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A Double-Blind, Placebo-Controlled Randomized Trial Evaluating the Ability of Low-Level Laser Therapy to Improve the Appearance of Cellulite

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Background and Objective: Cellulite is present in 90% of post-adolescent women. Several technologies have been developed for treating cellulite; however, they all involve some degree of massage or mechanical manipulation. The purpose of this study was to assess the effectiveness of a low-level laser light device employing green 532 nm diodes as a stand-alone procedure without massage or mechanical manipulation for improving the appearance of cellulite in the thighs and buttocks.

Study Design/Materials and Methods: This double-blind study randomized subjects to undergo treatment with the LLLT device ($N = 34$) or sham treatment ($N = 34$). During a 2-week treatment phase, each subject received three weekly treatment sessions 2–3 days apart. During each session, the front and back of the hips, thighs, and waist were exposed for 15 minutes (30 minutes total).

Results: Nineteen subjects in the LLLT group achieved a decrease of one or more stages on the Nurnberger–Muller grading scale (55.88%) versus three subjects (8.82%) in the sham-treated group ($P < 0.0001$). Two LLLT-treated subjects achieved 2-stage improvements on the Nurnberger–Muller Scale at the 2-week study endpoint and four did at the 6-week follow-up evaluation versus none of the sham-treated subjects at either time point. Subjects treated with LLLT achieved a significant decrease in combined baseline thigh circumference at the 2-week study endpoint and 6-week follow-up evaluation (for each, $p < 0.0001$ vs. baseline) versus no change for sham-treated subjects. LLLT-treated subjects also showed significant decreases in mean baseline body weight ($P < 0.0005$), BMI ($P < 0.001$), and percent BSA affected by cellulite ($P < 0.0005$) versus no change for any parameter among sham-treated subjects. Most LLLT-treated subjects (62.1%) were Very Satisfied or Somewhat Satisfied with the improvement in cellulite they received versus 25.8% of sham-treated subjects. There were no reports of adverse events.

Conclusions: Low-level laser therapy using green 532 nm diodes is safe and effective for improving the appearance of cellulite in the thighs and buttocks. In contrast with other technologies, LLLT is effective as a stand-alone procedure without requiring massage or mechanical manipulation. Future studies will assess the long-term benefits of LLLT for the treatment of cellulite. Lasers Surg. Med. 45:141–147, 2013.

Key words: 532 nm wavelength; aesthetic therapy; green diode; gynoid lipodystrophy; noninvasive therapy

INTRODUCTION

Gynoid lipodystrophy, or cellulite, refers to superficial pockets of trapped fat which causes the skin to have an uneven dimpling or "orange peel" appearance. Although rarely seen in men, it is present in 90% of post-adolescent women [1]. Cellulite is most commonly located on the thighs, buttocks, and lower abdomen but is unrelated to obesity which is due to an increase in the number and size of adipocytes.

The cause of cellulite appears to be multifactorial and not universally agreed upon, but is likely due to alterations in the intercellular matrix of subcutaneous tissue and changes in vascular and lymphatic microcirculation

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and have disclosed the following: [Steven Shanks is owner of the company that manufacturers the Erchonia laser used in this study. He also holds patents on the laser and patent pending application for the procedure. Mr. Shanks collaborated with a regulatory consultant during the design of the treatment protocol used in the study; however, at no time did Mr. Shanks have access to the clinical data until the study was completed or have any contact with the patients enrolled in the study].
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[2]. The formation of cellulite is also due to differences in the structural anatomy of subcutaneous tissue in women with a possible influence of estrogen [2,3]. Regardless of the underlying cause, herniation of subcutaneous fat occurs within fibrous connective tissue results in the characteristic appearance of cellulite.

Cellulite does not represent a disease state and there is no cure for it; however, numerous treatments have been developed to improve the appearance of cellulite. Among individuals with poor venous return, vigorous massage may enhance the removal of interstitial fluid by increasing circulation and lymphatic drainage and also break down adhesions [1]. A device consisting of rollers purportedly reduces cellulite by improving venous return and stimulating lipolysis and the production of collagen and elastin [4,5].

Other noninvasive systems have been developed which combine massage or mechanical manipulation with various technologies including bipolar radiofrequency, ultrasound energy, laser or infrared light, and suction [6–13]. Clinical studies performed with all of these devices have reported varying degrees of improvement in the visual improvement in cellulite and skin texture. Numerous topical cosmeceuticals are also promoted as treatments for cellulite which contain caffeine or methylxanthines, retinoids, alpha hydroxy acids, or a variety of herbal extracts [1]. While a few of these report beneficial results [14,15], there is little clinical evidence that the majority of these products can improve the appearance of cellulite [16].

In contrast to noninvasive treatments, mesotherapy involves microinjections of various combinations of drugs, vitamins, and natural extracts into the mesoderm where they reportedly provide beneficial effects by causing lipolysis [17,18]. The safety and efficacy of this procedure have not been established through randomized, double-blinded controlled studies. Consequently, there are no FDA-approved mesotherapy preparations. The use of mesotherapy for the treatment of cellulite has been associated with toxicity and other adverse effects [19,20].

The purpose of this randomized, double-blind, sham-controlled study is to determine the effectiveness of a low-level laser light device employing green 532 nm diodes for improving the appearance of cellulite in the thighs and buttocks. Unlike other technologies, low-level laser therapy will be used as a stand-alone procedure without massage or mechanical manipulation.

METHODS

Study Subjects

The study enrolled healthy subjects who were 18–55 years of age and expressed a desire to improve the appearance of their cellulite. Study subjects were rated as 1 or 2 on the American Society of Anesthesiologists Physical Status Classification System and had moderate bilateral thigh and buttock cellulite graded as Stage II or III on the Nurnberger–Muller scale. Each subject expressed their willingness to abstain from participating in any treatment designed to improve cellulite appearance, promote weight loss or improve body contouring during the study including but not limited to cellulite creams, lotions and gels; over-the-counter and prescription medications including dietary/herbal supplements/minerals and appetite suppressants; weight loss, diet, or exercise programs; light or heat treatments; mesotherapy; surgical procedures such as liposuction, abdominoplasty, stomach stapling, or lap bands; and alternative therapies such as acupuncture, body wraps, hypnotherapy, or massage. Each subject agreed to maintain their normal pre-study diet and exercise regimen.

Reasons for exclusion from the study included cellulite on their thighs or buttocks graded as Stage 0 or I on the Nurnberger–Muller scale; weight fluctuation >10 pounds during the prior month; prior attempts to reduce cellulite in the planned treatment areas during the previous 6 months; current use of any medication known to affect body weight or cause bloating or swelling which could not be safely discontinued during the study; a medical condition known to affect body weight levels or cause bloating or swelling; a history of irritable bowel syndrome; active infection, dermatitis, significant scarring, or trauma in the planned treatment areas; photosensitivity or contraindications to light therapy; diabetes mellitus requiring the use of insulin or oral hypoglycemic agents; cardiovascular disease or a history of cardiac surgery, deep venous thrombosis, or arterial disease of the legs; pregnancy, breast feeding, or planned pregnancy prior to the end of study; mental illness, developmental disability, or cognitive impairment that could prevent providing informed consent or jeopardize the study objectives; or participation in another clinical study during the prior 30 days.

Low-Level Laser Device

The LLLT device used in this study (Erchonia® GL Scanner; Erchonia Corporation, McKinney, TX; GLS) is fundamentally the same as a LLLT device described in previous studies [21] but utilizes six 532-nm green diodes instead of five 635-nm red diodes (Fig. 1). Four mounted diodes in the scanner device are positioned 120° apart from one another and titled at a 30° angle. The remaining two diodes are positioned 4″ from the center and tilted at a 15° angle. Internal mechanics of the GLS collect the laser light emitted from each diode and processes it through a proprietary lens which redirects the beam with a line refractor. The refracted light of each diode is bent into a random, spiraling pattern that is independent of the other diodes. The overlapping patterns of light ensure total coverage of the treatment area. The target area is approximately 8″ × 10″ in. (80 $in.^2$ or approximately 516 cm^2). Each diode has a mean power output of 17 mW and the total output of the six diodes is 102 mW.

The LLLT device used in the clinical trial could be activated with two buttons: based on the randomization schedule, the Investigator would push the button which activated the actual 17 mW, 532 nM laser or the button which activated a sham 1.25 mW, 532 nM green light-emitting diode (LED). When activated, the sham LED light is indistinguishable from green laser light. Subjects were provided with safety goggles during each procedure.

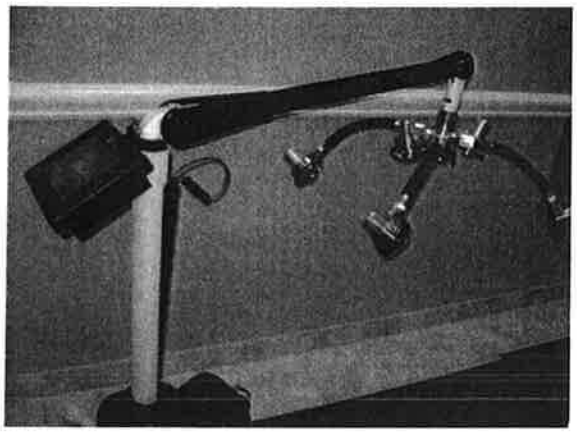

Fig. 1. The prototype LLLT device used in this study utilized six 532 nm green diodes. Each diode had a mean power output of 17 mW and the total output of the six diodes was 102 mW. Based on the randomized treatment for each patient, the Investigator pushed one button on the device which turned on the active 17 mW, 532 nM laser or the button which activated a sham 1.25 mW, 532 nM green light-emitting diode (LED). When activated, the sham LED light is indistinguishable from green laser light.

Procedure

Using a computer-generated sequence methodology, subjects were randomized to undergo LLLT or sham treatment. During the 2-week treatment phase, each subject received three weekly treatment sessions at least 2 days but not more than 3 days apart. Lying on their back, each subject was comfortably positioned on the treatment table. The center diode of the GLS was positioned 4 in. above the abdomen, centered along the body midline and focused on the navel. The device was activated for 15 minutes. Afterward, the subject turned over onto their stomach and the GLS was again positioned 4 in. above the back, centered along the body midline and focused above the navel. The GLS was again activated for 15 minutes.

Primary Outcome Measure

During pre-investigational device exemption (IDE) discussions, representatives of the Food and Drug Administration determined the primary efficacy outcome measure for this study should be the difference in the proportion of LLLT- and sham-treatment subjects achieving a bilateral decrease of one or more stages on the Nurnberger–Muller grading scale, a widely used tool for measuring cellulite [12,22]:

- Stage 0: No dimpling or apparent visible alterations to the skin surface upon standing or lying down or upon pinching the skin.
- Stage I: No dimpling or apparent visible alterations to the skin surface upon standing or lying down. Dimpling appears with the pinch test or muscular contraction.
- Stage II: Dimpling appears spontaneously when standing but not when not lying down. The orange peel appearance of the skin is evident to the naked eye, without need for manipulation.
- Stage III: Dimpling is spontaneously present when both standing and lying down, evident to the naked eye without need for manipulation. Orange peel skin surface appearance with raised areas and nodules.

In addition to classifying cellulite severity, the Nurnberger–Muller scale can be used to assess changes in severity following treatment intervention. Assessments using the Nurnberger–Muller scale were made at baseline, 2 weeks (following the last treatment session) and 6 weeks (4 weeks after the last treatment session).

Other Assessments

Other pre- and post-treatment assessments included circumferential measurements of the right and left thigh, body mass index (BMI), and the body surface area (BSA) covered by cellulite [23,24]. Thigh circumference measurements were made while the subject stood erect with their weight evenly distributed on both feet with legs slightly parted. The circumference of each thigh was measured 1 cm below the gluteal line or fold (buttock crease). The pressure-sensitive tape measure recorded circumference to within 1 mm. All measurements were made by the blinded Investigator.

Other assessments included the presence and location of existing irregularities on the thighs and buttocks such as scars, asymmetries, stretch marks, discoloration; clinical features associated with cellulite including the severity of "orange peel," sub-cyanotic white spots, pain upon skin palpation, hypothermic skin, paresthesias, and telangiectasias; or seroma formation. Enrolled subjects were queried about any changes in routine OTC and prescription medication use or other therapies and diet and exercise regimens reported during baseline assessments.

At the completion of the Week 2 study procedures, each subject was asked to rate how satisfied they were with any overall change in the appearance of the cellulite in their thighs and buttocks areas using the following five-point scale:

- Very Satisfied
- Somewhat Satisfied
- Neither Satisfied nor Dissatisfied
- Not Very Satisfied
- Not at All Satisfied

Safety

Safety assessments consisted of adverse events reported by subjects during the study and any adverse effect in the treatment area observed by the investigators.

Statistical Analysis

The primary endpoint was the proportion of subjects achieving a decrease of ≥ 1 grades of the right and left

thigh and buttocks on the Nurnberger–Muller Scale. Fisher's exact test was used to compare the LLLT- and sham-treated groups. A one-tailed test was applied with an alpha value of 0.05. Changes in secondary outcome measures were assessed across and between treatment groups using *t*-test, ANOVA, ANCOVA and linear regression analysis.

Ethics

The protocol used in this study was approved by an independent institutional review board (Ethical & Independent Review Services, Corte Madera, CA). Each subject provided informed consent prior to participating in any treatment-related activities.

RESULTS

Demographics

The study enrolled 34 subjects in each treatment group (Table 1). All 68 subjects completed the study. There were no significant between-group differences in mean baseline Nurnberger–Muller Scale stages, body weight, BMI, thigh circumference measurements or the amount of BSA affected by cellulite.

Primary Outcome Measure

Nineteen subjects in the LLLT group achieved the individual success criteria (55.88%) versus three subjects (8.82%) in the sham-treated group ($P < 0.0001$; Table 2).

Secondary Outcome Measures

The per-protocol analysis for bilateral changes in Nurnberger–Muller Scale Stage is based on 52 subjects. Two LLLT-treated subjects achieved a 2-stage improvement on the Nurnberger–Muller Scale at the 2-week study endpoint and four did at the 6-week follow-up evaluation versus none of the sham-treated subjects at either time point (Table 3). The majority of sham-treated subjects demonstrated no change in Nurnberger–Muller Scale at the 2- and 6-week evaluations (88% and 79%, respectively).

Subjects treated with LLLT demonstrated a significant decrease in combined baseline thigh circumference at the 2-week study endpoint and 6-week follow-up evaluation (for each, $P < 0.0001$ vs. baseline) while subjects undergoing sham treatment showed no change (Table 4; Fig. 2). Similarly, LLLT-treated subjects showed significant decreases in mean baseline body weight ($P < 0.0005$), BMI ($P < 0.001$) and percent BSA affected by cellulite ($P < 0.0005$) while no change was observed for these parameters among sham-treated subjects (Table 5). Among the participants responding to the satisfaction survey, 62.1% of LLLT-treated subjects were Very Satisfied or Somewhat Satisfied with the improvement in cellulite they received from treatment versus 25.8% of sham-treated subjects (Table 6; Fig. 3).

Other Assessments

None of the participating subjects reported any deviation from baseline diet, exercise or medication use during the study that would impact any study measurements. No

TABLE 1. Subject Demographics

	LLLT-treatment ($N = 30$)[a]	Sham-treatment ($N = 33$)[a]
Female gender	30 (100%)	33 (100%)
Age, mean (SD)	39.87 (10.01)	39.94 (10.72)
Race/ethnicity, *N* (%)		
Caucasian	27 (90%)	31 (94%)
African American	1 (3%)	—
Middle Eastern	2 (7%)	2 (6%)

[a]Data were missing for four subjects in the LLLT group and one in the Sham group.

TABLE 2. Subjects Achieving Individual Success

	LLLT-treatment ($N = 34$)	Sham-treatment ($N = 34$)	Significance[a]
Subjects (%)	19 (55.88)	3 (8.82)	$P < 0.0001$

[a]Fischer's exact test for two independent proportions.

TABLE 3. Changes in Nurnberger–Muller Scale Stages, Per-Protocol Population

	LLLT-treatment ($N = 23$)	Sham-treatment ($N = 29$)
Week 2, *n* (%)		
Decrease of 2 stages	2 (9%)	—
Decrease of 1 stage	13 (56%)	1 (3%)
No change	8 (35%)	27 (94%)
Increase of 1 stage	—	1 (3%)
Week 6, *n* (%)		
Decrease of 2 stages	4 (17%)	—
Decrease of 1 stage	13 (57%)	4 (14)
No change	6 (26%)	27 (83%)
Increase of 1 stage	11	1 (3%)

TABLE 4. Change in Combined Thigh Circumference, Per-Protocol Population

	LLLT-treatment ($N = 23$)	Sham-treatment ($N = 29$)
Change (in.)	Mean (SD)	Mean (SD)
Pre-treatment	47.13 (4.16)	45.59 (4.36)
Post-treatment (Week 2)	45.27 (4.34)*	45.22 (4.35)
Follow-up (Week 6)	44.77 (4.76)*	45.18 (4.44)

*$P < 0.0001$ versus baseline.

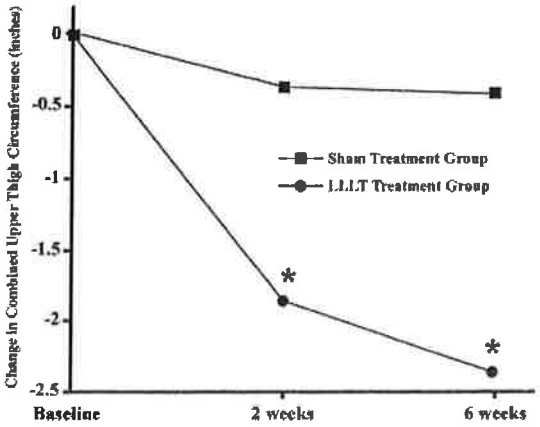

Fig. 2. Subjects treated with LLLT demonstrated a significant decrease in combined baseline thigh circumference at the 2-week study endpoint and 6-week follow-up evaluation while for subjects undergoing sham treatment showed no change. *$P < 0.0001$ versus baseline.

changes in any of the recorded baseline skin markers at any of the three-study evaluation visits were noted for any subject in the study. There were no reports of adverse events.

DISCUSSION

The results of this study indicate LLLT using a green 532 nm diode is an effective stand-alone method for improving the appearance of cellulite. These results are in contrast with other technologies which require massage or mechanical manipulation to achieve beneficial effects. It could be argued that massage may even play a role in the improvements reported following the application topical products for 4 and 12 weeks [14,15]. The repeated application of a cream or gel involves repeatedly rubbing the product into the skin and the act of massaging the affected areas with topical products may be responsible for these results [1].

A large and growing body of research is revealing the unique and diverse biological response that occurs following the application of low-level laser light to living tissue. LLLT has been shown to modify gene expression [25], cellular proliferation [26–30], intracellular pH balance [31], mitochondrial membrane potentials [32], generation of transient reactive oxygen species [33–36], calcium ion levels [33,37,38], proton gradients [39], and cellular oxygen consumption [40].

While the exact mechanism remains unknown, previous work by others has shown that 532 nm lasers induce a biological cascade at the cellular level resulting in observable clinical effects that include promoting collagen synthesis [41–47]. We propose that the use of 532 nm light may correct the irregular pattern of connective tissue associated with collagen and induce skin tightening by stimulating the synthesis of new collagen. The application of green laser may therefore serve as an effective

TABLE 5. Changes in Body Weight, BMI, and BSA Affected by Cellulite

	LLLT-treatment ($N = 23$)	Sham-treatment ($N = 29$)
Body weight (lb), mean (SD)		
Pre-treatment (Baseline)	154.55 (25.53)	154.34 (28.78)
Post-treatment (Week 2)	153.00 (25.26)*	154.05 (28.70)
Follow-up (Week 6)	152.77 (24.86)*	153.62 (28.45)
BMI (kg/m^2), mean (SD)		
Pre-treatment (baseline)	25.99 (3.04)	24.90 (2.69)
Post-treatment (Week 2)	25.73 (2.98)†	24.85 (2.66)
Follow-up (Week 6)	25.70 (2.95)†	24.79 (2.62)
BSA (%), mean (SD)		
Pre-treatment (baseline)	16.65 (6.23)	14.74 (6.92)
Post-treatment (Week 2)	12.76 (6.47)*	14.08 (6.55)
Follow-up (Week 6)	12.33 (6.77)*	13.58 (6.59)

*$P < 0.0005$, one-way ANOVA for correlated samples.
†$P < 0.001$, one-way ANOVA for correlated samples.

TABLE 6. Subject Satisfaction Survey, Per-Protocol Population

	LLLT-treatment ($N = 29$)	Sham-treatment ($N = 31$)
Response, N (%)		
Very satisfied	10 (34.5)	2 (6.5)
Somewhat satisfied	8 (27.5)	6 (19.4)
Neither satisfied nor dissatisfied	8 (27.5)	14 (45.2)
Not very satisfied	1 (3.5)	9 (29.0)
Not at all satisfied	2 (7.0)	—

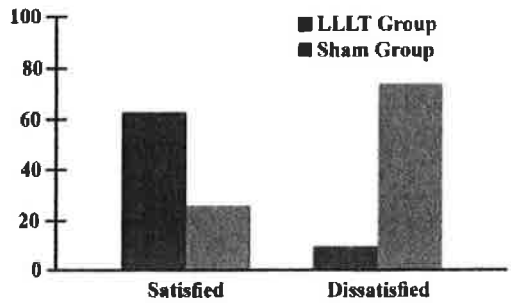

Fig. 3. Among the participants responding to the subject satisfaction survey, 62.1% of LLLT-treated subjects were Very Satisfied or Somewhat Satisfied with the improvement in cellulite they received from treatment versus 25.8% of sham-treated subjects.

method of decreasing the appearance of cellulite by tightening the skin.

The subjects in the study achieved significant improvement in the appearance of cellulite on the thighs and buttocks following six 30-minute treatment sessions over a period of 2 weeks. These improvements persisted for a minimum of 4 weeks following the last treatment. The number of subjects achieving 2-stage improvement on the Nurnberger–Muller Scale increased from two at the 2-week study endpoint to four at the 6-week follow-up evaluation suggesting clinical improvements may even continue to occur following treatment. Future studies will further assess the long-term benefits of LLLT for the treatment of cellulite.

CONCLUSION

Low-level laser therapy using green 532 nm diodes is safe and effective for improving the appearance of cellulite in the buttocks and thighs and buttocks after 2 weeks. In contrast with other technologies, LLLT is effective as a stand-alone procedure without massage or mechanical manipulation. The results from the current study indicate the beneficial effects of LLLT on cellulite persist for 4 weeks. Future studies will assess the long-term benefits of LLLT for the treatment of cellulite.

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