A Randomized, Controlled, Double-blind Study of Localized Low-Heat Treatment of Acne Lesions

Michael H. Gold, MD; Neil S. Sadick, MD; Virginia L. Bradshaw, NP-C; Molly M. Boring, FNP-C

Zeno™, a new handheld device, produces low-level heat (controlled to 46.5–49.0°C) that may be applied to acne vulgaris lesions via a small metal tip. The purpose of this study was to evaluate the efficacy and safety of Zeno when it was used at a treatment time 20% lower than in an earlier study. Our study was conducted at 2 clinical sites with a total of 15 subjects and was randomized and controlled within a single subject. Eligible subjects had 2 similar acne lesions on the face. One lesion was treated with Zeno and the other with a placebo device; both lesions were treated twice on the first day and once on the second day. Follow-up assessments were made immediately before the second treatment (typically 4 hours after the first treatment) and the third treatment (typically 24 hours after the first treatment) and on day 5. The primary end point was the time to resolution of treated acne lesions. Secondary end points, including investigator and subject assessments on a blemish-change assessment scale, were evaluated. Any adverse events were reported. One subject failed to appear for appointments and was lost to follow-up and not included in the analysis. In 7 of the remaining 14 subjects, lesions improved or resolved sooner with Zeno than with placebo. In 3 subjects, improvement or resolution times were the same; in the 4 remaining subjects, placebo-treated lesions improved earlier. Adverse events were not observed with each device in the 14 subjects. Zeno appears to be an effective, safe take-home device for use alone or as adjunctive therapy with prescribed medications. There may be a link between dosage and efficacy.

Dr. Gold is Clinical Assistant Professor, Department of Dermatology, Vanderbilt University School of Medicine and Vanderbilt School of Nursing, Nashville, Tennessee, and Medical Director, Gold Skin Care Center and Tennessee Clinical Research Center, Nashville. Dr. Sadick is Clinical Professor of Dermatology, Weill Medical College of Cornell University, and in Private Practice, Sadick Dermatology, New York, New York. Ms. Bradshaw and Ms. Boring are Nurse Practitioners , both at Gold Skin Care Center, Nashville.

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Acne vulgaris affects 70% to 80% of people aged 11 to 30 years.[1] A variety of oral, systemic, and physical methods, alone or in combination, are available for treatment (Table 1). Choice of treatment depends on grade and duration of acne, scarring, and a patient's psychological health.[2] Topical medications suppress lesions by no more than 60% and often produce an irritating dermatitis, thus reducing compliance.[3] Antibiotic use produces resistant strains of *Propionibacterium acnes*.[3-5] These limitations, as well as increasing prevalence of antibiotic-resistant *P acnes*

TABLE 1

Acne Treatments

Chemical
Retinoids
Adapalene
Antibiotics
Benzoyl peroxide
Azelaic acid
Salicylic acid
Physical
Comedone extraction
Electrocautery
Chemical peels
Light energy
Laser energy
Photodynamic therapy
Glucocorticoids*
Hormonal
Androgens
Antiandrogens
Estrogens
Oral contraceptives

*Glucocorticoids are considered physical treatments when given intralesionally.

TABLE 2

Demographics of Subjects Treated With Zeno™ and Placebo for Facial Acne Lesions

Subject	Age, y	Sex	Race
1	20	Female	Hispanic
2	30	Female	African American
3	27	Female	White
4	29	Female	White
5	30	Female	White
6	30	Female	White
7	21	Female	White
8	34	Female	White
9	43	Female	White
10	18	Male	White
11	34	Female	White
12	26	Female	European
13	33	Female	White
14	22	Female	East Indian*

*Refers to an ethnic group based in Mumbai, formerly known as Bombay, India.

strains, necessitate new therapies for mild to moderate acne.

To meet this need, Bruce et al[6] postulated that targeting *P acnes* within developing acne lesions might accelerate the resolution of these lesions and that *P acnes* colonies would be susceptible to low-level intermittent heat. Their preclinical experiments showed that the amount of heat required to reduce colony counts from treated anaerobic cultures of *P acnes* was tolerable to human skin. These researchers then developed a handheld prototypic device with a small treatment tip that could deliver a controlled amount of heat to an individual acne lesion.

After optimizing temperature level, exposure time, and treatment frequency, the researchers conducted a double-blind, placebo-controlled clinical trial of the prototypic device in 50 human subjects with mild to moderate acne. In that clinical trial, each heat dose was 2.5 minutes in duration. The results showed that treatment with this handheld device, which delivered heat with a proprietary technology (ClearPoint™), improved the resolution time for individual acne lesions compared with the placebo device.[6]

This article outlines a study evaluating the efficacy and safety of Zeno™ when it was used at a treatment time 20% lower than in the study by Bruce et al.[6]

MATERIALS AND METHODS

The study was conducted at 2 clinical sites with 15 subjects altogether and was randomized and controlled within a single subject. Eligible subjects had 2 similar acne lesions on the face. One lesion was treated with Zeno and the other with a placebo device; both lesions were treated twice on the first day and once on the second day. Follow-up assessments were made immediately before the second treatment (typically 4 hours after the first treatment) and the third treatment (typically 24 hours after the first treatment) and on day 5. The primary end point was the time to resolution of treated acne lesions. Secondary end points, including investigator and subject assessments on

TABLE 3

Investigator-Subject Assessments of Treatment With Zeno™ and Placebo for Facial Acne Lesions*

Patient	Investigator						Subject						First to Improve/ Resolve
	Lesion 1			Lesion 2			Lesion 1			Lesion 2			
	A1	A2	A3	A1	A2	A3	A1	A2	A3	A1	A2	A3	
1†	NC	I	R	NC	I	R	NC	I	I	NC	I	R	Placebo
2†	NC	I	I	NC	NC	I	NC	I	I	NC	I	I	Same
3†	NC	I	R	NC	NC	I	NC	I	R	NC	I	I	Zeno
4†	NC	I	I	NC	I	I	I	I	NC	I	I	R	Placebo
5‡	I	I	R	I	R	R	NC	I	NA	I	R	NA	Zeno
6†	I	I	R	I	NC	I	I	I	R	NC	NC	R	Zeno
7‡	NC	NC	I	NC	NC	I	NC	NC	NC	NC	NC	NC	Same
8‡	NC	I	I	NC	I	R	NC	I	R	NC	I	R	Zeno
9‡	NC	NC	R	NC	I	R	NC	NC	I	NC	I	I	Zeno
10†	I	R	R	I	I	R	NC	NC	I	I	I	I	Zeno
11‡	NC	R	R	I	R	R	NC	R	R	NC	I	I	Zeno
12†	NC	I	I	NC	I	I	NC	I	I	NC	I	I	Same
13‡	NC	I	I	NC	NC	I	NC	I	I	NC	NC	NC	Placebo
14†	NC	NC	NC	NC	I	I	NC	I	NC	NC	I	I	Placebo

*A1 indicates evaluation before second treatment; A2, evaluation before third treatment; A3, evaluation at day 5; NC, no change; I, improved; R, resolved; NA, not available.
†Lesion 1 treated with Zeno; lesion 2 treated with placebo.
‡Lesion 1 treated with placebo; lesion 2 treated with Zeno.

a blemish-change assessment scale, were evaluated. Any adverse events were reported. The study was approved by the IntegReview institutional review board. All subjects provided signed informed consent.

SUBJECTS

Eligible subjects had 2 similar facial acne lesions (papules or cysts of similar pathological state and duration) and provided a complete medical history and list of medications taken. Subject demographics are shown in Table 2. Excluded subjects were those who were taking oral antibiotics; had severe acne requiring prescription medication; had known skin sensitivity to heat, sunburn, or chemical agents; had a rash from known metallic materials; had been treated with topical facial antibiotics within 24 hours of the procedure; or were unable to understand the informed consent procedure without language assistance. Each subject was asked to record (in a diary) changes in tenderness and appearance of each lesion during the morning and evening of each day of the study. Tenderness was graded as extreme or absent. Changes in lesion appearance were recorded as worsened, no change, improved, or resolved. Subjects were asked to record data until both lesions resolved or until the fourteenth day after the first treatment, whichever came first.

STUDY DESIGN

The study was randomized and controlled within a single subject. One lesion was treated with Zeno set to deliver a shorter-than-normal treatment of 2 minutes, the other with a placebo device that delivered no heat. Treatments were given twice on the first day and once on the second day. The primary end point was the time to resolution of treated lesions. Secondary end points, including investigator and

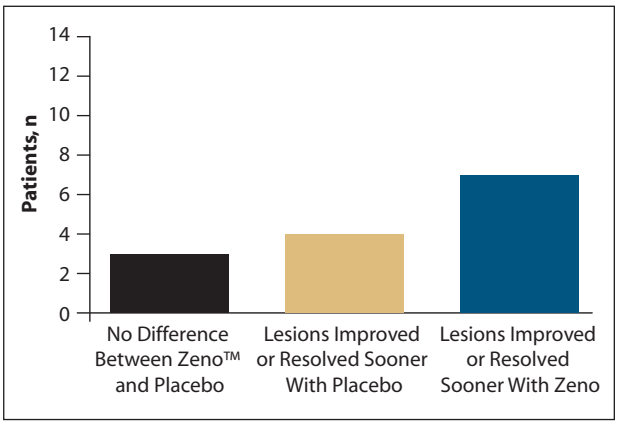

Figure 1. Comparative performance of Zeno™ versus placebo in 14 subjects at day 5.

subject assessments on a blemish-change assessment scale, were evaluated. Any adverse events were reported.

PROTOCOL

On day 1, the investigator selected, evaluated, and, if possible, obtained photographs of 2 facial acne lesions on each subject. The first treatment was given on the morning of day 1. The investigator applied Zeno to 1 lesion for 2 minutes and the placebo device to the other lesion for 2 minutes. The second treatment was administered in the same manner 1 to 4 hours after the first; the third treatment was given approximately 24 hours after the first. The investigator assessed changes immediately before the second and third treatments and on day 5. Subjects were told that discomfort, temporary local redness, and skin drying, flaking, and peeling may occur with treatment.

PRELIMINARY DATA ACQUISITION

The demographics of subjects with complete data (n=14; age, 28.4±6.7 years [mean±SD]) are shown in Table 2. One subject failed to appear for appointments and was lost to follow-up and not included in the analysis. Subjects ranged in age from 18 to 43 years. Baseline lesion tenderness and use of isotretinoin were recorded. Subjects washed their faces at least twice daily and were not restricted in their use of over-the-counter facial products (acne creams, facial cleansers, astringents, makeup removers, moisturizers, soaps, or sunscreens). Subjects recorded the names of each product they used and how often they used it. One subject had used isotretinoin previously.

RESULTS

Subjects were generally pleased with their results (Table 3). In 7 of the 14 subjects, lesions improved or resolved sooner with Zeno than with the placebo device. In 3 subjects, improvement or resolution times were the same; in the 4 remaining subjects, placebo-treated lesions improved earlier. The results are presented graphically in Figure 1. In most cases, the investigator and subject agreed on the improvement and resolution times.

Figure 2. Subject just before treatment with Zeno™ (subject's right side) and placebo (subject's left side) for acne lesions between the brow (A). The Zeno-treated lesion resolved 3 days earlier than the placebo-treated lesion. Lesions between the subject's brow immediately before the second treatment of the first day (B). The white circular spot has been placed just above the location of the placebo-treated lesion at the end of the treatment period (day 5)(C). The white circular spot has been placed just above the location of the Zeno-treated lesion at the end of the treatment period (day 5)(D). Photographs courtesy of Michael H. Gold, MD.

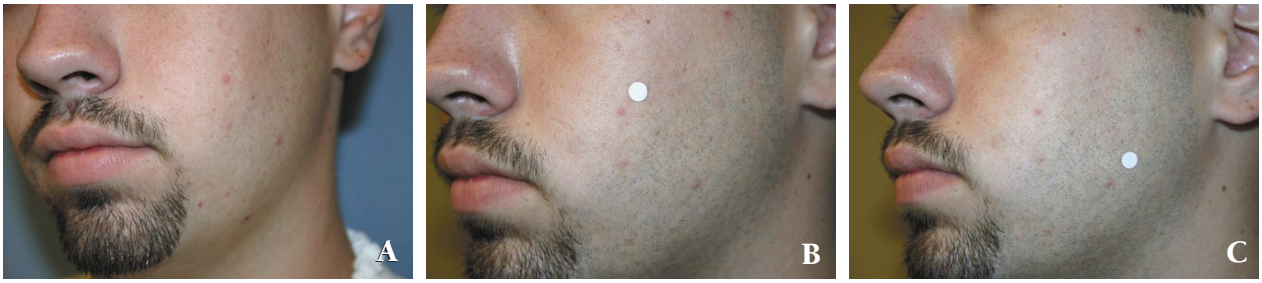

Figure 3. Subject treated with Zeno™ (lesion between the nasolabial fold and the ear) and placebo (the lower lesion to the rear of the cheek) for acne lesions on the left cheek (A). The Zeno-treated lesion resolved 3 days earlier than the placebo-treated lesion. The white circular spot has been placed above the location of the Zeno-treated lesion just before the third treatment (B) and above the location of the placebo-treated lesion just before the third treatment (C). Photographs courtesy of Michael H. Gold, MD.

Lesion tenderness was absent or slight in 11 subjects and changed little with continued Zeno or placebo treatment. In 1 subject, extreme initial tenderness in both lesions improved with treatment (Zeno and placebo). In another subject, moderate tenderness persisted throughout the treatment period for both lesions. Adverse events with each device were not observed by investigator or subjects. Clinical examples are shown in Figures 2 and 3.

COMMENT

In an earlier double-blind, placebo-controlled clinical trial, Bruce et al[6] used a prototypic Zeno device to treat 51 subjects with mild to moderate acne who were not using systemic medications. Treatment time was approximately 2.5 minutes, 20% longer than the 2 minutes used in the present study. The median time to resolution for Zeno-treated lesions was 96.7 hours (≈4 days) compared with 151.8 hours (>6 days) with the placebo device, which, as with the present study, did not deliver heat. Zeno-treated lesions also showed improvement sooner than placebo-treated lesions (median, 12.8 hours vs 35.6 hours, respectively). This suggests a dose-response relationship that warrants further study.

CONCLUSION

Based on these preliminary results, Zeno appears to be effective in improving or resolving mild to moderate acne lesions more quickly in approximately 50% of treated subjects when compared with placebo. Zeno seems to be an effective, safe take-home device for use alone or as adjunctive therapy with prescribed medications. In addition, the level of efficacy suggested by these preliminary results, when compared with the results from an earlier clinical trial at a higher dosage, may indicate a link between dosage and efficacy. Further studies are warranted to confirm this link.

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