Low-Level Light Therapy for Androgenetic Alopecia: A 24-Week, Randomized, Double-Blind, Sham Device–Controlled Multicenter Trial

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BACKGROUND   Androgenetic alopecia (AGA) is a common disorder affecting men and women. Finasteride and minoxidil are well-known, effective treatment methods, but patients who exhibit a poor response to these methods have no additional adequate treatment modalities.

OBJECTIVE   To evaluate the efficacy and safety of a low-level light therapy (LLLT) device for the treatment of AGA.

METHODS   This study was designed as a 24-week, randomized, double-blind, sham device–controlled trial. Forty subjects with AGA were enrolled and scheduled to receive treatment with a helmet-type, home-use LLLT device emitting wavelengths of 630, 650, and 660 nm or a sham device for 18 minutes daily. Investigator and subject performed phototrichogram assessment (hair density and thickness) and global assessment of hair regrowth for evaluation.

RESULTS   After 24 weeks of treatment, the LLLT group showed significantly greater hair density than the sham device group. Mean hair diameter improved statistically significantly more in the LLLT group than in the sham device group. Investigator global assessment showed a significant difference between the two groups, but that of the subject did not. No serious adverse reactions were detected.

CONCLUSION   LLLT could be an effective treatment for AGA.

The authors have indicated no significant interest with commercial supporters.

Androgenetic alopecia (AGA) is the most common form of alopecia in men and women, and its prevalence is increasing,[1–3] but the Food and Drug Administration has approved a limited number of treatment methods for AGA with respect to efficacy and safety: finasteride and minoxidil for men and minoxidil for women.[4] Patients who have adverse reactions or contraindications or a poor response to these agents have no proper treatment substitutes. There are many off-label medications in use, but evidence of their safety and efficacy is weak or controversial.[5]

Low-level light therapy (LLLT) was first reported in the 1960s and was known to induce a variety of therapeutic effects associated with a range of wavelengths, from red to infrared. Thereafter, LLLT was reported to be effective for short-term pain relief in rheumatoid arthritis, osteoarthritis, tendinopathy, and in cutaneous wound regeneration. LLLT has also been shown to have a stimulatory effect on hair growth, and numerous studies have been performed since the first report.[6] Generally, LLLT appears to be safe and effective in hair loss treatment, but the evidence remains anecdotal and nonscientific, and

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only one controlled study has been reported.[7,8] We conducted a double-blind, sham device–controlled study to evaluate the efficacy and safety of a helmet-type LLLT device in the treatment of AGA.

Methods

Study Design

We designed a randomized, double-blind, sham device–controlled trial at two research centers: Seoul National University Bundang Hospital and Kyungpook National University Hospital. The institutional review board of each center approved this study.

Patient Population

This study included men and women with AGA. Each subject was required to exhibit a Norwood-Hamilton classification of III to VII for men or a Ludwig classification of I to III for women. We excluded individuals who had used topical or systemic medications affecting hair growth, such as finasteride, cyclosporine, or minoxidil, within the past 6 months or who had hair disorders other than AGA or systemic diseases that might affect the results. Informed consent was obtained from all subjects.

Intervention

The Oaze (Won Technology, Daejeon, Korea) is a helmet-type 3R LLLT device with a light source consisting of light-emitting diodes (LEDs) emitting wavelengths of 630 nm (3.5 mW, 24 units, L-513EC-A) and 660 nm (2.5 mW, 18 units, L-513LRC) and laser diodes (LDs) emitting 650 nm (4 mW, 27 units, DL3147–060; Figure 1). All of the diodes run simultaneously through six cycles, each consisting of 2 minutes 50 seconds on and 10 seconds off. The mean energies per unit of each light source with Orion-PD ROHS (Ophir Optronics Ltd., Jerusalem, Israel) were 3.4 mW for 630-nm LED, 2.5 mW for 660-nm LED, and 4.1 mW for LD. Supposing that each light source was tangent to the scalp and the adjoining scalp was flat, each
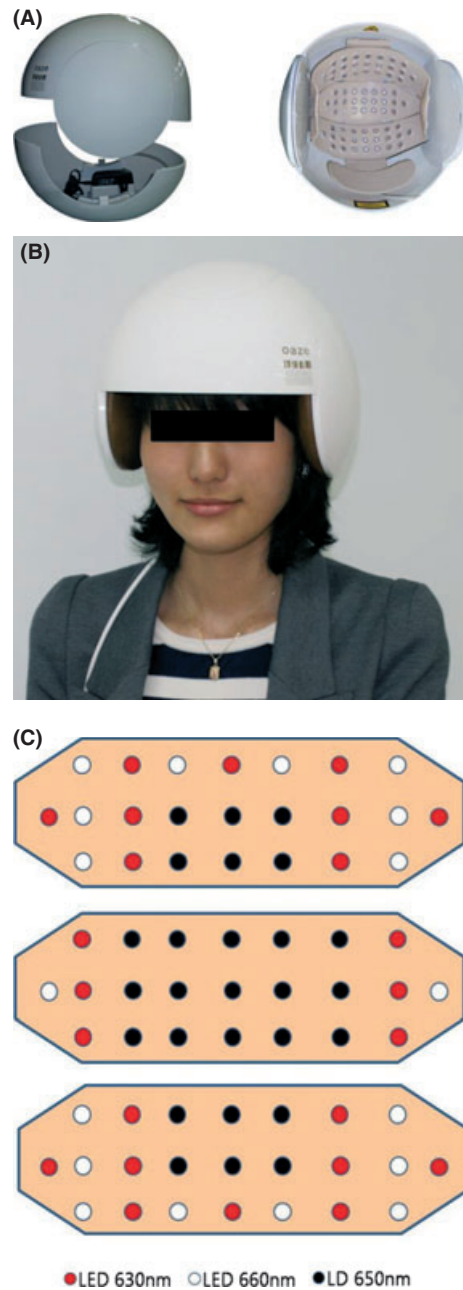
Figure 1. Outward appearance of the low-level light therapy device (A), a person wearing it (B), and the distribution of light sources inside it (C).

energy density per unit of light source was 60.7 mW/cm^2 for the 630-nm LED, 182.8 mW/cm^2 for the 660-nm LED, and 115.4 mW/cm^2 for the LD; total energy density of the LLLT device was 92.15 mW/cm^2. Energy fluence was 47.90 J/cm^2 for 18 minutes of treatment. The sham device was identical in appearance and its regulator operated,

although it emitted no light. We randomly assigned all of the subjects who satisfied the inclusion and exclusion criteria to the LLLT or sham device group, and they were totally blinded. Subjects were instructed on how to operate each device at the baseline visit and scheduled to use it for 18 minutes once daily for 24 weeks. Follow-up visits were scheduled 1, 12, and 24 weeks after the study began to evaluate subjects.

Efficacy Assessment

The primary endpoint was change in hair density in the target area between baseline and after 24 weeks of treatment, as measured using a phototrichogram (Folliscope, LeadM, Seoul, Republic of Korea). The secondary endpoints were changes in the hair shaft in the same lesion according to phototrichogram and global assessment of hair regrowth according to the subject and the investigator. The degree of subjective satisfaction that the subject experienced was also surveyed. The investigators in charge of efficacy assessment were totally blinded.

Phototrichogram Assessment

At the baseline visit, an area of 70 mm^2 was delineated in a target area where miniaturized hairs were prominent on the frontal or vertex area. A tattoo was placed at the center of the area. Thereafter, hair density and thickness were measured using phototrichogram at the baseline, and the 12- and, 24-week visits. The results of phototrichogram for hair density were converted to hair count per square centimeter.

Global Assessment of Hair Regrowth

The investigator and subjects performed global assessment. Subject global assessment was measured on a visual analogue scale, with the designation 0 indicating no growth or aggravation and 10 indicating 100% restoration of AGA at the 1-, 12-, and 24-week visits. The investigator assessed the subjects using visual inspection and digital photographs at the baseline and 12- and 24-week visits. A 5-point

scale (excellent, good, slight, no growth, worse) was used for interpretation. The digital images were standardized for light, angle, and position.

Subjective Satisfaction

The survey for subjective satisfaction was conducted using an 11-point scale from 0 to 10 at the 1-, 12-, and 24-week visits.

Compliance and Safety Evaluation

The running time of each treatment device was checked at each visit, and adherence (total running time (minutes)/3,024 minutes ×100) was calculated from it. A questionnaire regarding discomfort or adverse reaction was administered at the 1-, 12-, and 24-week visits.

Statistical Analysis

Statistical analysis was conducted using SPSS (SPSS 12.0KO for Windows, SPSS Inc., Chicago, IL). Hair density and thickness were analyzed using the t-test, and the global assessment of hair regrowth and degree of subjective satisfaction were analyzed using the Wilcoxon rank sum test. The chi-square test was used for the analysis of adherence and adverse reactions. All statistical analyses were two-sided at a 5% level of significance.

Results

Study Population

Forty subjects, 20 subjects each from two research centers, were enrolled and underwent randomization. The intention-to-treat population included all subjects who underwent randomization. An analysis for demographic characteristics and safety evaluation was performed with the intention-to-treat population. The baseline characteristics of the two groups, the LLLT and the sham device group, are described in Table 1.

After the initiation of the study, two subjects from the sham device group withdrew consent. Nine

TABLE 1. Baseline of Subject Characteristics

Characteristic	Sham Device, n = 20	Low-Level Light Therapy, n = 20
Male, n (%)	12 (60.0)	14 (70.0)
Norwood-Hamilton classification, n		
III	4	6
IV	4	2
V	3	1
VI	1	5
Female, n (%)	8 (40.0)	6 (30.0)
Ludwig classification		
I	8	5
II	0	1
Age	44.5 ± 11.4	43.9 ± 12.2
Height, cm, mean ± SD	167.4 ± 6.6	169.8 ± 7.8
Weight, kg, mean ± SD	65.7 ± 11.8	67.9 ± 10.2
Hair density/cm^2, mean ± SD	130.4 ± 23.3	113.9 ± 18.4
Mean hair thickness, μm, mean ± SD	58.0 ± 11.9	56.1 ± 17.7
Duration of hair loss, months, mean ± SD	100.55 ± 84.8	114.3 ± 86.2

SD, standard deviation.

subjects (5 LLLT, 4 sham device) showed less than 50% adherence. The per protocol set includes the subjects who exhibited greater than 50% adherence and were assessed more than three times (LLLT, n = 15; sham device, n = 14). An analysis for phototrichogram assessment, global assessment of hair regrowth, subjective satisfaction, and adherence was conducted with the per protocol set.

Primary and Secondary Endpoint

Hair density and thickness results of the sham device and LLLT groups are summarized in Tables 2 and 3. There was a significant difference between the two groups in mean changes in hair density and thickness (Table 4). Investigator global assessment of hair regrowth is summarized in Table 5; degree of improvement between the two groups was significantly different (p < .05), but subject global assessment and subjective satisfaction between the two groups were not significantly different.

Adherence and Safety Evaluation

Adherence was not significantly different between the two groups. Of 33 adverse reactions (LLLT, n = 15; sham device, n = 18) in 24 subjects (LLLT, n = 11; sham device, n = 13), 31 were considered to be possibly related to the device. Headache was the most common adverse reaction observed in both groups (LLLT, n = 9; sham device, n = 7), followed by dermatologic problems (LLLT, n = 5; sham device, n = 4), including skin pain, pruritus, erythema, and acne; no severe adverse reactions were noted. There was no significant difference between the two groups in terms of incidence of adverse reactions.

Discussion

The first study on LLLT was published in 1967.[6] Thereafter, many studies demonstrated that exposure of tissue to low-power light (600–1,400 nm) induced a positive biologic response. LLLT, also known as cold laser, soft laser, biostimulation, and photobiomodulation, had many clinical uses such as pain reduction and promotion of wound healing.[9–11] Originally, these properties were thought to be confined to coherent light sources, but noncoherent light sources were later found to share them.[12] The term "low level" was designated because the optimum energy level was lower than those of other forms of laser therapy, such as ablation, cutting, and thermal coagulation of tissue.

TABLE 2. Hair Density and Mean Hair Thickness of Sham Device Group (Per-Protocol Set)

Patient No.	Hair Density/cm²			Mean Hair Thickness, μm		
	Baseline	24 Weeks	Difference	Baselines	24 Weeks	Difference
KU-4	110	106	−4	45	47	2
KU-5	144	120	−24	46	57	11
KU-7	115	90	−25	38	34	−4
KU-8	130	122	−8	70	76	6
KU-10	103	119	16	71	85	14
KU-15	120	127	7	44	58	14
KU-17	96	129	33	51	62	11
KU-18	172	134	−38	51	50	−1
SU-1	175	167	−8	59	50	−9
SU-2	110	112	2	74	69	−5
SU-5	130	143	13	49	51	2
SU-8	124	131	7	47	56	9
SU-14	120	117	−3	78	83	5
SU-17	98	100	2	49	48	−1
Mean ± SD	124.8 ± 24.5	122.6 ± 18.9	−2.1 ± 18.3	55.1 ± 12.8	59.0 ± 14.6	3.9 ± 7.3

SD, standard deviation.

TABLE 3. Hair Density and Mean Hair Thickness of Low-Level Light Therapy Group (Per-Protocol Set)

Patient No.	Hair Density/cm²			Mean Hair Thickness, μm		
	Baseline	24 Weeks	Difference	Baseline	24 Weeks	Difference
KU-2	136	141	5	64	78	14
KU-3	113	134	21	43	57	14
KU-9	116	129	13	66	82	16
KU-13	74	82	8	22	59	37
KU-16	81	131	50	54	66	12
KU-20	117	129	12	42	65	23
SU-3	110	124	14	53	55	2
SU-4	110	122	12	56	65	9
SU-6	115	120	5	65	67	2
SU-9	137	167	30	36	52	16
SU-10	124	136	12	85	84	-1
SU-15	142	153	11	57	75	18
SU-16	141	153	12	45	53	8
SU-19	116	136	20	63	76	13
SU-20	126	159	33	92	98	6
Mean ± SD	117.2 ± 19.6	134.4 ± 20.2	17.2 ± 12.1	56.2 ± 17.9	68.8 ± 13.2	12.6 ± 9.4

SD, standard deviation.

The basic biological mechanism of LLLT on the molecular level is considered to be the absorption of red and near-infrared light by chromophores contained in the protein of components of the respiratory chain of mitochondria, in particular cytochrome c oxidase, which results in photodissociation of inhibitory nitric oxide from cytochrome c oxidase, leading to greater enzyme activity, electron transport, and production of adenosine triphosphate.[13] A recent study showed that LLLT also affected the expression of genes such as activator protein 1, nuclear factor kappa B,

TABLE 4. Summary of Means of Changes in Hair Density and Mean Hair Thickness of Sham Device and Low-Level Light Therapy (LLLT) Group (Per Protocol Set)

Group	Hair Density/cm²	Mean Hair Thickness, μm
Sham device, mean ± SD	−2.1 ± 18.3	3.9 ± 7.3
LLLT, mean ± SD	17.2 ± 12.1	12.6 ± 9.4
p-value (t-test)	.003	.01

SD, standard deviation.

hypoxia-inducible factor 1, leading to protein synthesis that triggered further effects downstream to increase cell proliferation and migration and modulation in cytokine and growth factor levels.[14–16]

Although the first report on LLLT addressed its stimulatory effect on hair growth in 1967,[6] the significance of this beneficial action was re-evaluated in the recent decade. With increased prevalence of alopecia and limited treatment methods, the stimulatory effect of LLLT on hair growth began to make a mark. Thereafter, many studies were reported, and the results indicated positive effects on hair growth in an animal model[17] and a clinical study,[18,19] although there have not been enough well-designed, controlled studies to prove the effect convincingly.

The wavelengths of light used for LLLT fall into an optical window at red and near-infrared wavelengths, as mentioned above, and LLLT with a wavelength of 632.8 nm and 655 nm was demonstrated to have a positive effect on hair growth.[6,8,14] Thus, the wavelength of the light source in the device used in this study was determined nearby the effect-proven wavelengths. Characteristics of the light source were also considered. The emitted light from the laser was notable for its greater degree of spatial and temporal coherence than that from a noncoherent light source, but high electricity consumption, high price, and the need for eye protection were limitations in use. Herein, a coherent (LD) and a noncoherent (LED) light source were employed in the device. Not only the type of light source, but also the number and distribution of each light source were set up in order to generate sufficient energy for biologic effect within electrical capacity and to guarantee safety. Consequently, LEDs of two wavelength (630 and 660 nm) and LD (650 nm) were selected as light sources for the helmet-type LLLT device.

In this study, LLLT improved the hair density and thickness of the subjects with AGA significantly, which objectively supports a positive effect on hair growth. Investigator global assessment also indicated a significant difference, although there was not a significant difference in subject global assessment or subjective satisfaction between the two groups. The discrepancy in these results was probably because improvement in global appearance required a sufficient accumulation of microscopic change. No serious adverse reactions were observed.

The helmet-type device was simple and easy to use and covered the entire affected area, permitting standardization of treatment protocol and quality control to be achieved more easily than with a comb-type device in which interpatient variations in usage were inevitable regardless of the treatment protocol.

TABLE 5. Investigator Global Assessment of Hair Regrowth at the 24-Week Visit

Assessment	Sham Device, N (%)	Low-Level Light Therapy, N (%)	Total, N (%)
Excellent	0 (0.0)	1 (6.7)	1 (3.4)
Good	0 (0.0)	3 (20.0)	3 (10.3)
Slight	1 (7.1)	4 (26.7)	5 (17.2)
No change	11 (78.6)	7 (46.7)	18 (62.)
Worse	2 (14.29)	0 (0)	2 (6.9)

p = .002 (Wilcoxon rank sum test)

Nevertheless, it was difficult to individualize the protocol with the helmet-type device, and the shape of head and density and volume of the hair might affect its efficacy. In addition, the helmet itself might cause discomfort, such as headache, pain, and pruritus, although these effects were not serious. The small number of subjects is a limitation of this study. Although a 24-week treatment was sufficient to evaluate the effects of LLLT, studies concerning the long-term efficacy and safety are necessary, considering the gradual progression of AGA over a long period and the proper evaluation of change in the global appearance, which was not significantly different between the two groups when assessed by subjects in this study. Furthermore, additional studies are suggested to find optimal conditions for wavelength, energy density, and treatment duration for hair regrowth.[14]

In summary, the results of this study suggest that LLLT might be an effective, safe, well-tolerated treatment for AGA. In the authors' opinion, LLLT can be used as an alternative treatment for patients who respond poorly to approved therapies or as an adjuvant treatment with an approved therapy.

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