132	5, 98	6, 102	5, 88
Adverse Events Per-Protocol Cohort				
Category	All	Device Related Mild	Device Related Moderate	Protocol Related
Subjects ≥ 1 Adverse Event	104 (100.0%)	103 (99.0%)	1 (1.0%)	1 (1.0%)
Acneiform Flare-up	46 (44.2%)	44 (42.3%)	1 (1.0%)	1 (1.0%)
Dryness	19 (18.3%)	19 (18.3%)	0 (0.0%)	0 (0.0%)
Edema	102 (98.1%)	102 (98.1%)	0 (0.0%)	0 (0.0%)
Erythema	104 (100.0%)	104 (100.0%)	0 (0.0%)	0 (0.0%)
Itchiness	2 (1.9%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
Oiliness	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Prolonged Erythema	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Skin Sensitivity	2 (1.9%)	2 (1.9%)	0 (0.0%)	0 (0.0%)
Subject Assessment Per-Protocol				
My skin looks better		4-Week FU	12-Week FU	26-Week FU
Agree		70 (78.7%)	78 (87.6%)	63 (79.7%)
Disagree		19 (21.3%)	11 (12.4%)	16 (20.3%)
My skin is smoother				
Agree		70 (78.7%)	76 (85.4%)	65 (82.3%)
Disagree		19 (21.3%)	13 (14.6%)	14 (17.7%)

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FIGURE LEGENDS

Figures 1 and 2 – Clinical photos of a male patient (skin type II) taken at baseline pre-treatment (left) and at 26 weeks follow-up post final treatment (right).

Figures 3 and 4 – Clinical photos of a female patient (skin type VI) taken at baseline pre-treatment (left) and at 26 weeks follow-up post final treatment (right).

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Title:

Picture-based Acne Lesion Counts: A Validation Study to Assess Accuracy & Reliability of Acne Lesion Counts Via Photography

Running Title:

Acne Lesion Count Validation

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Conflict of Interest:

Dr. Michael Gold is a consultant and performs clinical research for Cutera, Inc. Dr. Ashish Bhatia is on the Medical Advisory Board, is a consultant and performs clinical research for Cutera, Inc. Authors Arshdeep Kaur, Margot Doucette, and Amogh Kothare are employees of Cutera, Inc.

Ethical Statement:

This validation study was approved by IntegReview IRB on Nov 13, 2020. The study was conducted in accordance with IRB and federal regulations as well as ICH-GCP requirements. The collection and evaluation of all protected patient health information was performed in a HIPAA compliant manner. General Study Informed Consent and Photo Informed Consent was obtained prior to performing study procedures and taking photos. Permission for publication was also ascertained during the informed consent process.

Statement of Contribution:

Conceptualization and design: A.K., M.D., A.K.; study completion: A.K., M.D., A.K.; data analysis: A.K., M.D., A.K.; writing – original draft: M.G., A.B., A.K. and A.K.; writing – review and editing: M.G., A.B., and A.K.; final review and approval of the manuscript: M.G., A.B., A.K., M.D., and A.K.

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ABSTRACT

Background: Acne lesion counting (ALC) is widely used to evaluate efficacy of new acne treatments. Although such evaluations are precise and highly discriminative, if assessed live, it can be a time-consuming and intrusive measurement. Photographic assessment is a viable mode for ALCs and for training and/or qualifying evaluators.

Aims: The purpose of this study was to validate photographic methods for performing ALCs and to provide an objective measurement tool to train and/or qualify lesion count evaluators for deployment in both small and large-scale investigational studies.

Patients/Methods: Assess accuracy and reliability of acne lesion counting via photographic methods in 8 subjects aged 16 to 40 years, with Fitzpatrick Skin Types I to VI. Frontal and 45°angle images taken at the single in-clinic visit. Each subject underwent 3 counts per 4 evaluators: 1 set of live counts and 2 sets of photo counts. Intra-evaluator and inter-evaluator reliability measures for photo counts were evaluated using calculations of intraclass correlation coefficients (ICCs).

Results: Eight subjects (2 male, 6 female), ages between 16 to 40 (min 16-years, max 25-years) diagnosed with facial acne vulgaris participated in the study. Fitzpatrick Skin Types ranged from III to V (three Type-III, four Type-IV, and one Type-V). ICC values for intra-evaluator reliability were found to be > 0.95 for each evaluator and ICC for inter-evaluator reliability was found to be 0.98.

Conclusions: Photographic lesion count methodology is a reliable and accurate tool for objective measurement of ALCs and additionally, for training and/or qualifying evaluators.

Key Words: Acne Vulgaris, Acne Lesion Counts, Inflammatory Acne Lesion, Photographic Acne Lesion Counts, Photographic Acne Assessment, Acne Lesion Count Measurement Tool

INTRODUCTION:

Historically, lesion counting has been a powerful tool in acne assessments due to its reliance in objective assessments of individually categorized acne lesion types. The qualitative grading and

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assessment of acne lesions is vital for routine clinical care and clinical trials. Acne lesion counting (ALC), which involves tallying different lesion types at the individual level, has been used widely in the evaluation of new acne treatments and modalities. Although lesion counting is a precise, objective, and highly discriminative measurement, it is also time-consuming and, if assessed live at a clinic, can be intrusive for the patient due to the assessor palpating the skin.[1] Lesion counting requires specialist knowledge plus comprehensive training and is dependent on variables such as office lighting, the assessor's visual capacity, available visual assessment aids, and the patient's underlying skin quality.[1]

Additionally, ALC is reliant on assessor reliability, synonymous with consistency, under both clinical and research specific settings. Accounting for reliability when evaluating acne and measurement tools for ALCs is vital for treatment success. Failure to show such measures of reliability, can result in assessments which are inept at answering the diagnostic or research specific questions at hand. Intra-rater reliability (agreement between lesion counts performed by the same evaluator over time) tends to be high with experienced, trained lesion count evaluators; however, inter-rater reliability (agreement between lesion counts performed by different evaluators) tends to have more variability.[2] Although lesion counting via palpation methods provides consistency within a clinical scenario, its instrument reliability (extent to which an instrument or measurement tool consistently represents the data specifics) is a method that needs to be further assessed from a research scenario. Furthermore, for single arm studies, concerns over how to adequately blind assessors performing live acne lesion counts while emphasizing reliability have also been voiced.

To address the topics mentioned above, there is a focus on ALCs using a photographic measurement tool for this study. Photography is an objective and usable technique for measuring acne and a valuable technique for both training and qualifying graders.[3] Using photographic methods allows for images to be randomized and for labels to be masked prior to counts taking place, such that each evaluator is blind to the study timepoint being assessed. Conducting photo ALCs further allows for counts to occur under remote, flexible conditions (i.e., when evaluators are not available at all sites, amidst pandemic / pandemic-like conditions such as Covid-19, etc.). It presents an opportunity for an assigned number of evaluators for a clinical study to independently perform acne lesion counts on all subjects. This is in lieu of having one evaluator at each individual study site performing counts for each subset of subjects.

The limited number of lengthy office-based visits required is particularly attractive to patients who already have difficulty complying from a timing stand-point and / or during pandemic / pandemic-like scenarios. Photo ALCs allow for patients to bypass long visits by simply posing for standardized images that can be assessed at a later time point. This is especially important for clinical studies within which particular study visits are extensive and can take a couple of hours to complete. This measurement technique may be most supportive of patients who have moderate to severe acne, the facial severity grading classifications generally used to categorize higher number of acne lesions globally.

Some drawbacks of this approach as noted in past literature, include (1) photographic methods not allowing palpation to ascertain lesion depth, (2) small lesions being difficult to visualize

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when viewing photographically, and (3) difficulty standardizing photographs (i.e., difficulty maintaining constant lighting, distance between the patient and camera, and photo development procedure). [3-5] However, photographic advancements, have been shown to improve accuracy of assessment by solving problems with standardized settings, clarity, sharpness, and depth visualization. [5] Having set photographic standardization methods further aids in qualitative and quantitative consistency across sessions and individual counters.[3]

Keeping the advancement of digital technology in mind, this study was designed to validate photographic methods for performing acne lesion counts through demonstrating (1) accuracy between live and photographic ALCs and (2) inter- and intra-evaluator agreement of the ALCs based on blinded photographic review. Validation results will further act as an objective measurement to train and/or qualify lesion count evaluators for deployment in large-scale studies and/or evaluations.

MATERIALS AND METHODS:

Study Population & Study Design

Eight subjects with Fitzpatrick Scores ranging from III to V who presented with facial acne attended one visit at the single study site. Every attempt was made to include a variety of inflammatory (papules, pustules, and nodules) and non-inflammatory (open/closed comedones) acne lesion types as well as a variety of Fitzpatrick Skin Types within the study population. General study informed consent and photo informed consent was obtained prior to performing study procedures and taking photos.

Once enrolled, during the on-site visit, standardized facial photographs were taken of each subject from frontal, 45-degree and 90-degree angles within a standardized photography room. After photos were taken, standardized live acne lesion counts were performed and documented by four trained acne lesion count evaluators in succession. The four evaluators were chosen based on their extensive experience performing acne lesion counts in clinical, research and / or other professional settings. Each of the four evaluators underwent a comprehensive lesion count training session that focused on live and photographic lesion assessments prior to the live counts being conducted.

Photographs taken during the on-site visit were used to create a validation set of images on which the photographic acne lesion counts were performed using a software interface that allowed for real-time, manual tallying of each acne lesion type. A few days following this visit, the same evaluators who performed the live lesion counts performed independent photographic lesion counts according to standardized Photographic Lesion Count Assessment procedures using the validation set of images.

Study Standardization & Training - Acne Lesion Nomenclature & Definitions

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For the purposes of standardizing nomenclature and definitions, the different active (primary) acne lesion types were categorized as inflammatory (papules, pustules, nodules) and non-inflammatory (open/closed comedones) lesions. Within the two categories, each of the lesion subcategories received a detailed definition. Papules were defined as an erythematous, raised lesion less than 5 mm in diameter. Pustules were defined as erythematous, raised lesion containing white exudate or pus, less than 5 mm in diameter. Nodules were defined as deep-seated, erythematous lesions greater than or equal to 5 mm in diameter. Open comedones were defined as widely dilated sebaceous follicle plugged with darkly pigmented sebum and close comedones as small, closed sebaceous follicle distended with sebum, having a skin colored-appearance.

Study Standardization & Training - Acne Lesion Counting

All lesion count evaluators completed a comprehensive training via Digital Science Technologies LLC (Washington Crossing, PA, USA), a professional training and patient education company specializing in dermatology, to perform standardized live and photographic acne lesion counts. Training objectives included understanding and retaining definitions of the different acne lesion types, identifying methods to distinguish active versus healing acne lesions, and defining facial boundaries for the lesion count area.

During the training, lesion count evaluators reviewed and standardized a method of counting that would be applicable to both the live and photographic assessments. To note, standardization took into account, evaluator-specific elements subject to variability for not just this study but general research practice, including differences in height, vision, and other intrinsic attributes of the individual that may impact the assessment results. Evaluators were warned about counting fatigue and errors that can arise when counting in large numbers or recalling facial areas that have already been counted.[6, 7] Training emphasized counting lesions by choosing a count-clockwise or counter-clockwise 360-degree sweep around the face and dividing the face into segments to help reduce human error. Instructions were provided to not include lesions on the ears, neck, eyelids, nose and on the borders of the lips, jaw, and eyebrows. The angle of the mandible was used to define the inferior border of the face and the hairline was used to define the superior angle of the face. Acne scarring, Fitzpatrick Skin type categories, tanning, excoriation, lesion morphology, pigmentary effects, dryness, residual erythema, and edema are a few of the in-depth concepts targeted for review and conversation in order to ensure assessment consensus amongst all four evaluators.[8] In addition, training reviewed effects of inconsistent lighting, photo angles and their effects, facial/body positioning, and neutral facial appearance.

After the interactive training modules were completed, all evaluators were asked to complete and pass an 18-question multiple-choice quiz independently. A passing score of 80% or higher was required to ensure adequate understanding of the training topics prior to live and photographic lesion counts.

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Study Standardization & Training - Lesion Count Software

After the multiple-choice test, the evaluators also completed training using the real-time tallying open-source software, DDG or DotDotGoose (Developed by Center of Biodiversity and Conservation, American Museum of Natural History, New York, NY, USA).[9] A set of mock photos, excluding patients within this validation study, were set up on the lesion counting software for the training. The computer set-up that would be used during study along with the standardization requirements for counting were mimicked for this mock session. The evaluators were instructed on the key features of the software (i.e., onscreen 5mm ruler, zoom features, lesion category selection), what the maximum and minimum magnification levels were, and how to use the software to count each lesion category separately, one at a time. The mock photographic review session contained images that portrayed the in-depth topics evaluated during the multiple-choice test (i.e., scarring, dryness, excoriation, etc.). This mock software session was completed to ensure the nomenclature, definitions and insights from the trainings were retained and understood.

Study Standardization & Training - Facial Photography

To ensure there are no variations introduced by the photographic process itself and there is continuity plus reproducibility, during the on-site visit, standardized facial photographs of the left and right sides of the face were taken for each subject by one trained photographer.[10] Subjects were asked to maintain a neutral facial expression for photos, such that all facial muscles are relaxed with no animation. Front facing, left and right 45-degree oblique angles, plus left and right 90-degree oblique angles were taken in order to create a validation set of photographs on which photographic ALCs were performed by the four evaluators. The same high-resolution camera (Cannon EOS Rebel T7 set to Manual Capture mode), zoom lens (Canon EF-S 18-55 mm f / 3.5-5.6 IS II Standard Zoom), and external flash system (Neewer External Ring Flash) was used for all subjects. To maximize sharpness by depth of field, the camera lens was positioned parallel to the face, maximally zoomed in, while the photographer stood directly behind the stationary tripod housing the camera. Prior to every image, the shutter was manually depressed halfway in order to focus on the acne lesion prior to capturing the image at each of the angles. Multiple images of each angle were taken to ensure focused, high-quality images with the full face are obtained for photographic lesion counts. Camera settings used per subject were recorded, ISO values (range 100 to 6400) being the only setting that could be adjusted based on Fitzpatrick Skin Types while aperture (f/20) and shutter speed (1/20 sec.) was kept the same per subject.

All subject images were taken using a black background, in the same room, under the same lighting conditions, and without any disrupting office traffic. To assure consistent camera-to-subject distance, a floor foot-grid and wall stickers were used to mark the angles of interest (i.e., frontal plus left and right 45-degrees and 90-degrees) and a stationary tripod was used to fix the point-and-shoot camera in place.[10] Subject were directed to move from one angle to the next. The foot-grid provided the lines a subject needed to match their feet up to for particular angles.

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This further helped prevent variability in camera positioning with respect to the subject and lighting. Prior to images, make-up, skin-care, jewelry, clothing or hair that might obscure the area of interest were washed, removed, or pulled back.[10] For standardized subject positioning, all subjects were directed to place their feet flat on the floor, sit up straight, place their hands flat on their lap, relax the neck, and stare directly into the camera prior to closing the eyes for images.

The photographic review was completed on high-resolution Dell computer monitors (Model: High Resolution Ultrasharp 24 Monitor U2419H). Each evaluator was provided the exact same workstation for the lesion counts, including the keyboard and wired mouse. Lighting and display-aspect settings were standardized across all monitors and checked prior to the start of each lesion count session. All four evaluators counted lesions separately on their own workstations.

All subject images on which the counts were tallied, were loaded into the lesion count software by a proctor. DotDotGoose was then used for real-time tallying of individual photographic lesion count data. For each counting session, scoring took place in an environment free from outside influence and distraction. No persons other than the evaluator and the proctor were present for the counts. Each subject image set (left and right facial sides) was randomized using a computer-generated randomization list. Each subject image set was assigned a numerical value as the identification code to ensure all details regarding the subject remained confidential during both live and photographic assessments.

Study Assessments During Live and Photographic Counts

During live counts at the onsite visit, evaluators individually counted all active facial acne lesions in the presence of a proctor. Prior to counts, the four evaluators were reminded to keep the review from the standardization lesion count training in mind during assessment. Evaluators used routine eyewear only and utilized the same counting methodology, subject position, room, lighting, and evaluator-to-subject distance.

First of the two photographic lesion count sessions followed approximately 2.5 weeks after the live counts were completed (Figure 1). Prior to each photographic counting session, the 45-degree left and right sided images were paired together for each subject. This allowed for evaluators to view the left and right side of the face at the same time within the counting software. All subject image sets were randomized, and all labels were masked. To ensure the same lesion was not counted more than once, a midline from the hairline to the chin was drawn to create a boundary for clear left and right facial side distinction. The frontal view and 90-degree angle images of the left and right sides of the face were provided for reference only, as needed. For each image set, counts were recorded prior to the evaluator moving onto the next image set. After a count was made, the evaluator could not change his or her previously made count. At no point during the study did the evaluators have access to their previous counts. The study proctor gathered all tallies individually for each evaluator and subject image set.

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STATISTICAL ANALYSIS:

SAS JMP v16.1 was used to perform the analyses.

Live counts were compared to photographic counts by using the average of each subject's two photo counts and comparing them to their corresponding live counts to derive the Subject Count Percent Deviation. A separate Subject Count Percent Deviation is calculated for each subject-evaluator combination, resulting in a total of 32 Subject Count Percent Deviation results (8 subjects x 4 evaluators). An evaluator's accuracy is the average of the individual Subject Count Percent Deviation results for that evaluator.

The intraclass correlation coefficient (ICC) was used to evaluate the reliability. ICC values closer to 1 indicating good reliability whereas values closer to 0 indicating poor reliability.[6, 11] Intra-Evaluator (with-in counter) ICC was calculated as the ratio of the variance between subjects to the total variance based on the Evaluator's Photo Counts. Inter-Evaluator (between counter) was assessed via the same methodology, by calculating the ICC for the Photo Counts from all Evaluators combined. The Analysis of Variance (ANOVA), with Day, Week, and Subject as terms in the model as applicable, was used to estimate the variances used in the calculations of ICC for each Evaluator and calculations of Overall ICC.[6, 11] The validity of the model fit to the data was assessed before calculating ICC.

Measurement System Analysis (MSA) was completed to assess quality and integrity of the Inflammatory Lesion Counts derived from photographic assessments across all four evaluators. Average (X-bar) and Range Control Charts (R-charts) are used to evaluate and depict repeatability, stability, and reproducibility of the measurement system (photo lesion counts) and of the complete process of obtaining measurements.

RESULTS:

Of the 8 subjects (6 male and 2 female) who were initially consented and enrolled (Table 1), all completed the single site, on-site clinic visit, which included multi-angle photography and the live lesion count assessment portions of the study (n=0 withdrawals). Ages of the subjects ranged from 16 to 25 years (average 18.9 ± 3.0). There were 5 (62.5%) subjects who identified as white and 3 (37.5%) as Asian, of which 7 (87.5%) are not Hispanic/Latino and 1 (12.5%) is Hispanic/Latino. Fitzpatrick skin types included 3 subjects (37.5%) being Type-III, 4 (50.0%) being Type-IV, and 1 (12.5%) being Type-V. All subjects enrolled had a medical history of acne vulgaris.

Within the live and photographic count comparison, results show non-inflammatory acne lesions provided the most variance in counts amongst evaluators and subjects, while papules, pustules and nodules were the most aligned. Figure 2 presents the total live and photo-based lesion counts by subject and evaluator. Inflammatory lesions are represented separately while open and closed comedones are represented as combined within the non-inflammatory umbrella term for Figure

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2. There is one dot per evaluator for the live counts, while there are two dots per evaluator for the photographic counts. The two dots represent the first and second photographic lesion count sessions. The solid line within the two dots represents the average of the two photo count sessions. When comparing the two photo count sessions, it is seen that counts in Photo Session 2 were consistent and similar to the count ranges of Photo Session 1 for inflammatory acne lesions, variability increased when counting open and closed comedones. This trend was consistent amongst all four evaluators. Comparison of average photo counts versus live counts further depicts non-inflammatory lesions being the most inconsistent but papules, pustules and nodules showing the most reliability across evaluators. Overall, visual comparison of the two graphs in Figure 2 show that photo counts are more precise and repeatable across the four evaluators, whereas during the live session, Evaluator #2 was tallying less lesions for multiple subjects compared to the other three evaluators.

Subject Count Percent Deviation results for each evaluator and lesion type (Figure 3) shows accuracy when comparing live counts versus average photo counts. For each subject, the average of the two photo counts compared to the corresponding live count shows only a slight Percent Deviation. Since the inflammatory lesion counts are comprised of nodules, papules, and pustules, any over- and under- counting contributing to the deviation seen is counterbalanced. Additionally, although non-inflammatory have the most variability when reviewing Figure 2, the Percent Deviation by counter (Figure 3) shows overall accuracy when evaluators had to identify the open and closed comedones from inflammatory acne.

Figure 4 summarizes the Subject Count Percent Deviation for Inflammatory Lesion Counts made by each evaluator. Of the four counters, three were consistent when assessing the overall total count of all papules, pustules, and nodules. Evaluators #1, #3, and #4 are consistent in their Inflammatory Lesion Counts when counting lesions live and when counting lesions using photos. However, Evaluator #2 tended to overcount pustules and papules on photos than when counting live, resulting in their Inflammatory Lesion Photo Counts being higher than when counted live.

For all eight subjects, under test re-test conditions, when assessing Photographic Inflammatory Lesion Counts intra-evaluator reliability and inter-evaluator reliability was found to be greater than 0.95 for each of the four evaluators and 0.98 overall (Table 2). The high Overall ICC measure for all evaluators combined (0.98) shows the evaluators closely resemble each other when counting inflammatory lesions photographically. The high Evaluator ICC for each of the four evaluators (> 0.95 per) shows each evaluator is consistent with their own counts when counting Inflammatory Lesion Counts photographically. Interpretation of the ICC was measured based on commonly referenced statistical reliability standards. Such that, ICC values approximating below 0.75 indicated poor or moderate reliability and were deemed unacceptable for this study. Coefficient values above 0.75, but less than 0.90, indicated good reliability while values approximating 0.90 to 1.0 indicated excellent reliability.[6]

The Measurement System Analysis (MSA) graphs in Figure 5 illustrate the average data and average range (or spread) of data for photographic measurements in order to assess variability

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and quality aspects. The Range Control Chart (R-control) depicts there is normal deviation within the Upper (UCL) and Lower Control Limits (LCL). It shows the measurement tool (photographic assessment) is operating within control and there are no statistical points that are out of control or problematic – no points are above or below the Range UCL and Range LCL, respectively. The R-chart provides evidence that supports the data within the Average Control Chart (X-bar). On average, each evaluator is shown to measure in the same manner across subjects and each evaluator is also counting lesions in the same manner as other evaluators. Although Evaluator #2 tended to overcount papules and pustules when counting photographically as compared to live, the X-bar demonstrates that the consistency of Evaluator #2's photo counts closely resemble the consistency of the photo counts made by other evaluators when counting inflammatory lesions photographically.

DISCUSSION:

Clinical photographs are invaluable tools in helping document the progression of a disease or response to treatment over time. The ability to reliably assess photographs of acne is a significant advantage to the lesion counting method. In this study, validation was accomplished by demonstrating accuracy between live and photographic lesion counts for eight subjects along with demonstrating reliability in inter- and intra-evaluator agreement of the lesion counts based on standardized, blinded photographic review. The study represents a critical appraisal of a standardized photographic acne lesion count methodology (at times referred to as "instrument of measurement" or "measurement tool") that can be used across the board for diverse acne and non-acne eligibility criteria and study designs, while supporting quality driven data.

Sample Size:

Regarding sample size approximation, determination of the ICC does not always require a large sample size, particularly if the objective is to ascertain a high level of agreement with a large ICC value. The minimum sample size will not differ too greatly if the total number of observations made by each evaluator is large (i.e., multiple acne lesion counts available per subject for data analysis). [12] ICC methodology studies have shown that as the total number of observations made by each evaluator increase, the minimum sample size required will decrease.[12]

Evaluator Selection:

Photographic review allows future outcome studies and clinical trials to include multiple evaluators to reduce bias and add to the reproducibility, validity, and quality of the results. A total of four evaluators were assigned to the study to boost reliability, although past studies often have used two to three.[3] Purpose of including multiple evaluators plus training each one prior to any lesion counting was to improve agreement within and between evaluators.[6]

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Statistical Considerations:

An ICC value close to 1 indicates high reliability, which refers to the consistency of a measure, in this case, consistency of photographic lesion counts under test re-test conditions. The high ICC values (> 0.95 intra-evaluator reliability, 0.98 inter-evaluator reliability) for this validation delivers excellent reliability (Table 2). Thus, providing evidence to reason that the instrument of measurement used is receptive to the dynamic nature of acne and its defining features along with evaluator differences.

Photographic ALCs are shown to be sensitive to population representativeness (i.e., acne severity gradings, Fitzpatrick Skin Types, ethnicity, gender, age, etc.) and the morphology of acne – features commonly discussed when reviewing what quality criterion needs to be met for more precise clinical review.[1] Similar to live lesion counts, photographic ALCs takes into account non-active acne stages and other skin transformations face. This includes, acne scarring, climate induced skin changes, post-treatment effects, and excoriation. Regardless of the fact that both methods can assess such skin transformations, the naked eye still requires magnification tools for more precise assessments. Even if clinical personnel are able to determine depth and palpate the suspect lesions, the counts during live sessions are more dispersed (Figure 2). Although photographic assessment does not allow for palpation[6], it allows for easy magnification that permits quality visual evaluation of lesion characteristics, including photographic depth evaluation, leading to accurate ALC measurements. This further suggests that photo ALCs can accurately capture differences prior to, during, and after treatments focused on progression of acne or such dermatological indications.

Moreover, the high ICC reliability presents evidence that the need for in-person lesion count assessments is lessened, especially within a clinical research environment (Table 2).[13] Evaluators for this study have shown they are consistent with their own counts as well as when compared to one another for live and average photo ALCs – with the two separately assessed photo counts being more precise and repeatable across counters. Regardless of standardization measures taken during live counts, the variances in lighting (i.e., due to heights of evaluators and subjects) contributed to variances in perception, leading to more spread-out data for this session (Figure 2). With photographic counts, due to the standardized image taking process, same workstation set-up, and same monitor brightness, ALCs via photographic assessments lends itself to more consistency (Figure 2).

ICC and MSA statistics combined help justify the claim that photographic acne counts approach is a validated method to distinctly identify lesion types of varying sizes, shapes, and characteristics across standardized evaluators. The X-bar and R-charts (Figure 5) depict measurement system agreement (photo count agreement) and consistency across the four evaluators for all subjects. Although all measurement systems are subject to variation, the type of variation is dependent on how data falls within the upper and lower limits – which can be due to random chance variation or assignable variation. Since all of the data points in the R-chart within Figure 5 are in control – not above the upper limits or below the lower limits – any variation that

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is seen within photo counts is due to chance, which is an inherent form of variation in most measurement tools and devices. The control limits for the X-bar are assessed based on the R-chart. Since data points from the R-chart are in control, X-bar can be interpreted to depict photographic lesion counting as a validated measurement tool. Although there are four data points on the X-bar for each evaluator that are outside of the UCL and LCL, they are not irregularities. They are simply high lesion counts which are attributed to varying acne severities of the subjects enrolled within the study. Overall, the X-bar shows the photo counts for the four evaluators are consistent, repeatable, and reproducible across all subjects when counting inflammatory acne lesions.

Lesion counting has constantly proven to be a sensitive indicator of acne progression and severity because it distinguishes small differences in therapeutic response and allows for singularized assessment of each lesion classification.[11] Subject inflammatory count percent deviation (Figure 4) results show Evaluator #2 is overcounting papules and pustules during photo ALCs. This can be attributed to higher visibility, increased time of assessment, set lighting on monitors, and/or standardized point-and-shoot methodology, all of which present practical and viable reasons for counting higher number of lesions photographically versus live.

This level of sensitivity in ALCs can be useful when attempting to understand the evolution of treatment effect on individual lesions and acne morphogenesis over the course of a treatment regimen. Although counting individual lesions is time consuming, one of the primary take aways is that more exact delineations are being made by evaluators photographically (Figure 3 and 4). This in turn, leads to more efficacious results within clinical trials and an overall consensus which increases validity when using photographic lesion assessments.

Lesion Count Standardization:

In order to objectively evaluate the lesions of interest and validate a photographic method of lesion counting, it is imperative that images are both comparable and standardized in order to enhance the visual field of the evaluators. Shadows, camera lighting, lesion shape, lesion surroundings, and lesion coloration are just some of the visual patterns used along with standardized screen magnification rules for stationary images. Such factors help facilitate fine-tuned monitoring of acne and potentially other dermatological conditions across short-term and long-term clinical / study durations using photo counts. The data from this study, supports the conclusion that when compared to live lesion counts, photographic lesion counting is a valid, quantifiable measurement tool which will further enhance the rigor of trials using a photographic end-point.

CONCLUSIONS:

The methods outlined within this validation study are practical, robust, and reproducible. To note, strengths of the described photographic methodology include the standardization aspects plus all captured images being uniform and interpretable by blinded lesion count evaluators.

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Despite the use of a standardized protocol, occasional human errors did occur as shown with the minor, but assumed discrepancies between the four evaluators. Special attention was paid to the standardization of camera equipment and photography technique for precise measurements and consistency in counts within evaluators. However, variables to take into account, which may or may not have impacted the results, are evaluator-specific attributes – such as height and vision of the individual. Such intrinsic factors may impact the results in an unforeseen manner, regardless of standardization.

A constraint when using digital images for endpoint evaluation is the inability of assessors to make clinical decisions using the supplementary senses of hearing (i.e., patient feedback) and contact when provided only with the image. Regardless, scenarios where specialized acne or other dermatological lesion evaluators are not readily available or amidst pandemic-like situations, standardized digital photography of patients can easily be used to allow trained evaluators to manage patient portfolios in remote locations.

Although live counts were completed at one clinic for this study, photographic lesion counts were completed independently by four evaluators using the same computer, lighting, software set-up in different offices. It is proposed for future iterations, multiple evaluators within various settings (including remote) provide photographical lesion counts for assessment and further statistical reliability check.

Future trials may benefit from adopting this protocol within a greater patient population, in multiple locations to further test validity and replicate the consistency of the findings. The larger sampling of subjects may also add to significance of the photographical lesion count design across multiple dermatological indications that require capturing high quality digital images for study end-points.

With the advancement of photography in mind, this study has validated a photographic method for accurately performing acne lesion counts. Validation results support the photographic method as an objective measurement providing results comparable to those obtained from traditional live lesion counts. It has shown to be a valuable tool to have in hand for training and/or qualifying lesion count evaluators for deployment in future studies and/or evaluations – such as those using device modalities which target mild, moderate, and severe acne severities.

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Table 1: Subject Demographics

VARIABLE		**(N = 8)**
Age (years)		*Standard Deviation
	Mean ± SD*	18.9 ± 2.997*
	Median (P25, P75)	18.5 (16.25, 20.50)
	Min, Max	16, 25
Gender		
	Female	2 (25%)
	Male	6 (75%)
Race		
	White	5 (62.5%)
	Black/African American	0 (0%)
	Asian	3 (37.5%)
	American Indian/ Alaskan Native	0 (0%)
	Native Hawaiian/Other Pacific Islander	0 (0%)
Ethnicity		
	Hispanic/Latino	1 (12.5%)
	Not Hispanic/Latino	7 (87.5%)
Fitzpatrick Skin Type		
	Skin Type - I	0 (0%)
	Skin Type - II	0 (0%)
	Skin Type - III	3 (37.5%)
	Skin Type - IV	4 (50.0%)

	Skin Type - V	1 (12.5%)
	Skin Type - VI	0 (0%)

Table 1 Description: The table lists a comprehensive summary of the subject demographics collected at the Screening/Baseline visit.

Table 2: Photographic Lesion Counts ICC

Acne Lesion Photo Counts Intraclass Correlation Coefficients (ICC)		
	ICC Value	**Reliability Interpretation of ICC**
Overall ICC (all lesion count evaluators)	0.9778	> 0.90 indicates excellent reliability
Evaluator 1 ICC	0.9978	
Evaluator 2 ICC	0.9734	
Evaluator 3 ICC	0.9772	
Evaluator 4 ICC	0.9502	

Table 2 Description: ICC values approximating < 0.75 indicated poor or moderate reliability. Coefficient values above 0.75 to 0.90 indicated good reliability while values > 0.90 indicated excellent reliability. Excellent reliability is seen depicted in this table for Overall ICC and individual Evaluator ICC values.

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Figure 1: Study Flow Diagram

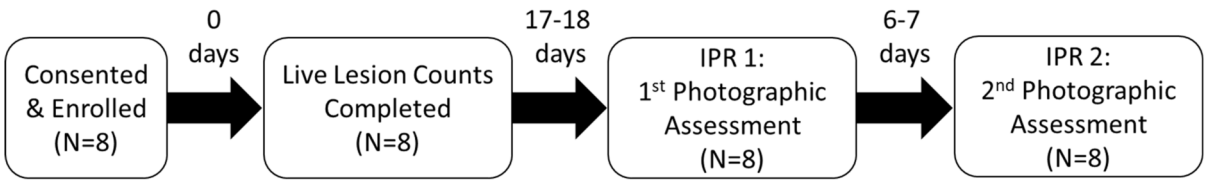


Figure 1 Description: The flow diagram shows the disposition of subjects throughout the multiple phases of the study. The first two boxes represent tasks completed at the single, on-site clinic visit while the latter two boxes represent the photographic assessments completed on dates separate from the on-site clinic visit (each visit was proctored).

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Figure 2: Lesion Counts by Subject and Evaluator Per Lesion Type

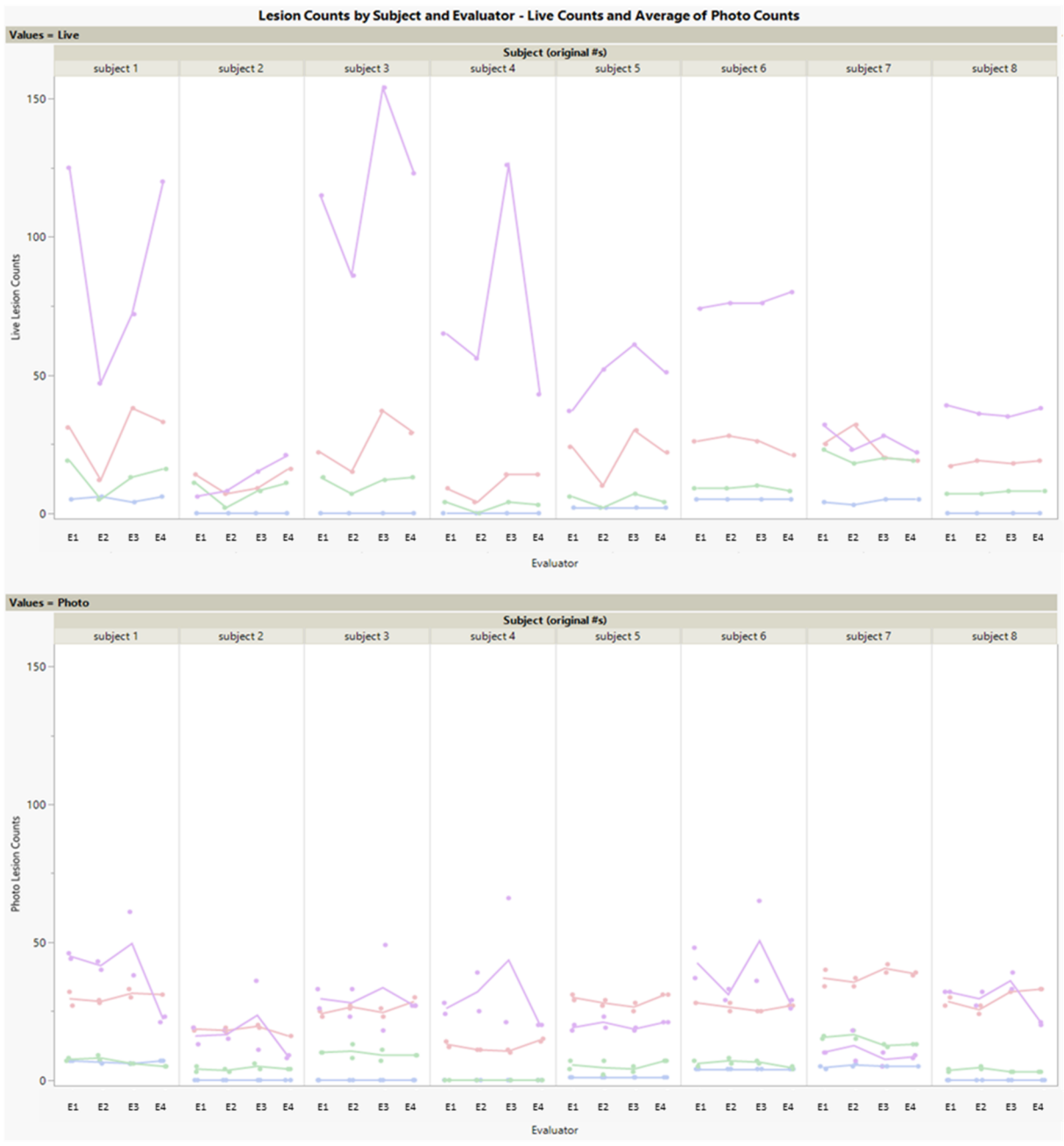


Figure 2 description: (E stands for "Evaluator") Figure depicts the live counts versus the average of the two photo counts sessions. Top graph represents the live counts, and the bottom graph represents the average of the two photo counts. Figure color key for Type of Acne Lesion is as follows: — Nodules; — Papules; — Pustules; — Non-Inflammatory.

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Figure 3: Subject Count Percent Deviation by Counter and Type of Lesion

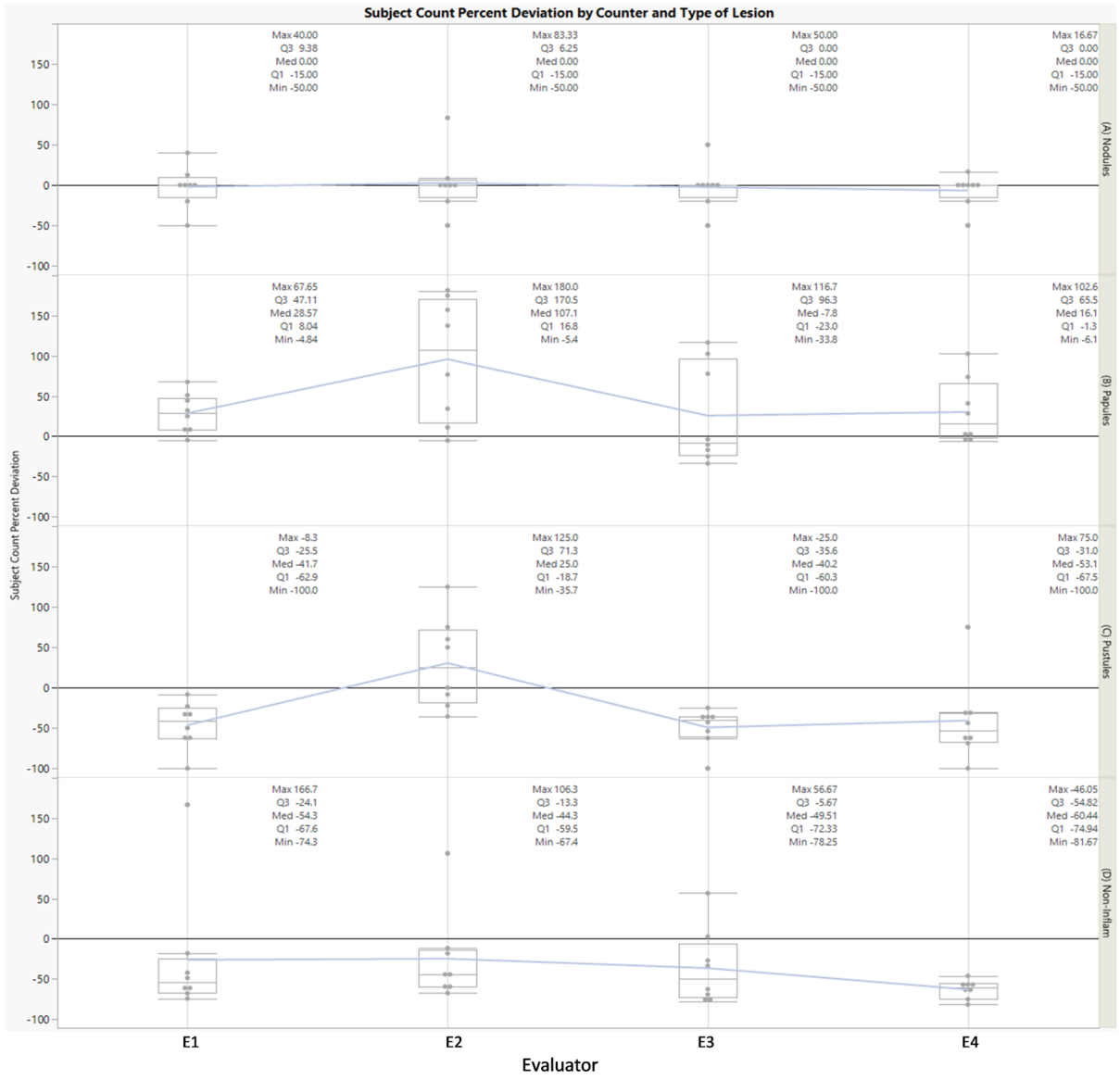


Figure 3 Description: (E stands for "Evaluator") Subject Count Percent Deviation is one hundred times the difference of the average photo count minus live counts, divided by live count. The average of each subject's two photographic lesion counts was compared to their corresponding live count. Figure color and symbol key are as follows: ⊡ Data; ● Data; ▬ Mean.

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Figure 4: Subject Inflammatory Count Percent Deviation

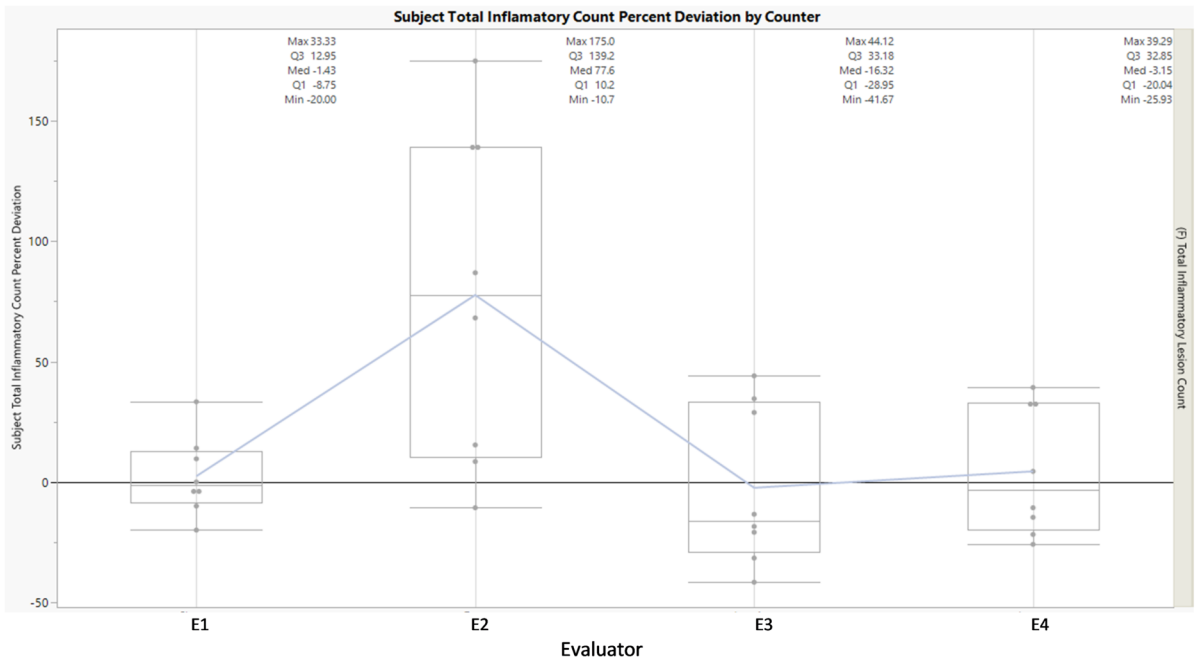


Figure 4 Description: Evaluators (E) #1, #3, and #4 are consistent in inflammatory lesion counts when counting live and photographically. Evaluator #2 overcounted pustules and papules during photo counts, resulting in their photo counts to be higher than when counted live. Figure color and symbol key are as follows: ⊡ Data; ● Data; ▬ Mean.

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Figure 5: Measurement Systems Analysis for Inflammatory Lesion Photo Data

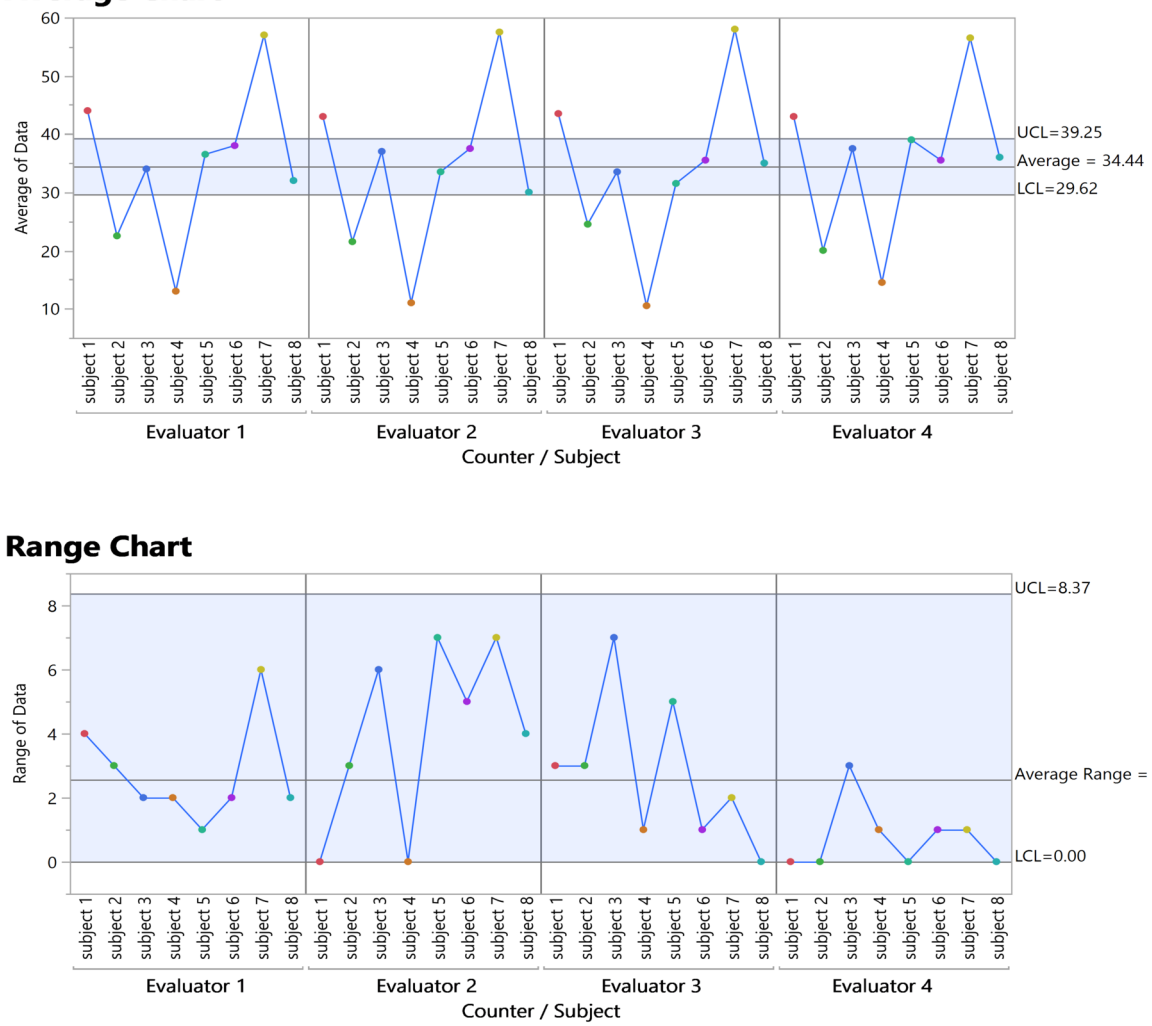


Figure 5 Description: The Average Control Charts (X-bar) and Range Control Charts (R-chart) the MSA depict consistency, repeatability, and reproducibility amongst the four evaluators when assessing photo count values for inflammatory acne lesions.

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ORIGINAL ARTICLE

A novel 1726-nm laser system for safe and effective treatment of acne vulgaris

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Abstract
Selective photothermolysis of the sebaceous glands has the potential to be an effective alternative for treating acne vulgaris. However, the translation of this technique to clinical settings has been hindered by a lack of appropriate energy sources to target sebaceous glands, concerns surrounding safety, and treatment-related discomfort and downtime. In this work, we introduce the first FDA-approved system that combines a 1726-nm laser and efficient contact cooling to treat mild, moderate, and severe acne effectively while ensuring safety and minimal patient discomfort without adjunct pain mitigation techniques. Light transport and bioheat transfer simulations were performed to demonstrate the system's efficacy and selectivity. The resulting thermal damage to the skin and sebaceous glands was modeled using the Arrhenius kinetic model. Numerical simulations demonstrated that combining laser energy and optimal contact cooling could induce a significant temperature increase spatially limited to the sebaceous gland; this results in highly selective targeting and maximum damage to the sebaceous gland while preserving other skin structures. In vivo human facial skin histology results corroborated the simulation results. The studies reported here demonstrate that the presented 1726-nm laser system induces selective photothermolysis of the sebaceous gland, providing a safe and effective method for the treatment of acne vulgaris.

Keywords 1726-nm laser · Sebaceous glands · Acne · Laser acne treatment · Contact cooling

Introduction

Acne is the most common skin condition in the USA, affecting up to 50 million Americans yearly. In addition to discomfort and psychological distress, acne is associated with long-term effects, such as permanent skin scarring and poor self-esteem, ultimately resulting in significant psychosocial impact and lower quality of life [1–4].

Traditional acne treatments follow a well-established approach based on topical and systemic drugs [5]. While drug-based treatments for acne can be effective, they cause significant side effects ranging from skin irritation from topical therapies to teratogenicity and depression associated with systemic drugs like isotretinoin.

Recently, research efforts have been focused on developing effective alternative treatments that eliminate the need for drugs and rely, instead, on energy-based techniques. For example, it has been shown that radiofrequency (RF) devices and infrared light lasers can treat acne by targeting and destroying sebaceous glands, curbing excess sebum production, and, consequently, reducing *C. acnes* proliferation [6]. Infrared devices, such as 1320 and 1450 nm lasers, proved to be effective in treating acne but often caused intense pain and skin damage in treated subjects, a common limitation to some of these treatments [7].

The root cause of such undesirable effects can be identified in the lack of selectivity of those laser devices. Water is the most abundant component of soft biological tissue, and its absorption coefficient becomes significant in the infrared range. As a result, most of the energy delivered into the treatment region is absorbed by the water present in the tissue, causing a non-selective temperature rise that affects all the skin structures indiscriminately. During this process, sebaceous glands eventually become damaged by the increased temperature, but it comes at the price of intense discomfort and collateral skin damage for the patient.

A better strategy would be to selectively deliver light energy to specific target chromophores within the sebaceous gland having a higher absorption coefficient than

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water, resulting in selective damage with minimal alteration of the surrounding tissue. For example, the sebum in the glandular region is a viable endogenous target since it exhibits a narrow local absorption peak higher than water at 1726 nm, with a preferential absorption of 1.8:1 [8, 9], as shown in Fig. 1.

The concept of selective damage of the sebaceous glands is based on the theory of selective photothermolysis introduced in 1983 by Anderson and Parrish [10]. More recently, Sakamoto et al. successfully demonstrated that optical pulses with a wavelength of 1700–1720 nm could be used to destroy sebaceous glands in ex vivo human facial skin samples with minimal injury to other skin structures [11].

However, practical and technological challenges have hindered the application of selective photothermolysis for acne treatment in clinical settings. For this to happen, three primary requirements must be met: effectiveness, safety, and pain control.

A treatment is considered effective in achieving long-lasting acne clearing when a large temperature increase is induced inside the targeted glands for a long enough time, resulting in necrosis of the sebocytes. For this to happen, according to the theory of selective photothermolysis, the optical pulse width must be shorter than the target's thermal relaxation time (TRT), defined as the time required to lose 50% of the accumulated heat after energy is delivered. The mean TRT for human facial sebaceous glands is estimated to be around 60 ms [11]. Therefore, the laser system must be carefully designed to generate a significant and fast temperature rise inside the target, satisfying precise spectral and spatial requirements. First, the optical bandwidth of the laser should be narrow and centered at 1726 nm to match the selectivity peak of the sebum. Second, the beam diameter should be fine-tuned to provide large fluence values — inversely proportional to the squared beam radius — and penetration depth, proportional to the beam diameter [12].

At the same time, ensuring the patient's safety throughout the treatment is paramount. In this context, safety translates into the absence of severe or long-lasting adverse events potentially requiring medical intervention, such as skin burns and blistering, which result in permanent scarring. We have observed that such detrimental side effects can be prevented by keeping the temperature of the dermal–epidermal junction (DEJ) below 50 °C. However, considering that the preferential absorption of sebum is approximately two times higher than water, a substantial portion of the light energy is still absorbed by the epidermis and dermis, potentially resulting in temperature peaks higher than 50 °C. As a result, additional cooling strategies are required to preserve the integrity of the skin and achieve the thermal damage selectivity necessary for a safe treatment.

The third requirement, especially significant in clinical settings, is minimizing the discomfort experienced by patients during treatment. In fact, a patient may be reluctant to undergo or complete a painful session, despite the promises of safety and effectiveness. This consideration is particularly valid for treatments based on thermal ablation or photothermolysis since heat stimulates the pain receptors in the skin. It has been demonstrated that the typical heat pain threshold for skin is between 42 and 45 °C, but it is also affected by the duration of heat exposure [13, 14].

To sum up, the successful application of selective photothermolysis in clinical settings must ensure effectiveness and safety while managing the pain experienced by the patients. These requirements can be satisfied by finely balancing the heating and cooling of the treated skin. In this paper, we introduce a

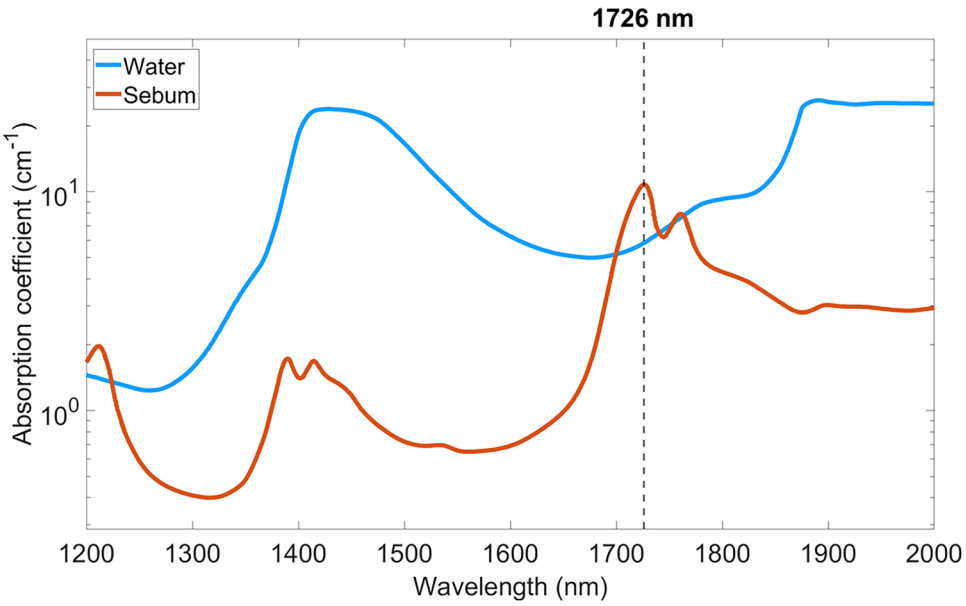


Fig. 1 Measured absorption coefficient (μ_a) of water and sebum in the mid-infrared range [8]

novel system based on a 1726-nm laser, specifically designed to precisely target sebaceous glands. In addition, a highly efficient contact cooling system integrated into the system's handpiece protects the skin from hyperthermia-induced side effects, ensuring safety and pain control throughout the treatment.

Methods

Laser system

The core of the laser system is a fiber-coupled 100-Watt diode laser emitting light at $\lambda = 1726$ nm. Laser pulses (up to 50 ms) are delivered through a custom-designed handpiece, featuring an efficient contact cooling system deploying a sapphire window that is actively cooled between 0 and 5 °C. Compared to other traditional temperature-control alternatives for clinical applications, contact cooling provides faster and more localized heat extraction than convective methods [15] and does not cause cryonecrosis, a side effect sometimes observed with cryogen spray cooling [16]. Furthermore, the skin compression resulting from pressing the sapphire window onto the skin brings deeper targets closer to the output of the handpiece, reducing the physical thickness of the interposed tissue and increasing the fraction of energy reaching buried glands [16].

The main limitation of contact cooling is the perfect-contact requirement of the clear aperture of the sapphire, meaning that optimal heat extraction can be achieved only when the entire sapphire window area is in direct contact with the skin surface. For this reason, contact and pressure sensing technology is embedded on the tip of the system's handpiece to prevent laser-firing unless the sapphire window makes adequate contact and is uniformly pressed onto the skin.

Each treatment session includes multiple applications over the area affected by acne, and each application consists of three phases: pre-cooling, energy delivery accompanied with parallel cooling, and post-cooling. The pre-cooling phase starts when the cooling window is applied to the skin and ends when the laser pulse is fired. This first step is designed to lower the initial temperature of the epidermis, dermis, and DEJ, limiting the temperature rise and preventing collateral thermal damage.

Laser energy is delivered to the pre-cooled area through the sapphire window, which continues to cool the skin surface during energy delivery. The post-cooling phase starts right after the laser pulse is fired and the energy is delivered to the treatment region. This phase lasts long enough to offset the potentially harmful thermal blooming when the heat accumulated inside the gland is quickly released to the surrounding tissue. Moreover, post-cooling contributes to quickly restoring physiological skin temperature, minimizing the duration of pain stimuli.

Numerical modeling

Light transport and heat transfer numerical models were implemented to characterize the operating parameters of the presented system and the resulting thermal damage. Several assumptions were made to reduce the computational cost of such models, detailed in the subsequent sections below. Therefore, the presented results are not intended to be exact but to provide a good understanding of the thermal distribution and damage to the tissue for different combinations of parameters.

Light transport

The fluence resulting from the interaction of the laser beam with skin tissue and the sebaceous gland was modeled using an open-source Monte Carlo light transport simulator (Monte Carlo eXtreme v2020, http://mcx.space). The 3D simulation domain was implemented as a 10 mm × 10 mm × 5 mm homogeneous skin volume with a voxel size of 10 µm × 10 µm × 10 µm. A sebaceous gland, modeled as a simple sphere with a diameter of 0.24 mm, was positioned 0.8 mm deep into the tissue, aligned with the center of a 3-mm wide circular laser beam with a uniform profile (top-hat) incident on the skin surface.

The refractive index and the anisotropy factor of the tissue at the wavelength of 1726 nm were set to $n = 1.363$ and $g = 0.9$, respectively. Absorption coefficients μ_a and scattering coefficients μ_s for skin and human fat used to approximate the optical properties of the sebum are listed in Table 1 [8, 17, 18].

Bioheat transfer

The fluence data obtained from the Monte Carlo simulations were used as an input for a finite element (FE) model (COMSOL Multiphysics 6.0, COMSOL Inc., USA) to estimate the temperature rise within the target tissue.

A schematic view of the simulation domain is reported in Fig. 2, showing the actively cooled sapphire window placed on the top surface of the skin. A 2-layer model that includes epidermal and dermal layers was used to represent the skin,

Table 1 Optical parameters used for the Monte Carlo light transport simulations

Component	Absorption coefficient μa (mm^{-1})	Scattering coefficient μs (mm^{-1})	Anisotropy factor g	Refractive index n
Skin	0.59	8.5	0.9	1.363
Sebaceous gland (fat)	1.062	8.0	0.9	1.363

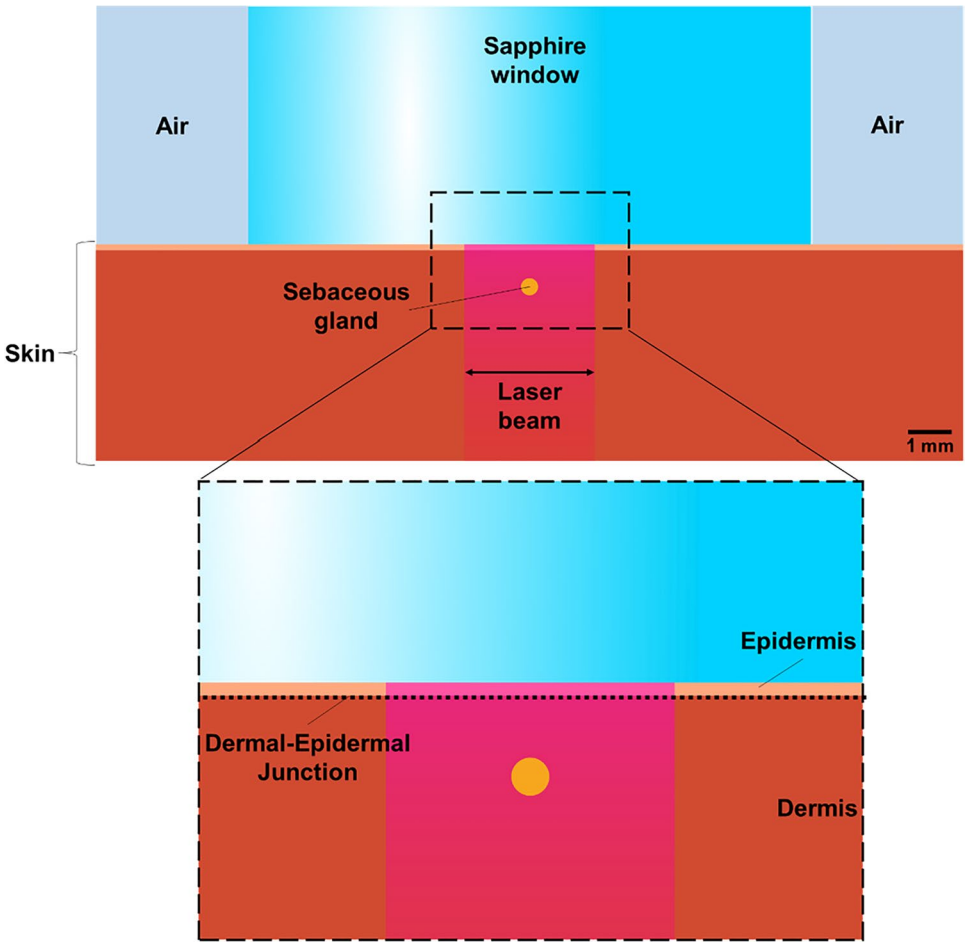


Fig. 2 Schematic representation of the bioheat transfer simulation domain

allowing for tracking the temperature evolution at the dermal–epidermal junction (inset of Fig. 2) is critical to assess the safety of the treatment.

In this model, a single laser pulse was emitted from the center of the sapphire window, traveling through the skin layers and the sebaceous gland, modeled as a sphere of human fat at a depth of 0.8 mm. The thermal parameters used for the simulations are reported in Table 2 [12, 19, 20].

The spatiotemporal temperature distribution within the simulation domain was calculated by numerical solution of the Pennes' bioheat transfer equation.

Table 2 Thermal parameters used for the bioheat transfer numerical simulations

Component	Thermal conductivity k (W/(m·K))	Density ρ (kg/m^3)	Specific heat c_p (J/(kg·K))
Sapphire	23.1	3980	761
Epidermis	0.5	1200	3600
Dermis	0.53	1200	3800
Fat (sebum)	0.21	911	2348

Thermal damage estimation

The traditional Arrhenius kinetic model was used to estimate the thermal tissue damage caused by hyperthermia as a function of heating time and temperature [21]. The dimensionless damage parameter Ω is defined as the logarithm of the ratio of the native tissue concentration before ($C(0)$) and after ($C(\tau)$) the tissue heating, is calculated as:

$$\Omega(\tau) = ln\left(\frac{C(0)}{C(\tau)}\right) = \int_0^\tau Ae^{\left[\frac{-E_a}{RT(t)}\right]}dt \quad (1)$$

where τ is the total heating time, A is the pre-exponential frequency factor, E_a is the activation energy, R is the universal gas constant, and $T(t)$ is the absolute temperature at time t.

Table 3 Arrhenius model parameters used for estimating the thermal damage

Tissue temperature	Frequency factor A (s^{-1})	Activation energy Ea (J/mol)
$T \leq 53$ °C	8.82×10^{94}	6.03×10^5
$T > 53$ °C	1.297×10^{31}	2.04×10^5

The Arrhenius parameters used in our model are reported in Table 3 [21, 22].

Results

Light transport

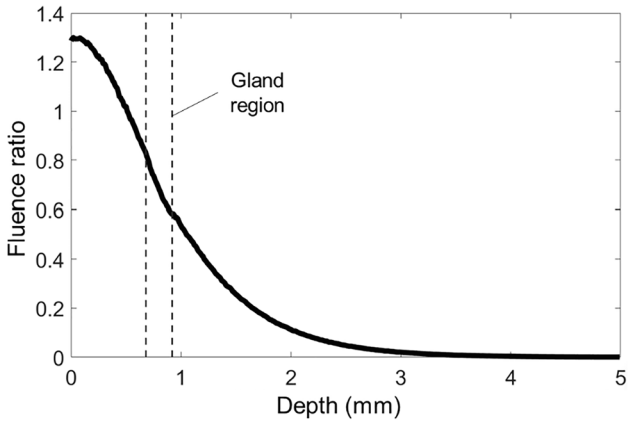


Fig. 3 Simulated fluence ratio versus tissue depth measured at the center of a 3-mm wide laser beam

Monte Carlo simulation results for laser light transport at 1726 nm through the skin were analyzed to estimate the fluence ratio, defined as:

$$F_{ratio}(z) = \frac{F(x,y,z)}{F_0(x,y)} \tag{2}$$

where F_0 represents the initial fluence measured at the output of the handpiece. Figure 3 reports the fluence ratio measured at the center of the laser beam as a function of depth, showing that 60–80% of the initial fluence is delivered to the targeted gland.

Bioheat transfer

Effect of pre-cooling phase

The FE model was used to estimate the effect of the pre-cooling phase, defined as the time between applying the cooling window on the skin and the moment the laser pulse is fired.

The sapphire window temperature in the FE model was set to 2 °C. Domain and boundary thermal probes were added at the dermal–epidermal junction (T_{DEJ}), sebaceous gland (T_G), and the upper region of the dermis (T_D), as schematically shown in Fig. 4a. Such probes were used to measure and track the temporal evolution of average temperatures at these critical locations, as reported in Fig. 4b. The simulation results indicate that the average temperature at the DEJ decays quickly within 0.5 s, which is expected considering the proximity to the cooling system. In contrast, the average temperatures of the dermis and gland present an expected cooling delay since they are farther away from the sapphire window.

The pre-cooling phase must ensure the maximum cooling of the DEJ and dermis to prevent side effects caused by hyperthermia and reduce the perceived pain during the treatment. At the same time, the cooldown of the gland should be minimal to avoid affecting the amount of thermal damage caused by the laser beam.

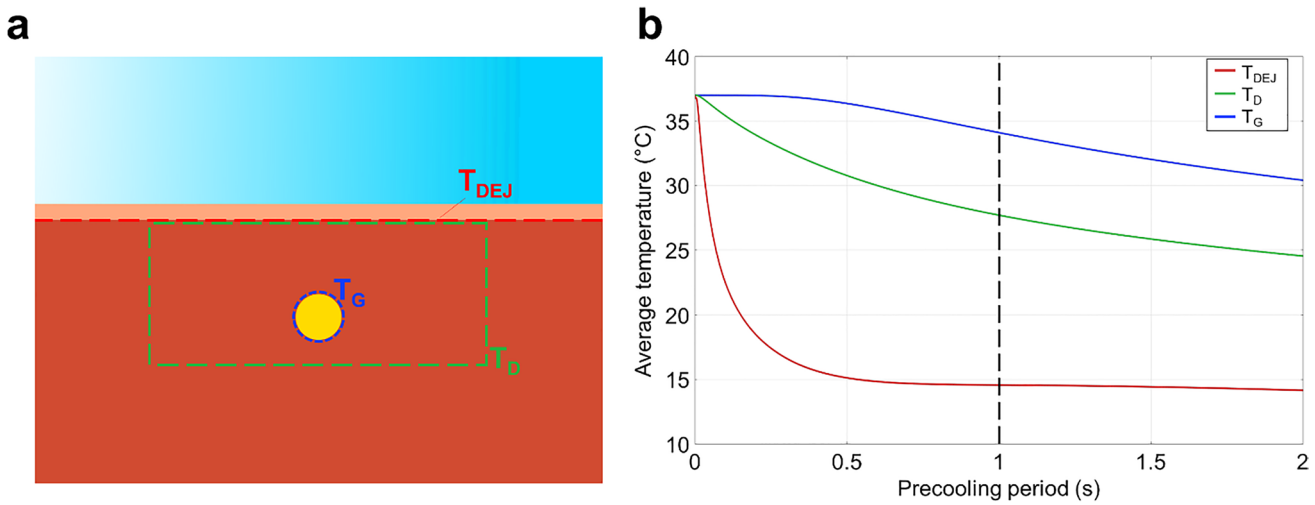


Fig. 4 **a** Schematic illustration of the domain and boundary probes used to track the temperature at the dermal–epidermal junction (T_{DEJ}), inside the gland (T_G), and in the dermal region surrounding it (T_D). **b** Average probe's temperatures plotted versus the pre-cooling period duration

Simulation results show that a pre-cooling period of 1 s at a temperature of 2 °C (dashed line in Fig. 4b) meets both the requirements, as the T_{DEJ} reaches an average temperature of 14.6 °C, and T_D is reduced by 9.3 °C. Moreover, T_G shows just a minor variation (~ 3 °C) compared to its initial value.

Laser-tissue interaction

Bioheat transfer simulations were performed to evaluate the thermal damage caused by the combination of heating and cooling provided by the system on skin and sebaceous gland.

The fluence ratio profile shown in Fig. 3 was imported into the bioheat transfer model, and the initial fluence was set to $F_0 = 20.5$ J/cm^2, delivered through a single laser pulse. Next, the cooling temperature was set to 2 °C, and the contact cooling system was modeled as continuously active starting at 1 s before the laser pulse (pre-cooling) to 2 s after (post-cooling).

A 2D cross-section of the temperature distribution within the skin and sebaceous gland immediately after the pulse (Fig. 5a) shows that the rise in temperature within the gland is significantly larger than in any other region irradiated by the same laser pulse. The plots in Fig. 5b illustrate the temporal evolution of the maximum temperatures measured by the probes during the entire application. It is possible to observe that the maximum temperature at the dermal–epidermal junction never exceeds the safety threshold ($T_{DEJ} < 50$ °C). In contrast, the maximum temperature inside the gland rises quickly up to 98.2 °C. Moreover, the maximum temperature of the dermis falls below the pain threshold by the end of the post-cooling period, suggesting an effective reduction of the discomfort experienced by the patients.

Figure 5c shows that the peak difference between the gland's and dermis's maximum temperature is $\Delta T_{DG} = 32.8$ °C, further corroborating the selectivity of the thermal damage, primarily confined to the target structure.

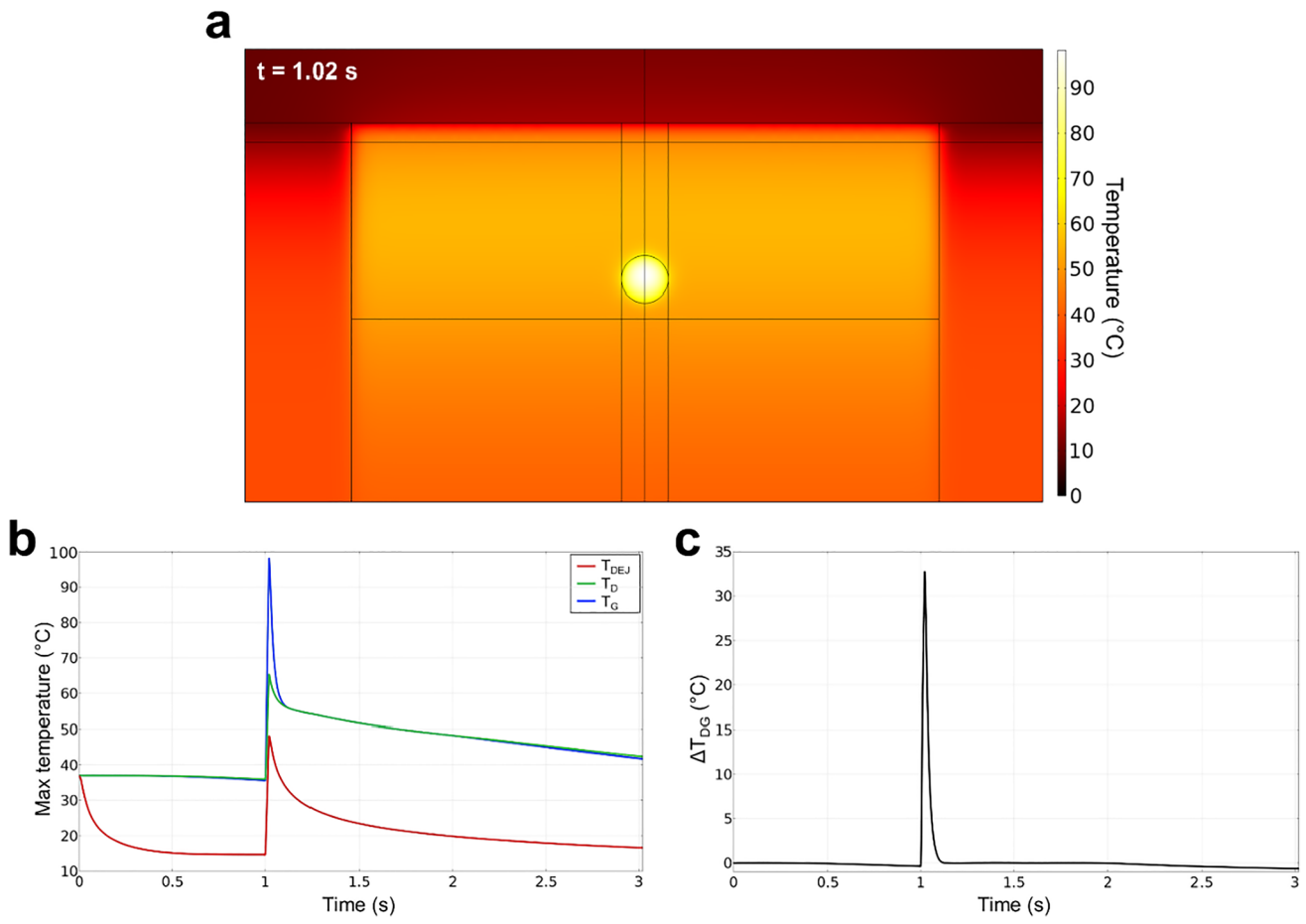


Fig. 5 **a** 2D cross-section of the temperature distribution within the skin and sebaceous gland immediately after the laser pulse is delivered. **b** Maximum temperatures tracked over time by the probes shown in Fig. 4a. **c** Difference between the maximum temperatures of gland and dermis, showing a thermal selectivity peak right after the laser pulse (ΔT_{DG})

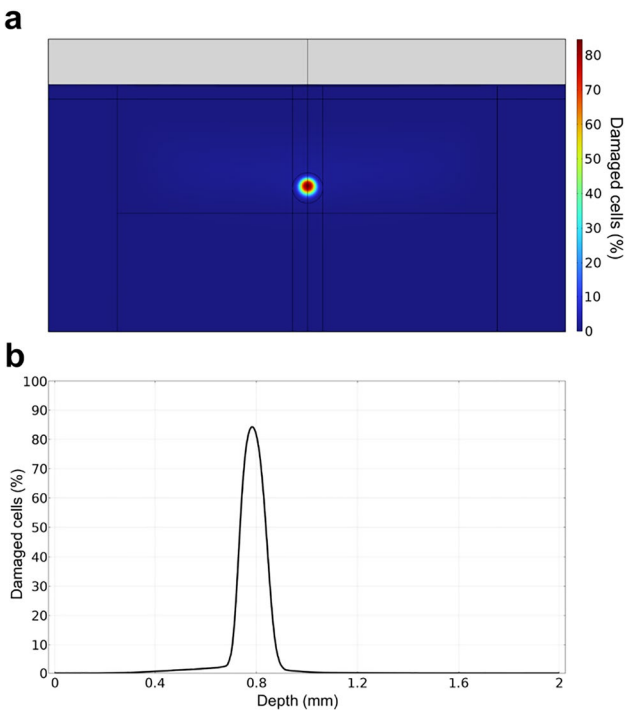


Fig. 6 **a** Cross-section of the skin model, showing that thermal damage selectively affects cells within the glandular region. **b** Highest percentage of damaged cells at each depth

Thermal damage

The percentage of cells damaged by laser-induced hyperthermia was estimated by using the following equation derived from Eq. 1:

$$\text{Damaged cells } (\%) = \left(1 - e^{(-\Omega)}\right) \times 100 \tag{3}$$

The 2D map reported in Fig. 6a shows the spatial distribution of damaged cells after a single application, exhibiting an expected correlation with the temperature distribution shown in Fig. 5a. The plot in Fig. 6b reports the maximum percentage of damaged cells at each depth, showing a peak value of 84.3% inside the sebaceous gland, which results in irreversible necrosis of the sebocytes. Additionally, the negligible fraction of damaged cells (< 3%) outside the glandular region suggests insignificant collateral damage to the dermis and epidermis.

In vivo tissue response to laser treatment

Findings of the finite element modeling were evaluated in postoperative histological examination of an in vivo human facial skin model. Human facial skin around the ear was exposed to therapeutic energy settings determined by the model. The treated skin was excised 5 days post laser exposure, and the corresponding microscopic sections are shown in Fig. 7a-b, with a magnification of 40 × and 200 ×, respectively. Epidermal tissue showed no signs of continuing inflammation 5 days post-treatment during the biopsy. Total necrosis of the sebaceous gland was observed with complete sparing of the epidermis and follicular epithelium. The damage to the sebaceous gland was observed across the length of the gland.

Figure 8 shows the photos taken from an IRB-approved study of a skin type III patient affected by moderate acne, before and after a cycle of three treatments with the presented system. Comparing the pictures, it is possible to appreciate the efficacy and the long-lasting effects induced by the selective photothermolysis of the sebaceous glands.

Conclusion

In this work, we presented a novel energy-based system for treating acne vulgaris through selective photothermolysis of the sebaceous gland, aimed at curbing excess sebum production and *C. acne* proliferation.

Numerical simulations for light transport and bioheat transfer, based on Monte Carlo methods and Pennes' equation, respectively, were performed to identify suitable treatment parameters and demonstrate that selective photothermolysis of the sebaceous gland could be safely achieved. Simulation results showed that a 1-s pre-cooling period is

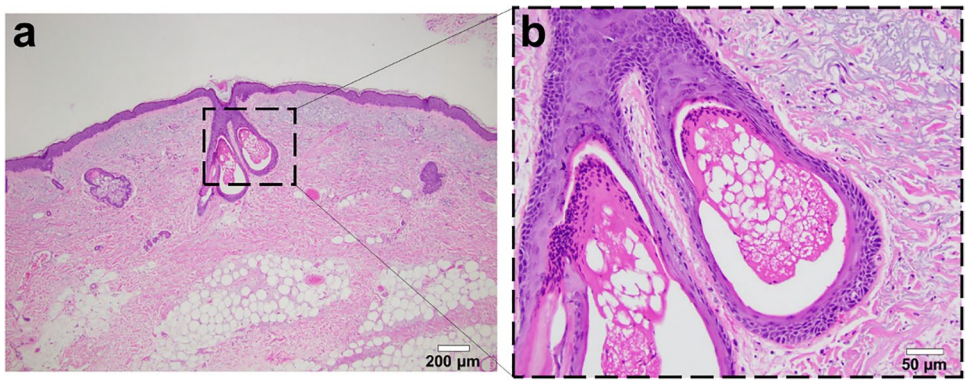


Fig. 7 **a** Histology of treated human facial skin after treatment. **b** Closer view of the damaged sebaceous glands

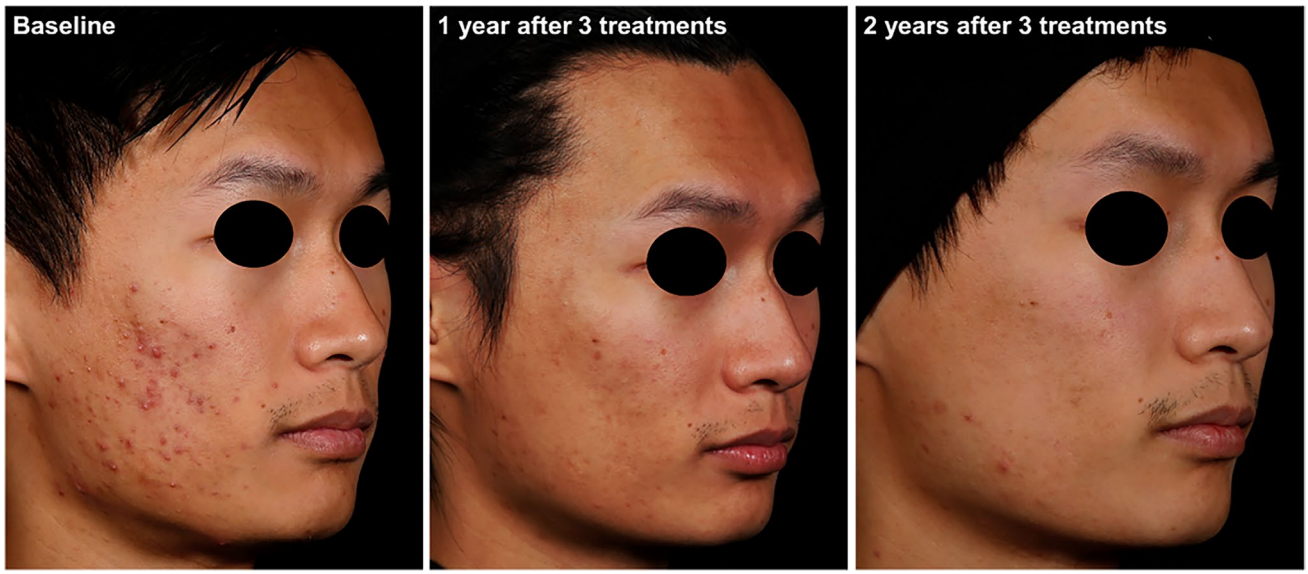


Fig. 8 Long-lasting acne clearing of a patient treated with the presented system

sufficient to protect the skin without significantly affecting the temperature of the sebaceous gland, and a single laser pulse with an initial fluence of $F_0 = 20.5$ J/cm^2 can induce a significant temperature increase within the gland, selectively damaging sebocytes. Furthermore, thanks to the contact cooling system, the temperature of the dermal–epidermal junction does not exceed the critical value of 50 °C when light energy is delivered to the tissue, indicating serious side effects like blistering and skin burning are successfully prevented. Finally, the 2-s post-cooling phase effectively contrasts the thermal blooming after the energy is delivered to the gland and quickly lowers the dermis's temperature below the pain threshold (42–45°), reducing the discomfort experienced by the patients.

In conclusion, the presented system can effectively induce selective photothermolysis of the sebaceous gland while preventing collateral damage to the dermis and epidermis and managing patients' discomfort. Results from clinical trials will be published in future manuscripts.

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Declarations

Ethics approval and consent to participate Clinical data presented in this article was collected under an IRB-approved study (C-19-AC-01). The Institutional Review Board approving this study was IntegReview, LLC, Austin, USA. All contents adhered to the tenets of the Declaration of Helsinki. The participant has consented to the publication of the images in Fig. 8.

Competing interests Matteo Giuseppe Scopelliti, Amogh Kothare, and Michael Karavitis are employees of Cutera, Inc., USA.

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Isotretinoin therapy for acne: Results of a multicenter dose-response study

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One hundred fifty patients with treatment-resistant nodulocystic acne were entered into a double-blind clinical study. Three different dosing levels (0.1, 0.5, 1.0 mg/kg/day) were used in equal-sized groups. In addition to the clinical response, the clinical side effects, the laboratory abnormalities, and the duration of the induced remissions were evaluated with each dose of the drug. There was a highly significant clinical response to treatment with all three dosages of isotretinoin. There was no significant difference in the clinical response between dosages. However, 42% of the patients who received 0.1 mg/kg/day of isotretinoin required retreatment with the drug. This finding, coupled with only minor differences in the clinical side effects and the laboratory abnormalities, indicates that higher dose levels of isotretinoin are indicated for treatment of nodulocystic acne. (J AM ACAD DERMATOL **10:**490-496, 1984.)

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The efficacy of oral isotretinoin (13-*cis*-retinoic acid) in the therapy of severe nodulocystic acne is now well established.[1-9] However, there remain a number of unanswered questions about its use and its mechanism of action. This report is based on a double-blind study of 150 patients with severe, treatment-resistant, nodulocystic acne who were treated with three different dosages of isotretinoin

Table I. Results of questionnaire survey from patients treated with isotretinoin 12 to 18 months previously

	0.1 mg/kg/day (%)	0.5 mg/kg/day (%)	1.0 mg/kg/day (%)
Current status of acne			
Gone entirely	23.3	25.7	53.3
Still present, but improved	40.0	34.3	33.3
Still present, but about the same	6.7	8.6	6.7
Worse	30.0	31.4	6.7
If acne is worse, is it as severe as it was before therapy?	37.5	26.7	0
If acne has recurred, have you begun any acne therapy?	73.7	40.0	46.2

Table II. Characteristics of the three treatment groups

	Isotretinoin dose (mg/kg/day)		
	0.1	0.5	1.0
Number of patients	46	46	49
Male	42	38	47
Female	4	8	2
Age	23.3 yr	23.1 yr	22.2 yr
Duration of acne	8.8 yr	8.5 yr	7.8 yr
Duration of isotretinoin treatment	128.5 days	136.9 days	131.2 days

Table III. Lesion counts during isotretinoin therapy

	Lesion counts					
	0.1 mg/kg/day		0.5 mg/kg/day		1.0 mg/kg/day	
Time	Face	Trunk	Face	Trunk	Face	Trunk
Baseline	14.0	40.3	12.1	33.9	15.3	38.8
Week 4 (15-28 days)	10.5	28.1	10.2	26.7	11.3	32.1
Week 8 (29-56 days)	6.7	23.8	7.6	22.3	6.5	28.4
Week 12 (57-84 days)	4.3	20.3	4.2	17.9	4.8	28.1
Week 16 (85-112 days)	4.8	15.1	3.8	11.7	3.2	25.4
Week 20 (113-140 days)	2.9	14.8	2.6	9.6	1.7	20.0
Week 4 posttherapy	2.9	8.9	2.0	4.5	0.9	9.2
Week 8 posttherapy	2.5	7.9	2.3	6.5	0.8	9.7
Week 12 posttherapy	1.3	4.4	1.3	5.7	0.7	10.0

in order to determine whether there is a dose-dependent clinical response, a dose-related incidence of clinical side effects and laboratory abnormalities, and a dose-dependence in the duration of the induced remissions.

METHODS

Fifty subjects with severe nodulocystic acne were entered into the study in each of the three participating centers. All patients were required to have a minimum of ten inflammatory nodulocystic acne lesions at least 4 mm in diameter on the face, back, or chest. Initial evaluations were made after the patient had been off all therapy for at least 1 month. After written informed consent had been obtained, baseline counts of all facial and truncal inflammatory lesions, 4 mm or greater in diameter, were made, and pretreatment laboratory tests were done. The laboratory tests included a complete

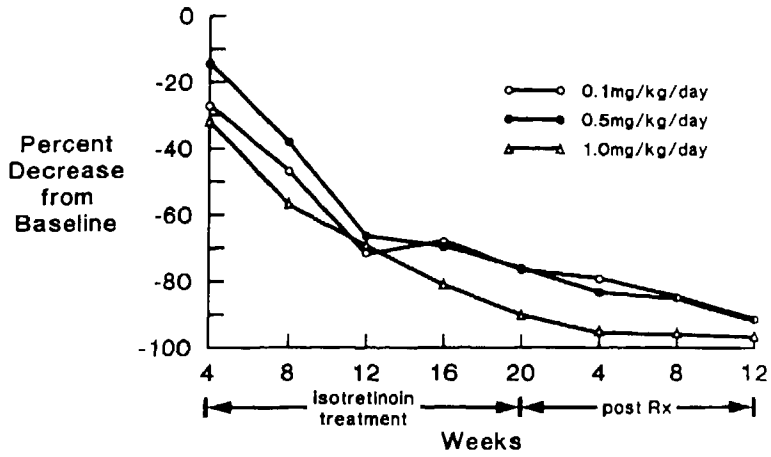


Fig. 1. Percent decrease in inflammatory lesions greater than 4 mm in diameter on the face during isotretinoin therapy.

Table IV. Incidence of clinical side effects

	0.1 mg/kg/day (%)	0.5 mg/kg/day (%)	1.0 mg/kg/day (%)	Overall (%)
Chapped lips	77	90	93	87
Dry skin	56	88	82	76
Dry nose	51	81	78	70
Irritation of eyes	44	51	58	52
Itching	47	36	68	48
Red, scaly face	24	43	68	45
Nosebleed	18	30	53	41
Fingertip peeling	18	31	50	33
Rash	23	26	45	30
Hair loss	26	26	35	29
Skin fragility	16	31	38	29
Fatigue	26	17	38	27
Excessive thirst	31	24	23	26
Bone/joint pain	18	24	30	24
Insomnia	26	13	28	22
Headache	23	12	25	20
Sore mouth	13	14	30	19
Nausea	31	10	13	18
Muscle cramps	18	10	23	17
Decreased appetite	21	14	15	17
Eye pain	18	12	18	16
Abdominal pain	18	5	18	14
Sunburn	15	10	10	12
Double vision	8	5	8	7
Fever	10	5	3	6
Bruising	5	5	8	6
Increased appetite	3	7	5	5

blood count (hemoglobin, hematocrit, reticulocyte count, white blood count, differential, platelet count), blood chemistries (fasting blood sugar, blood urea nitrogen, serum creatinine, serum albumin, total protein, serum billirubin, aspartate transaminase [AST; SGOT], alanine transaminase [ALT; SGPT], alkaline phosphatase), blood lipids (triglycerides, cholesterol, and high-density lipoproteins [HDL]), and a routine urinalysis. Female patients were required to have a negative pregnancy test within 2 weeks prior to starting therapy.

The patients were then treated with oral isotretinoin

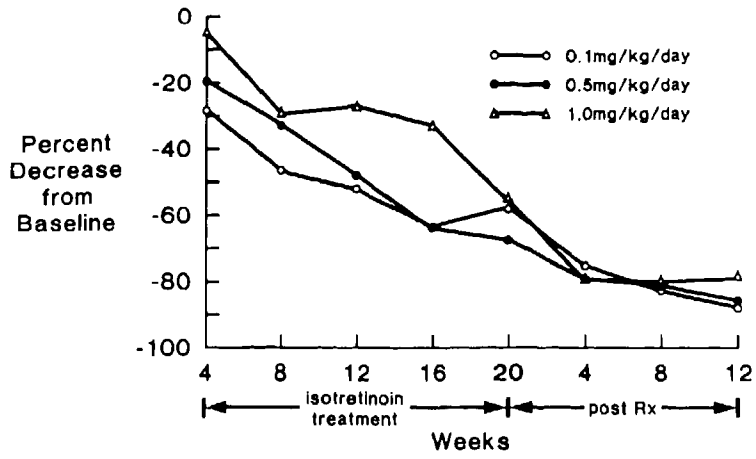


Fig. 2. Percent decrease in inflammatory lesions greater than 4 mm in diameter on the back and chest during isotretinoin therapy.

Table V. Incidence of laboratory abnormalities*

	0.1 mg/kg/day (%)	0.5 mg/kg/day (%)	1.0 mg/kg/day (%)
Hematologic			
Increased platelets	4.4	11.4	8.3
Hepatic			
Increased AST	17.8	15.2	18.4
Increased LDH	25.0	23.9	20.4
Increased total protein	17.8	4.3	10.2
Lipids			
Increased triglycerides	4.4	10.9	24.5
Decreased HDL	13.6	20.5	16.7
Urinary			
Increased specific gravity	6.7	11.8	15.6
Increased white blood count	4.4	4.4	15.2

* 10% or greater for one or more dosage levels.

in one of three dosages, 0.1, 0.5, or 1.0 mg/kg/day, with the use of 1.0, 5.0 and 10 mg capsules of drug. Assignment of individual dosing schedules was done by a randomized, computer-generated code and was made by time of entry into the study in each institution. The study was conducted in a double-blind fashion so that the investigator doing the lesion counts did not know the dosage of drug for any individual. The isotretinoin was to be administered for 20 weeks, but therapy could be stopped when a 70% to 80% reduction in the number of lesions had been obtained. The protocol design allowed participating patients to be retreated with isotretinoin in an open study beginning at least 8 weeks after the completion of the first course of therapy if optimal improvement (less than a 95% reduction in lesions) had not been achieved in the first course.

Clinical evaluations during the period of isotretinoin administration were done at 2, 4, 8, 12, 16, and 20 weeks, and at monthly intervals for 2 to 3 months after treatment was discontinued. At each visit, the patient completed a checklist which included most of the known clinical side effects of the drug. The symptoms on the checklist were as follows: fatigue, insomnia, fever, bone/joint pain, muscle cramps, hair loss, rash, itching, sunburn, dry skin, bruising, fingertip peeling, decreased appetite, increased appetite, nausea, excessive thirst, abdominal pain, headache, double vision, irritation of eyes, eye pain, nosebleed, dry nose, sore mouth, red, scaly face, skin fragility, chapped lips, and palm/sole peeling.

Laboratory profiles were repeated at 4 and 8 weeks and at the end of treatment. If values were abnormal, tests were repeated as necessary.

In addition, 12 to 18 months after therapy was stopped, a questionnaire designed to evaluate the current status of the patients was sent to each patient who

Table VI. Mean values for liver function tests and blood lipid determinations before and at 4, 8, and 20 weeks of isotretinoin treatment

	0.1 mg/kg/day				0.5 mg/kg/day			
	0	4	8	20	0	4	8	20
Liver function tests								
AST (IU/liter)	25.8	32.4	27.3	22.6	21.2	24.8	23.8	26.1
ALT (IU/liter)	22.5	24.7	20.2	15.4	21.0	21.1	16.7	24.7
LDH (IU/liter)	161.2	155.9	165.0	164.5	155.1	173.4	153.1	167.1
Alkaline phosphatase (mU/ml)	71.5	73.1	71.1	64.4	63.8	76.6*	62.9	65.7
Blood lipids (mg/dl)								
Triglycerides	96.0	109.1	97.3	103.6	101.8	129.6*	139.5	176.1*
Cholesterol	180.1	190.2	182.4	189.8†	181.2	209.8	196.1	182.0
HDL	47.0	44.6	45.2	43.1	47.7	34.3	41.1*	43.4

*$p \leq 0.01$, compared to baseline. †$p \leq 0.05$, compared to baseline.

had received only one course of isotretinoin therapy. The specific questions asked appear in Table I.

As stated above, 150 patients with severe nodulocystic acne were entered into the study, with 50 patients being treated at each of the three participating centers. Data from a few of the patients was not complete and could not be used in the final analyses of the drug trial, but at least forty-six patients were used in the analyses of each group. Information on the number of patients, age, duration of treatment, and duration of acne for the three groups is shown in Table II. The three treatment groups were roughly comparable except for the inclusion of more women in the group receiving 0.5 mg/kg/day.

RESULTS

Clinical response. Tabulations of lesion counts were made individually for the face and trunk sites because of previous experience indicating that the clinical response is somewhat different for these two areas. The actual lesion counts are given in Table III, and the percent change from baseline is illustrated in Figs. 1 and 2 for the face and trunk, respectively. As can be seen from Table III and Figs. 1 and 2, the number of clinical lesions decreased with all three dosages on both the face and the trunk. One-sided comparisons* with baseline of individual changes in lesion counts were significant at all treatment and posttreatment observation periods at a level of $p \leq 0.01$ for the face except for 4 weeks of therapy with 0.5 mg/kg/day. For trunk lesions, one-sided comparison with baseline of the individual changes in lesion counts was significant at the $p \leq 0.01$ level at all treatment and posttreatment observation periods for the 0.1 and 0.5 mg/kg/day dosages. For the 1.0 mg/kg/day dose, significance was at $p \leq 0.01$ level at 8 and 20 weeks of therapy and at all posttreatment examinations, but only at a level of $p \leq 0.05$ at weeks 12 and 16 and not at week 4.

Two-sided comparison* between dosage levels disclosed significance ($p \leq 0.05$) for the face on comparison of 0.1 and 1.0 mg/kg/day only at 4 and 8 weeks' posttherapy and on comparison of 0.5 and 1.0 mg/kg/day only at 8 weeks' posttherapy. For trunk lesions, a statistically significant difference ($p \leq 0.05$) was seen in only two instances, namely, for a comparison of 0.5 and 1.0 mg/kg/day at weeks 12 and 16 of therapy.

Clinical side effects. The percentage of patients who recorded the presence of any of the listed side effects at least once during the course of therapy is given in Table IV. The reported symptoms are arranged in decreasing order of overall incidence. In general, there was an increase in side effects with the higher dosages of isotretinoin, particularly with those side effects that occurred frequently. Statistical analyses by the Fisher Exact Test disclosed significance at a level of $p \leq 0.05$

*Comparison of the lesion counts at any observation period for a single dose as compared to baseline.

*Comparison of the lesion counts at any observation period between different dosages.

1.0 mg/kg/day			
0	4	8	20
22.4	28.4	31.7*	32.4*
20.1	26.8	28.4*	20.5
155.0	148.1	161.9	163.4
69.2	71.8	75.2	80.1*
92.8	152.5*	157.3*	169.0*
172.7	203.4†	198.5*	207.2*
45.9	39.5*	38.3**	38.9*

for the following comparisons: chapped lips, 0.1 vs 1.0 mg; dry skin, 0.1 vs 0.5 mg; 0.1 vs 1.0 mg; dry nose, 0.1 vs 0.5 mg; 0.1 vs 1.0 mg; itching, 0.5 vs 1.0 mg; red, scaly face, 0.1 vs 1.0 mg; 0.5 vs 1.0 mg; nosebleed, 0.1 vs 0.5 mg; 0.1 vs 1.0 mg; fingertip peeling, 0.1 vs 1.0 mg; skin fragility, 0.1 vs 1.0 mg; and fatigue, 0.5 vs 1.0 mg dosages.

Laboratory abnormalities. The laboratory abnormalities encountered in a greater than 10% incidence with one or more of the three dosages at any time during therapy are listed in Table V. Mean values for various liver function tests and blood lipid determinations before and during isotretinoin therapy are shown in Table VI. The highest overall incidence was an increase in lactic dehydrogenese (LDH) (Table V), although the increases were minor as evidenced by no statistical increase in this enzyme with any of the three dosages (Table VI). There occurred less frequent elevations of AST, and only with the highest dose of 1.0 mg/kg/day were these changes statistically significant. The most frequent alterations occurred in the blood lipids, particularly with triglycerides. Clear-cut dose-responses were observed with the blood lipids measured, but with the lowest dose, 0.1 mg/kg/day, little change was seen (Table VI).

Follow-up status of treated patients. The current status of the patients who received a single course of isotretinoin is shown in Table I. These data, as stated in the "Methods" section, are based on a questionnaire sent to patients 12 to 18 months after their last clinic visit, and not on direct examination. As such, however, it is likely that fewer patients would report that their acne was clear from having received the smallest dosage. Similarly, more patients would be likely to report that their disease was worse with the smallest dosage. There was no difference in the response to these two questions from the patients treated with the lower dosages of 0.1 and 0.5 mg/kg/day, but clearly those who received the highest dose (1.0 mg/kg/day) fared far better in terms of fewer relapses.

Furthermore, and of greater importance, the need for retreatment with isotretinoin, as determined by the investigator, was dose-related (Table VII). Only 10% of the patients who had received 1 mg/kg/day needed to be retreated with a second course of drug. With a dosage of 0.5 mg/kg/day, 20% needed to be retreated; and with a dosage of 0.1 mg/kg/day, 42% of the patients were placed on further therapy with isotretinoin.

DISCUSSION

The results of this multicenter study involving a large group of patients, all of whom were treated under standard conditions, not only confirm the findings of previous studies but also provide considerable insight into the dosage requirements for patients being treated with isotretinoin for severe, nodulocystic disease.

Clinical response. In general, clinical improvement was essentially the same for all three groups studied, i.e., whether 0.1, 0.5, or 1.0 mg/kg/day was used. If anything, trunk lesions did not respond as well to the highest dose, but this is probably within the error of the clinical trial and could have been related to a slow response by a few patients. As has been reported by others, the response of lesions on the trunk is much slower than lesions on the face.[1,5,6] At the end of the 20-week treatment period, the groups were about equivalent in their clinical responses, and the maintenance of short-term improvement (up to 12 weeks posttreatment) was not very different either. Data for week 2 of isotretinoin treatment have not been presented because the number of patients who returned at that time was relatively small, but the flare-up that has been reported to

Table VII. Percent of patients requiring retreatment with isotretinoin

Dose (mg/kg/day) of isotretinoin on *first* course of therapy	Percentage
0.1	42
0.5	20
1.0	10

occur frequently when treatment is started,[9,10] was not reflected in the second-week lesion counts.

Clinical side effects. Those side effects that are seen more commonly tended to occur in a greater incidence with the highest dose used in the study, but the differences from the lower dosages were not very remarkable. Thus, there was no sufficiently consistent pattern to warrant the recommendation of using lower dosages with the expectation that side effects will be very much less of a problem. It should be noted, however, that the data reflect only the incidence of the side effects, and the severity of the side effects may still be dose-related.

Laboratory abnormalities. Two-sided comparisons of laboratory abnormalities from the various dosage levels did not disclose any consistent pattern of the smaller dosages producing fewer laboratory abnormalities. Although there were more changes in the laboratory parameters on comparison of baseline values with those from the higher dosages (Table VI), these changes were relatively small, with the exception of triglycerides.

Posttreatment follow-up. Long-term follow-up by questionnaire replies of isotretinoin-treated patients revealed rather convincingly that prolonged remissions are less likely in patients treated with the lowest dosage. Furthermore, more than 40% of those patients treated with the lowest dosage of drug required retreatment with isotretinoin, while only 10% of those treated with 1 mg/kg/day required a second course of therapy.

The design of our protocol differs from the multiple-dose study that has been published recently by the German Cooperative Study Group involving a comparable group of patients.[8] They found that higher dosages of isotretinoin were more effective, but their study is difficult to evaluate because their protocol allowed them to alter the daily dose during therapy. Furthermore, they did not have any long-term follow-up, which we considered critical to providing dosing information. Based upon the findings of this study, there is little evidence of any substantial difference in the clinical response of severe acne, the incidence of clinical side effects, or laboratory alterations from isotretinoin treatment in the dose range of 0.1 to 1.0 mg/kg/day. However, the maintenance of the clinical improvement was much greater when higher dosages of the drug were used. Therefore, at this time the low dosage of 0.1 mg/kg/day cannot be recommended, and 0.5-1.0 mg/kg/day of isotretinoin appears to be the optimal dose-range for the management of most patients with nodulocystic acne.

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REVIEW ARTICLE

Treatment of mild to severe acne with 1726 nm laser: A safe alternative to traditional acne therapies

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Abstract

Introduction: Acne is the most common reason for dermatology consultation in adolescents and young adults. Consultation is often delayed despite unsuccessful self-treatment. Postponing effective treatment places acne sufferers at higher risk for permanent acne scars and post-inflammatory pigment changes.

Aim: This review discusses clinical challenges with present therapeutic options for acne treatment and the role of a 1726 nm laser for acne.

Methods: Current acne treatment guidelines were reviewed. A literature review was conducted for trials of light-based acne therapy. The selectivity of previous light-based therapies was reviewed.

Results: Available acne therapy is effective, but treatment-related side effects are common. Acne treatment guidelines do not include recommendations for light-based treatments. Different types of light-based treatments have been tried but until now no wavelength specifically targeted sebaceous glands.

Conclusion: The 1726 nm laser is safe and effective for treating mild to severe acne in all Fitzpatrick skin types. Acne resolution is apparent within the first month and improves for up to 2 years beyond treatment.

KEYWORDS
acne vulgaris, laser, photo thermolysis

1 | INTRODUCTION

Acne vulgaris ("acne") is a multifactorial skin disease characterized by a prolonged course of recurrent breakouts with significant social, psychological, and physical consequences.[1,2] Acne is seen in all age groups, with most prevalence in adolescents and young adults.[1] Worldwide, the incidence and prevalence of acne continue to increase.[3] In our image-focused culture, peer status is linked to appearance, which creates anxiety and depression in adolescents and adults with acne.[4,5] Adults with severe acne are more likely to be

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unemployed when compared to age-matched controls.[6] Appearance bias may be more than just cultural; there is research to suggest evolutionary and subconscious influences.[7,8]

Acne is the most common reason for dermatology consultation in adolescents and young adults,[9] but even moderate to severe acne sufferers may not seek professional advice for a year or longer despite unsuccessful self-treatment.[10,11] Lack of early effective treatment places acne sufferers at higher risk for permanent skin changes such as erythema, post-inflammatory hyperpigmentation (PIH), and atrophic or hypertrophic scar formation.[10,11]

Current treatment guidelines[12,13] rely on topical and systemic therapies that are neither effective nor well tolerated in all patients. Interest in the potential of light-based therapies as alternative treatments is growing. This review discusses clinical challenges with present therapeutic options for acne treatment and the role of a 1726 nm laser device for acne.

2 | METHODS

Seven physicians plus an advisor with international scientific experience (the authors) met to discuss the literature on acne treatments. All physicians are dermatologists who were chosen for their clinical experience and medical expertise in treating acne-affected people of all ages. Following a discussion of the limitations of medical therapy and literature reviews of light-based therapy, the panel discussed the best practice use of a newly FDA-approved 1726 nm laser for acne treatment. The panel's expert opinions regarding the use of the 1726 nm laser to optimize acne outcomes were summarized.

2.1 | Literature review

A literature search of the National Library of Medicine PubMed Database for studies published from 2010 to February 2023 was conducted. Randomized controlled trials of novel acne treatments using light-based and laser therapy to prevent disease progression were reviewed. Inclusion criteria were English language studies, consensus papers, and other reviews that focused on light-based therapy designed to diminish the impact of the pilosebaceous inflammation that leads to acne. Exclusion criteria were articles with no original data (unless a review was deemed relevant) or published in a language other than English. Also excluded were studies that combined medical treatment with light-based modalities (such as isotretinoin, platelet-rich plasma, growth factors, facial peels, and others), or studies designed to measure improvement in acne scars.

3 | RESULTS

3.1 | Medical treatment for acne

A current understanding of the pathophysiology of acne helps to grasp the rationale for therapy. Acne comedones, papules, pustules, and nodules are primarily the result of four factors: hyperkeratinization of the pilosebaceous duct resulting in duct obstruction; ductal colonization with *Cutibacterium acnes* (*C. acnes*); androgen-driven increases in sebum production; and pilosebaceous unit inflammation.[2,12–15] Standard topical and systemic therapies target one or more of these features.

The decision to treat with one medication or multiple medications depends on acne severity, though there is no standardized acne-grading method.[13] Comedonal acne is noninflammatory. Inflammatory acne, which can be mild, moderate, or severe, refers to papules, pustules, nodules, and cysts. Acne severity can be rated clinically on a scale of 0–4, with 0 indicating "clear"; 1 is comedonal acne; 2 is mild–moderate papulopustular acne; 3 is severe papulopustular acne or moderate nodular acne; and 4 is severe nodulocystic acne or conglobate acne.[13]

3.1.1 | Topical therapy

Improvement in Type 1 and Type 2 acne can be achieved with topical treatment. A single topical agent, such as benzoyl peroxide (BPO) or a low-strength retinoid,[12] may be sufficient. The bactericidal activity of BPO is especially effective in controlling *C. acnes*, which plays a pivotal role in acne. *C. acnes* increases the proliferation and differentiation of keratinocytes; it activates innate immunity via toll-like and protease-activated receptors, which trigger the production of pro-inflammatory cytokines.[16]

Retinoids work by normalizing keratinization and reducing inflammation. Type 2, or mild papulopustular acne, may require a combination of two topical agents such as BPO plus a retinoid, or fixed combinations of a topical antibiotic + BPO, or a topical antibiotic + a retinoid.[12,13] Once control has been achieved, topical retinoids are ideal as monotherapy for long-term maintenance in all types of acne as they have the unique ability to prevent the formation of microcomedones.[17]

3.1.2 | Systemic therapy

Antibiotics are the most frequently added systemic therapy for acne that has not responded well to topical remedies. More antibiotics are prescribed by dermatologists than any other specialty.[18] For moderate to severe acne, tetracycline-derived antibiotics—minocycline and doxycycline—are most often used in combination with topical agents. Although their use is intended to reduce *C. acnes* numbers, oral tetracycline derivatives have anti-inflammatory qualities that add to their efficacy.[19] Due to increasing levels of bacterial resistance, oral antibiotics should be used for short periods of time, 3–4 months or less.[12,13,16]

Hormonal therapies are effective acne treatment adjuncts for women, yet oral antibiotics are prescribed more frequently.[20] Hormonal therapy can be achieved with spironolactone or oral contraceptives, which downregulate the effects of androgens on sebum production. Spironolactone, originally developed as a

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diuretic, has antagonistic effects on androgen and progesterone receptors. Spironolactone is helpful for adult-onset acne in women and in women with acne due to polycystic ovary disease. It can be safely used long-term in healthy women.[21,22] Oral contraceptives that contain estrogen and progestin reduce free testosterone which diminishes sebum production. In the United States, a few specific estrogen/progesterone combination oral contraceptives[21–23] have been approved for acne treatment. Improvement with these agents may take several months. Progestin-only oral contraceptives, and progestin-containing long-acting implants or depot products, can make acne worse.[23]

Isotretinoin

Isotretinoin should be considered when a patient with moderate to severe acne fails combination topical therapy plus a systemic agent. It can be started as first-line therapy in a severely affected patient.[12,13,24] Isotretinoin normalizes follicle keratinization, inhibits *C. acnes*, reduces inflammation, and reduces sebum secretion by shrinking sebaceous glands. It is the only disease-modifying acne therapy. When dosing and length of treatment are sufficient, there is the likelihood of durable shrinkage of the pilosebaceous unit that persists once the drug is discontinued,[25] resulting in prolonged and often permanent acne resolution. Isotretinoin does not permanently remove all sebaceous gland functions. Sebaceous gland function will renormalize to levels enough to sustain sebum production but not enough for excessive bacterial proliferation.

4 | LIMITATIONS OF CURRENT ACNE TREATMENTS

Available acne medications are effective, but adverse effects and delayed onset of action limit their use. The demographic with the most acne, adolescents and young adults, may become impatient with their perceived slow progress. Topical products such as BPO and low-strength retinoids routinely cause dry, flaking skin, that, although temporary, prompts many patients to discontinue therapy before optimal effects are achieved. In a study of 250 patients with a mean age of 18.6,[26] 45% abandoned therapy before an adequate therapeutic trial. Lack of response was cited by 62%, and 38% reported unacceptable side effects. Patients with severe acne were more likely to quit topical treatment early due to a lack of response.[26]

Beyond their skin irritant effects, topical retinoids may pose additional risks in adolescent and young adult women—groups with high pregnancy rates. Adapalene and tretinoin are both pregnancy category C, meaning animal data suggest fetal risks though human pregnancy data are lacking. Tazarotene is pregnancy category X, indicating it should not be used during pregnancy. The newest topical retinoid, trifarotene, has not been assigned a pregnancy-risk category.

Pregnancy or plans to become pregnant also limit use of tetracycline-derived antibiotics. Minocycline can cause skin and mucosal pigment changes, and it has been associated with a lupus-like syndrome with a higher incidence in young women.[27] Common side effects of tetracycline-derived antibiotics are photosensitivity, gastrointestinal upset, dizziness, and headaches. Pseudotumor cerebri (PTC) is a risk with this class of antibiotics and it can occur in children.[28,29] Subtle symptoms and early fundoscopic signs of increased intracranial pressure can be missed, allowing unrecognized PTC to progress to visual impairment.[28,29]

Systemic strategies with hormonal therapy have considerable side effect potential. Spironolactone leads to dose-dependent menstrual irregularities in 15%–30% of patients.[21] In lab animals, spironolactone has been shown to feminize a male fetus.[21] Oral contraceptives are often associated with nausea, breast tenderness, and breakthrough bleeding. Even the small chance of a thromboembolic event may discourage oral contraceptive use.

Despite decades of use, controversies still exist regarding the use of isotretinoin. As with oral tetracyclines, isotretinoin poses an increased risk of PTC[29] and the two should not be used together. Almost all patients treated with isotretinoin develop mucocutaneous and eye dryness that can be severe. Myalgias, liver enzyme abnormalities, and elevated triglycerides have been reported.[24,25] Severe depression has been reported though there is controversy about whether this is drug-related or due to the severe acne for which isotretinoin is prescribed.[30] Retinoid embryopathy is a known side effect and the use of isotretinoin involves the added administrative burden of enrollment in the iPledge program,[31] an FDA-mandated safety program intended to diminish the risk of isotretinoin's teratogenicity. Based on histological data that demonstrate a drastic decrease in the size, shape, and lipid content of sebaceous glands while undergoing isotretinoin treatment,[32,33] patients who can tolerate a long course of isotretinoin are rewarded with dramatic disease improvement.

5 | ENERGY DEVICES FOR ACNE

Energy-based devices fill a therapeutic need for patients who cannot tolerate or who do not respond to conventional acne therapy. Acne treatment guidelines[12,13] do not include recommendations for energy-based devices. Published summaries of light-based trials[21,34–39] underscore increasing interest in energy modalities.

A 2016 Cochrane review of randomized controlled trials of light treatments for acne concluded reliable synthesis of data could not be determined due to differences in patient selection, different wavelengths used, varying total doses and a number of sessions, and lack of standardized outcome measures.[40] More than half of the studies in the Cochran review were industry sponsored. Of the energy device trials reviewed, photodynamic therapy (PDT) was the most widely studied and was thought to have some usefulness.[40] In an evidence-based review of photodynamic therapy,[38] moderate to severe inflammatory and non-inflammatory acne responded to red light as a light source when the skin was pretreated with a photosensitizer for several hours before light exposure. PDT appears to be effective, but it can be painful, and the durability of response over time is unclear. Light-based therapies, their mechanisms of action, and common side effects are listed in Table 1.

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TABLE 1 Summary of light-based procedures that have been used for inflammatory acne.

Device	Mechanism of action	Side effects
Fractional CO_2 laser	Photothermolysis of sebaceous glands	Pain; erythema; bleeding; transient PIH
Potassium titanyl phosphate (KTP) laser	Thermal injury to sebaceous glands; reduction of *C. acnes*	None reported
Pulsed dye laser (PDL)	Targets dermal blood vessels; increases growth factor	Pain; erythema; edema; peeling; crusting; blistering; transient PIH
1064 nm Nd:YAG Infrared laser	Destroys sebaceous glands; reduces perifollicular stratum corneum; reduces inflammation	Erythema; dryness; burning; crusting; transient PIH
1450 nm Nd:YAG Infrared laser	Destroys sebaceous glands	Erythema; edema; transient PIH
1540 nm infrared laser	Destroys sebaceous glands	Erythema; edema; heat sensation
1565 nm nonablative fractional laser	Destroys sebocytes; reduces *C. acnes*	Erythema; edema, crusting; transient PIH
800 nm diode laser with gold microparticles	Selective destruction of pilosebaceous infundibulum and glands with gold-coated silica microparticles with strong absorption at 800 nm	Erythema; overall well-tolerated
Blue light 407–420 nm	Photoactivation of bacterial porphyrins; reduces *C. acnes*; reduces inflammation	Erythema; stinging
Red light 620–700 nm	Anti-inflammatory effects	Few side effects by itself; mild to severe discomfort following use of a topical sensitizer
Intense pulsed light (IPL) 400–1200 nm	Photothermolysis of sebaceous glands; activation of bacterial porphyrin; reduces *C. acnes*	Transient PIH; can worsen nodulocystic lesions
Photopneumatic therapy (IPL with suction)	Expels comedones with suction; thermal destruction of follicles; reduces *C. acnes*	Erythema; edema
Photodynamic therapy (PDT) after application of topical aminolevulinic acid (ALA) or methylaminolevulinate (MAL)	Destroys sebaceous glands; reduces *C. acnes*; reduces inflammation	Pain (intolerable with ALA 20%); erythema; edema

5.1 | Novel 1726 nm laser for acne

Table 1 illustrates that reduction of sebum production is the primary mechanism of action in light-based therapies. Energy delivered by lasers increase the skin's temperature because water is abundant in skin, and water's absorption coefficient is significant with infrared lasers.[41] Sebaceous glands are injured by the increased temperature, but discomfort and collateral damage to other skin structures cannot be avoided.[41]

A better approach is to selectively deliver energy to specific chromophores within the sebaceous gland that has a higher absorption coefficient than water. Sebum in the sebaceous gland is a favorable target because it has a narrow absorption peak, higher than water, at 1726 nm.[41,42] In 2012 Sakamoto et al. demonstrated optical pulses with wavelengths between 1700 and 1720 could destroy sebaceous glands in ex vivo human facial skin, with minimal damage to surrounding tissues.[42]

A novel infrared diode laser device with a nominal wavelength of 1726 nm was designed to generate a significant and rapid temperature rise inside the sebaceous glands to heat sebum, producing a controlled thermal injury of the glands.[41] As heat causes pain, the addition of skin cooling minimizes skin discomfort. Thermal protection for the epidermis and superficial dermis is provided by a temperature-controlled skin-contact cooling window.[41] In an in vivo model, human facial skin from around the ear was exposed to the energy settings determined to be ideal. The treated area was excised 5 days later. Total necrosis of the sebaceous gland was seen, with sparing of the epidermis and of the follicular epithelium.[41]

Performance testing to assess the safety and efficacy of the new 1726 nm laser was done in an open-label, prospective, multicenter clinical study prior to FDA approval.[43] A total of 104 patients, 57% female, 43% male, aged 16–40, with mild ($n = 1$), moderate ($n = 81$), or severe ($n = 22$) acne were enrolled. More than 20% of those enrolled had severe acne and 28% of total patients were males aged 16–19. The study's primary objective was to show that ≥50% of subjects attained treatment success defined as a reduction ≥50% in inflammatory acne lesions 12 weeks after their final treatment compared to baseline. Treatment consisted of a total of three 30-min laser facial treatments spaced 2–5 weeks apart. Photographs taken throughout the study were sent to a panel of three trained expert physicians for Investigator Global Assessment (IGA) grading. Noninflammatory and inflammatory acne lesion counts (ILC) were performed by lesion counters who were blinded to the study design. Results obtained at 12 weeks after the last treatment are summarized in Table 2.

Subjects were also assigned to subgroups by age, gender, Fitzpatrick skin type, and baseline IGA. Responder rates and device-related adverse events within these three subgroups were

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TABLE 2 Efficacy of a novel 1726 nm laser 3 months after a total of three treatments.

Efficacy measure	Percent of subjects improved 12 weeks after third treatment
IGA improvement 1+	87%
IGA improvement 2+	47%
IGA improvement clear/almost clear	36%
Inflammatory lesion count (ILC)	91%
ILC improvement >50%	80%
Nodule count reduction	67%
Comedonal count reduction	32%

compared. Adverse events were mild, and the rates were similar in all subgroups. Erythema (100% of subjects) and edema (98% of subjects) were transient, resolving within several hours to several days. Acne purging was the third most common adverse event reported by 45.2% of patients. All purging events were mild except for one described as moderate in a participant with a severe IGA at baseline. Mild dryness was experienced by 18.3%. There was no blistering, hyperpigmentation or hypopigmentation, or scarring. No patient with Fitzpatrick type V or VI skin dropped out of the study. Topical pre-procedural numbing was not performed. There were no differences in discomfort levels by skin type, with median discomfort levels rated as 5.0–5.1 (0–10 scale).[43] The results of this report that led to FDA approval are similar to those published by Goldberg et al in 2022.[44] In a study of 17 patients, statistically significant reductions in inflammatory lesions were seen beginning 4 weeks after treatment. Improvement continued well beyond the initial study. Subjects who continued follow-up showed progressive improvement, with a 97% reduction in inflammatory lesion counts at 2 years.[44]

6 | DISCUSSION

Nonadherence with topical and systemic therapy is high due to complicated, multistep treatments, topical and systemic side effects, and administrative burdens. Undertreatment of acne leads to pigment changes and scarring. Permanent acne scarring occurs across all levels of acne severity, a critical finding for practitioners who treat acne.[11] Of those affected by acne scarring, 20% fear that scarring will affect their employability.[11]

Until now, the benefits of laser therapy for acne came at the cost of undesirable skin discomfort and skin damage due to a lack of selectivity for sebaceous glands. Selective photothermolysis using a new 1726 nm laser ensures effectiveness and safety in mild to severe acne while managing discomfort with a contact cooling system. The 1726 nm laser was studied and is approved for ages 16 and above. Unlike the dozens of laser trials using non-selective wavelengths, pigment changes were not observed with the 1726 nm laser. Melanin is not a clinically meaningful absorbing chromophore at 1726 nm, so the new laser is safe for all skin types.

Adequate, early treatment is the key to acne remission without physical, social, or emotional sequelae. There are many effective topical products to treat acne and three options for systemic treatment. Of all available medications, only isotretinoin is disease-modifying. The 1726 nm laser may have a similar long-term effect on sebaceous glands as does isotretinoin. Both treatments have histological data that show a marked decrease in the size, shape, and lipid content of sebaceous glands in human skin after treatment.[44] However long-term follow-up of patients treated with 1726 nm laser compared to those treated with oral isotretinoin may provide conclusive evidence.

The new 1726 nm laser may represent a paradigm change in acne treatment, providing safe, effective, and convenient treatment for mild to severe acne in all skin types.

6.1 | Limitations

The review discusses clinical challenges with present therapeutic options for acne treatment and the role of a 1726 nm laser for acne. The review was limited to exploring the role of a 1726 nm laser for acne in view of currently used treatments. A review comparing various laser treatments is outside the scope of this paper.

Evidence-based guidelines rate the quality of evidence to support treatment options. Clinical consensus recommendations utilize expert opinion based on the experience of what treatment works well in particular situations. Laser treatment studies are challenging to design due to the difficulty in assessing a control group; patients often serve as their own controls. The 1726 nm laser was recently approved in 2022 which has limited widespread real-world clinical experience.

6.2 | Future directions

A clinical trial (clinicaltrials.gov identifier: NCT05430464) is recruiting participants to assess the benefits of the 1726 nm laser versus sham laser treatment.

AUTHOR CONTRIBUTIONS

DJG and AA performed the research for this manuscript. DJG, AA, ACB, MHG, ABL, MSL, JHM, and AR contributed to the development of the manuscript, reviewed it, and agreed with its content.

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DATA AVAILABILITY STATEMENT

The data supporting this manuscript's findings are available in PubMed [https://pubmed.ncbi.nlm.nih.gov/] and Google Scholar [scholar.google.com].

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