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Effect of a sphingolipid-mimetic compound on the promotion of hair growth: A randomized, double-blind, placebo-controlled clinical trial

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Abstract

Background: Pattern hair loss is a very common skin disorder, but more therapeutic modalities for hair growth are still required.

Objective: We investigated the effect of a newly synthesized sphingolipid-mimetic compound (pseudo-ceramide: bis-oleamide isopropyl alcohol [BOI]) on the promotion of hair growth for patients with mild pattern hair loss.

Methods: A total of 58 patients with mild pattern hair loss participated in this clinical trial. A randomized, double-blind, placebo-controlled clinical trial was conducted for 6 months. Participants in the experimental group applied 1% BOI lotion (ceramide HS) on the whole scalp once a day for 6 months. Participants in the control group applied simulacrum using the same protocol. We evaluated daily hair loss, hair density, hair thickness, and hair length at intervals of 3 months; patient satisfaction and adverse events were evaluated at 6 months.

Results: At 6 months in the experimental group, daily hair loss at baseline (52.52 ± 33.98) decreased to 40.41 ± 24.78, vertex hair density at baseline (131.07 ± 43.73) increased to 156.00 ± 39.59, frontal hair density at baseline (104.21 ± 30.72) increased to 124.10 ± 28.28, thickness of vertex hair at baseline (0.067 ± 0.012 cm) increased to 0.075 ± 0.014 cm, thickness of frontal hair at baseline (0.070 ± 0.009 cm) increased to 0.076 ± 0.012 cm, and hair growth rate was 16.17 ± 1.89 mm/month.

Conclusion: Ceramide HS may be a new candidate for the treatment of pattern hair loss.

KEYWORDS

ceramide, hair, pattern hair loss, shampoo, sphingolipid

1 | INTRODUCTION

Hair loss is a very common skin problem. The National Institutes of Health estimated in 2018 that approximately 50 million men and 30 million women suffer from pattern hair loss in the United States.[1] There is a strong demand for solutions to prevent hair loss. Oral finasteride and topical minoxidil are approved for the treatment of pattern hair loss by US FDA.[1] Minoxidil is a prodrug that is converted to its active form, minoxidil sulfate and promotes hair growth.[1] Although topical minoxidil is a very safe therapeutic agent, its efficacy remains low. Finasteride is a 5-alpha reductase inhibitor and is effective in the management

of pattern hair loss by reducing levels of dihydrotestosterone.[2,3] However, finasteride can produce an increase in the incidence of sexual dysfunction.

Although not yet approved by the US FDA, other medications and medical devices have been developed or evaluated for efficacy in pattern hair loss recently. Dutasteride is a 5-alpha reductase inhibitor; however, it can increase sexual dysfunction, such as impotence, decreased libido, and ejaculation disorder.[2,4] A preliminary study on topical cetirizine was reported for the treatment of pattern hair loss.[5] Valproic acid was studied for its effect on hair growth in 2012.[6] The efficacy and safety of 0.025% 17-alpha-estradiol solution and the possibility of using prostaglandin F2α analogs for the treatment of pattern hair loss were investigated.[7,8] Low-level laser therapy has been introduced as a safe and effective treatment for pattern hair loss.[9,10] Minimally invasive techniques, including mesotherapy,[11] microneedling,[12] carboxytherapy,[13] and platelet-rich plasma injection,[14] have been used to promote hair growth. Some botanical substances are currently under investigation. Oral saw palmetto (*Serenoa repens*),[15] pumpkin seed oil,[16] *Camellia sinensis* (green tea), *Panax ginseng*,[17] and essential oils[18] were investigated for the control of pattern hair loss. In addition, a complex of 5-aminolevulinic acid and peptides was reported as a novel therapeutic modality.[19] Nevertheless, much more therapeutic modalities are still required for treatment of hair loss and promotion of hair growth.

Pseudo-ceramides are structural substitutes of ceramide, and several have been used as cosmetic ingredients. Pseudo-ceramides have been reported to alter the enzymatic activities involved in de novo sphingolipid synthesis.[20] Until now, most pseudo-ceramides are synthesized with fully saturated acyl groups. A newly synthesized pseudo-ceramide with unsaturated acyl groups, bis-oleamide isopropyl alcohol (BOI, Figure 1), was newly introduced.[20] Park et al reported that BOI stimulated hair growth in cultured human hair follicles and animal models.[20] Therefore, we investigated the effect of the sphingolipid-mimetic compound, BOI, on promotion of hair growth for patients with mild pattern hair loss.

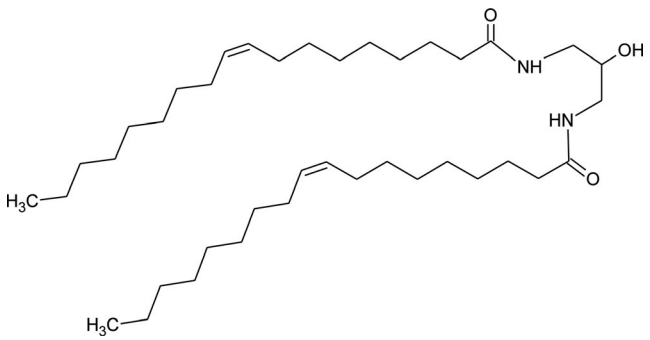

FIGURE 1 The chemical structure of bis-oleamide isopropyl alcohol (BOI)

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 58 patients (men: 53 and women: 5) with mild pattern hair loss (men: Norwood Hamilton classification type I or II, women: Ludwig grade I) participated in this clinical trial. Participants were 20-60 years of age (mean: 36.31 ± 10.60 years). Exclusion criteria included endocrine disorders, immune system disorders, systemic infectious disorders, use of hair-related products within 3 months, hair restoration surgery, and scalp disorders. Twenty-nine participants (men: 28 and women: 1) were included in the experimental group. Mean age was 35.59 ± 10.39 years. Twenty-nine participants (men: 25 and women: 4) were included in the control group. Mean age was 37.03 ± 10.77 years.

2.2 | Methods

2.2.1 | Preparation of sphingolipid-mimetic compound

BOI, a newly developed sphingolipid-memetic compound, was synthesized according to the protocol of Park et al[20] as follows: BOI was synthesized from ultra-pure oleic acid (Reuter Chemische Apparatebau KG, Germany) and 1,3-diamino-2-propanol (Sigma-Aldrich) using amide coupling reagents 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxybenzotriazole (HOBt) at room temperature for 4 hours. The reaction mixture was extracted with DCM and water. A solid compound was then obtained by recrystallization through methanol. The chemical structure of BOI was confirmed by spectral analysis using proton nuclear magnetic resonance (^{1}H-NMR) and liquid chromatography-mass spectrometry (LC-MS). ^{1}H-NMR spectra were recorded on a Varian 600 MHz FT-NMR spectrometer in CDCl3. LC-MS spectra were recorded on an Agilent Technologies Prep. LC/MSD separations module with electrospray ionization in positive ion mode.

2.2.2 | Clinical trial study design

A randomized, double-blind, placebo-controlled clinical trial was conducted for 6 months. Participants were divided into two groups. Participants in the experimental group applied a newly developed sphingolipid-mimetic compound lotion (ceramide HS), which is composed of 1% BOI, castor oil, and ethanol, to the entire scalp once per day for 6 months. Participants in the control group applied simulacrum, which is composed of castor oil and ethanol, to the entire scalp once per day for 6 months. This study was performed after approval by the Institutional Review Board of Kyungpook National University Hospital (IRB no. KNUH 2016-07-026). All patients provided written informed consent.

2.2.3 | Measurement

We evaluated daily hair loss, hair density, hair thickness, and hair growth at intervals of 3 months. Patient satisfaction and adverse events were evaluated at 6 months.

2.2.4 | Daily hair loss

Daily hair loss was measured at 0 (baseline), 3, and 6 months. Each morning, patients combed their hair and collected all of the fallen hairs, and then counted them.

2.2.5 | Hair density

Hair density within designated circular areas having a diameter of 1 cm at the vertex and frontal scalp of each participant were evaluated at 0 (baseline), 3, and 6 months using a phototrichogram technique (Folliscope; LeadM Corp.). The ratio of hair density at 3 and 6 months compared with baseline was calculated.

2.2.6 | Hair thickness

Hair thickness within designated circular areas having a diameter of 1 cm at the vertex and frontal scalp of each participant were measured at 0 (baseline), 3, and 6 months using the phototrichogram technique. The ratio of hair thickness at 3 and 6 months compared with baseline was calculated.

2.2.7 | Hair growth

Changes in hair length for 1 month within designated circular areas having a diameter of 1 cm at the vertex and frontal scalp of each group were measured using the phototrichogram technique.

2.2.8 | Patient satisfaction

We investigated patient satisfaction at 6 months. Patient satisfaction by a questionnaire in which responses were given on a 5-point scale with the following descriptors: worse, poor, moderate, good, and excellent.

2.2.9 | Adverse events

Adverse events were assessed with by patient responses to an open-ended questionnaire and the monitoring by the investigator at each visit. Volunteers reported subjectively about adverse events, and the investigator objectively evaluated clinical indications.

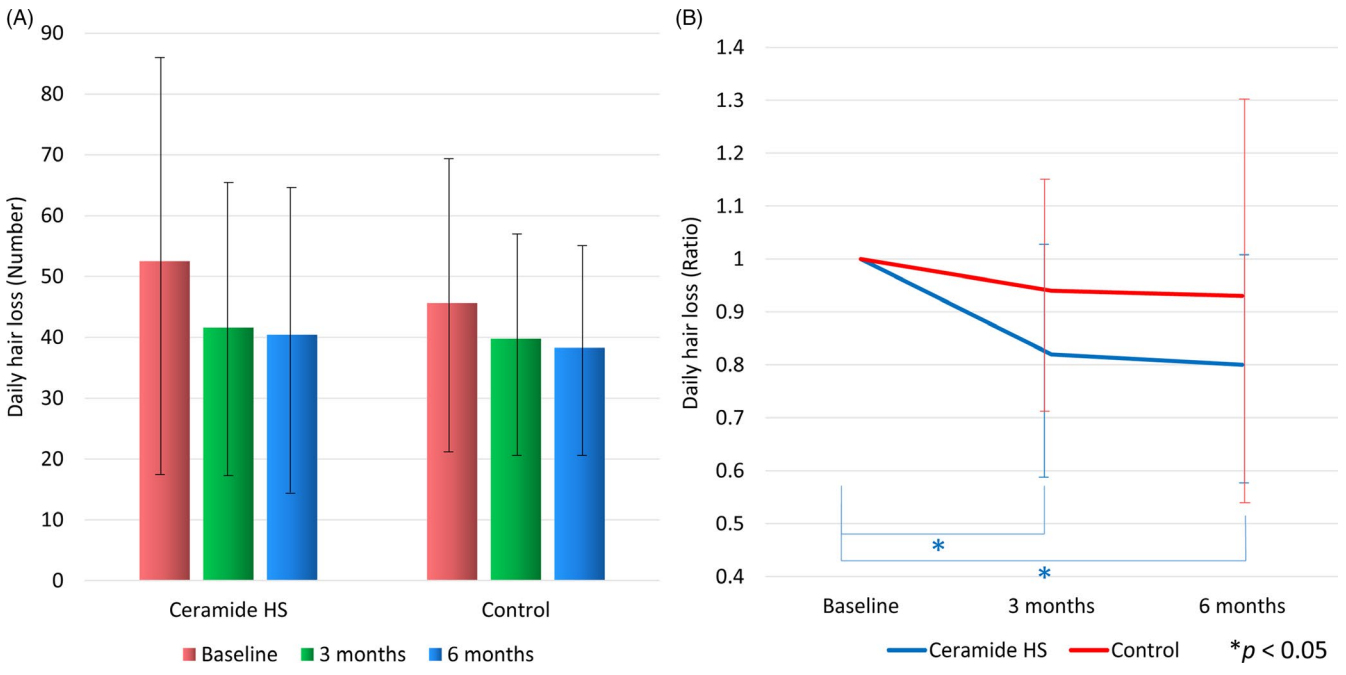

FIGURE 2 A, Daily hair loss. Daily hair loss at baseline (52.52 ± 33.98) decreased to 41.61 ± 24.55 at month 3 and 40.41 ± 24.78 at month 6 in the experimental group. Daily hair loss at baseline (45.64 ± 23.47) decreased to 39.75 ± 17.80 at month 3 and 38.26 ± 16.71 at month 6 in the control group. B, Daily hair loss ratio. In the experimental group, the daily hair loss ratio for month 3 to baseline was 0.82 ± 0.22 and that for month 6 to baseline was 0.80 ± 0.21. In the control group, the daily hair loss ratio for month 3 to baseline was 0.94 ± 0.22 and that for month 6 to baseline was 0.93 ± 0.37

2.3 | Statistical analysis

Statistical analysis was conducted with the Statistical Package for the Social Sciences (SPSS), version 18.0 (SPSS, Inc). Student's *t* test was done to determine differences in baseline demographics, the average ratio of daily hair loss, hair density, hair thickness, and hair growth at each visit between the experimental group and the control group. A repeated measures analysis of variance (ANOVA) was used to assess differences of daily hair loss, hair density, and hair thickness over time in each group. A *P*-value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Daily hair loss

Daily hair loss at baseline (52.52 ± 33.98) decreased to 41.61 ± 24.55 at month 3 and 40.41 ± 24.78 at month 6 in the experimental group (Figure 2A). Daily hair loss at baseline (45.64 ± 23.47) decreased to 39.75 ± 17.80 at month 3 and 38.26 ± 16.71 at month 6 in the control group (Figure 2A). There was no statistically significant difference. In the experimental group, the daily hair loss ratio for month 3 to baseline was 0.82 ± 0.22 and that for month 6 to baseline was 0.80 ± 0.21 (Figure 2B). In the control group, the daily hair loss ratio for month 3 to baseline was 0.94 ± 0.22 and that for month 6 to baseline was 0.93 ± 0.37 (Figure 2B). There was a statistically significant difference between the experimental group and the control group at months 3 and 6.

3.2 | Hair density

Vertex hair density at baseline (131.07 ± 43.73) increased to 132.21 ± 42.32 at month 3 and 156.00 ± 39.59 at month 6 in the experimental group (Figure 3A). Vertex hair density at baseline (139.69 ± 34.30) changed to 130.72 ± 31.93 at month 3 and 142.72 ± 33.02 at month 6 in the control group (Figure 3A). There was a statistically significant difference between baseline and month 6 in the experimental group. In the experimental group, the vertex hair density ratio for month 3 to baseline was 1.03 ± 0.26 and that for month 6 to baseline was 1.27 ± 0.39 (Figure 3B). In the control group, the vertex hair density ratio for month 3 to baseline was 0.97 ± 0.25 and that for month 6 to baseline was 1.04 ± 0.19 (Figure 3B). There was a statistically significant difference between baseline and month 6 in the experimental group. In addition, there was a statistically significant difference between the experimental group and the control group at month 6.

Frontal hair density at baseline (104.21 ± 30.72) changed to 97.14 ± 27.02 at month 3 and 124.10 ± 28.28 at month 6 in the experimental group (Figure 4A). Frontal hair density at baseline (93.28 ± 25.74) changed to 93.48 ± 19.13 at month 3 and 100.52 ± 20.35 at month 6 in the control group (Figure 4A). There was a statistically significant difference between baseline and

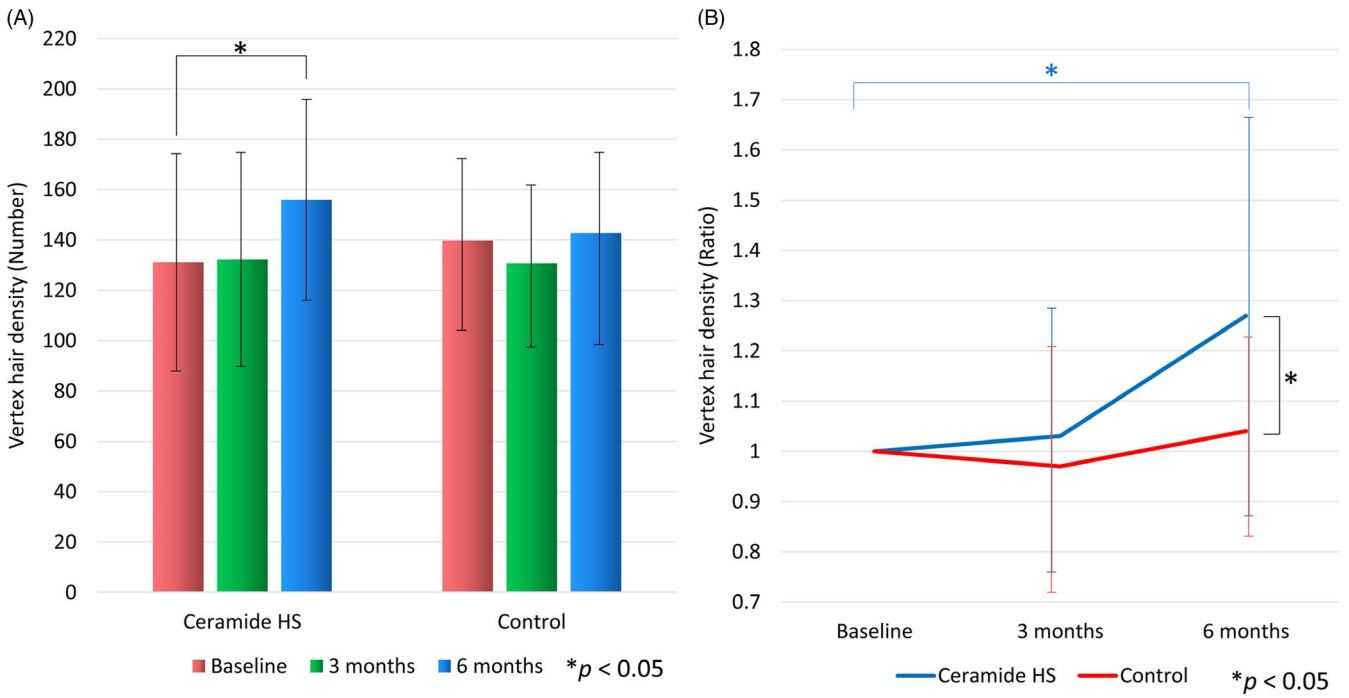

FIGURE 3 A, Vertex hair density. Vertex hair density at baseline (131.07 ± 43.73) increased to 132.21 ± 42.32 at month 3 and 156.00 ± 39.59 at month 6 in the experimental group. Vertex hair density at baseline (139.69 ± 34.30) changed to 130.72 ± 31.93 at month 3 and 142.72 ± 33.02 at month 6 in the control group. B, Vertex hair density ratio. In the experimental group, the vertex hair density ratio for month 3 to baseline was 1.03 ± 0.26 and that for month 6 to baseline was 1.27 ± 0.39. In the control group, the vertex hair density ratio for month 3 to baseline was 0.97 ± 0.25 and that for month 6 to baseline was 1.04 ± 0.19

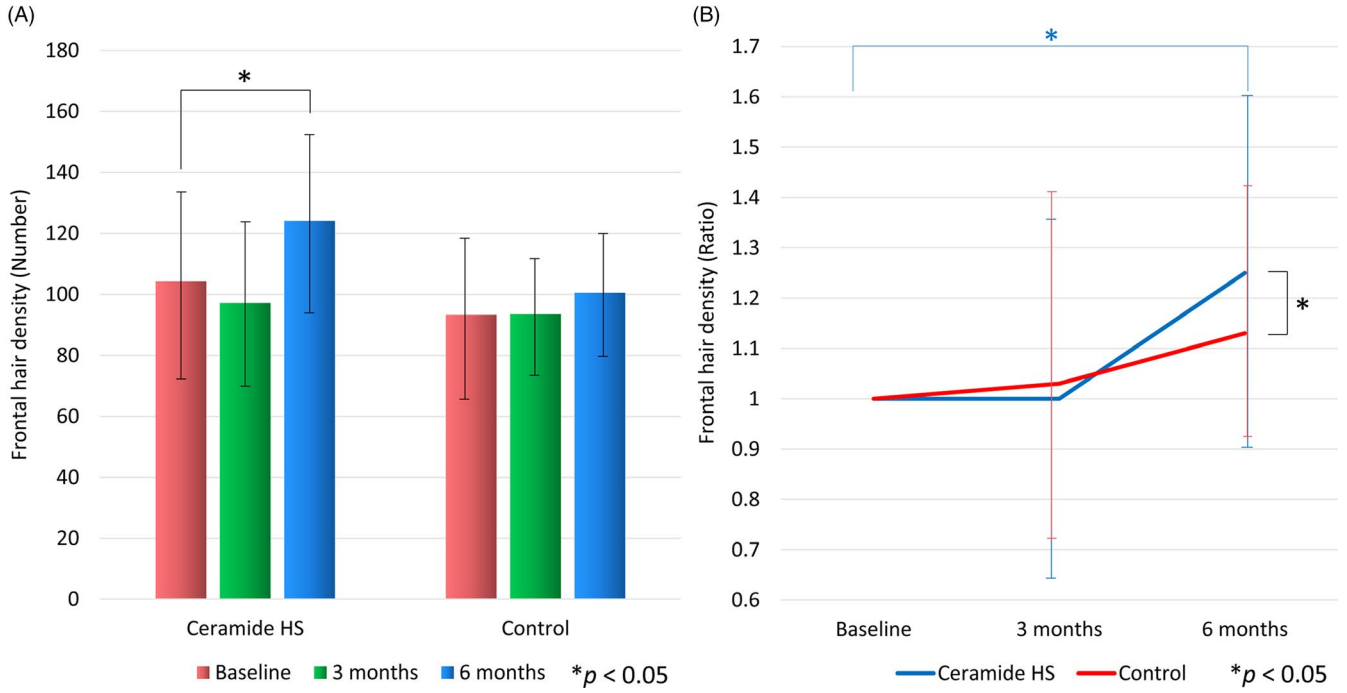

FIGURE 4 A, Frontal hair density. Frontal hair density at baseline (104.21 ± 30.72) changed to 97.14 ± 27.02 at month 3 and 124.10 ± 28.28 at month 6 in the experimental group. Frontal hair density at baseline (93.28 ± 25.74) changed to 93.48 ± 19.13 at month 3 and 100.52 ± 20.35 at month 6 in the control group. B, Frontal hair density ratio. In the experimental group, the frontal hair density ratio for month 3 to baseline was 1.00 ± 0.36 and that for month 6 to baseline was 1.25 ± 0.34. In the control group, the frontal hair density ratio for month 3 to baseline was 1.03 ± 0.23 and that for month 6 to baseline was 1.13 ± 0.29

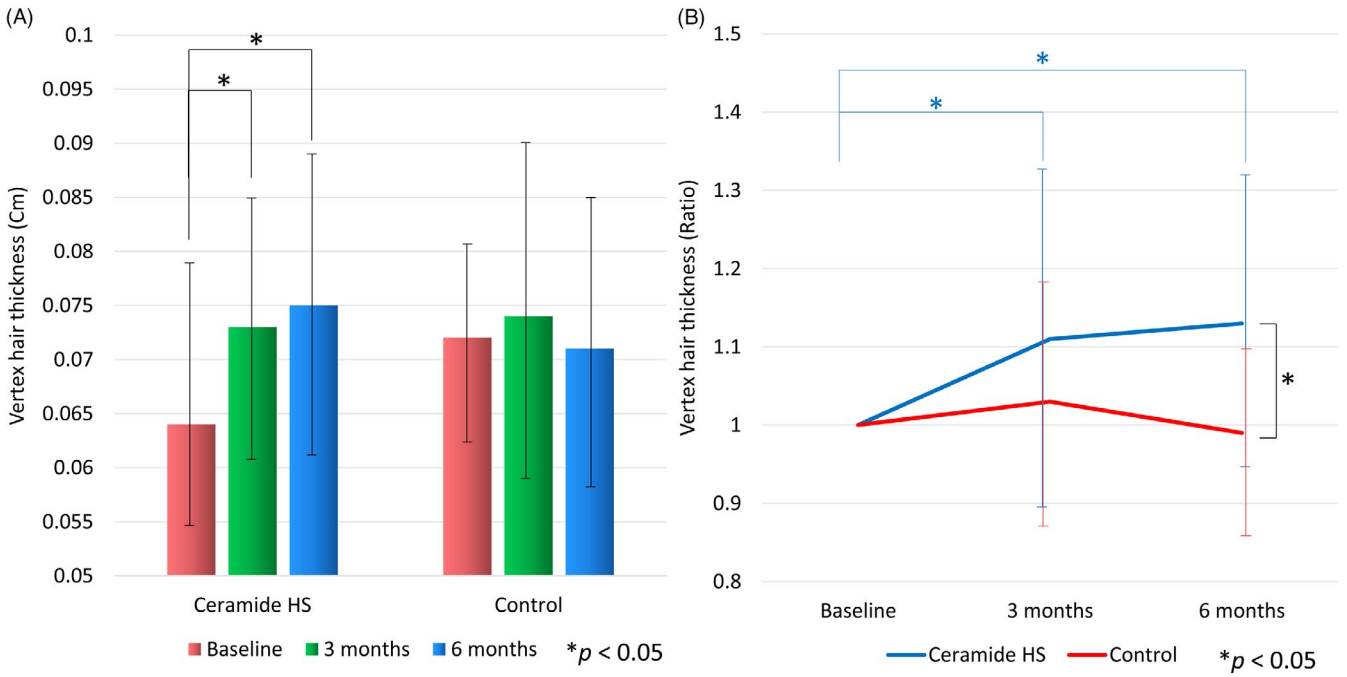

FIGURE 5 A, Vertex hair thickness. The thickness of vertex hair at baseline (0.067 ± 0.012 cm) changed to 0.073 ± 0.012 cm at month 3 and 0.075 ± 0.014 cm at month 6 in the experimental group. The thickness of vertex hair at baseline (0.072 ± 0.009 cm) changed to 0.074 ± 0.015 cm at month 3 and 0.071 ± 0.013 cm in the control group. B, Vertex hair thickness ratio. In the experimental group, the vertex hair thickness ratio for month 3 to baseline was 1.11 ± 0.21 and that for month 6 to baseline was 1.13 ± 0.18. In the control group, the vertex hair thickness ratio for month 3 to baseline was 1.03 ± 0.15 and that for month 6 to baseline was 0.99 ± 0.12

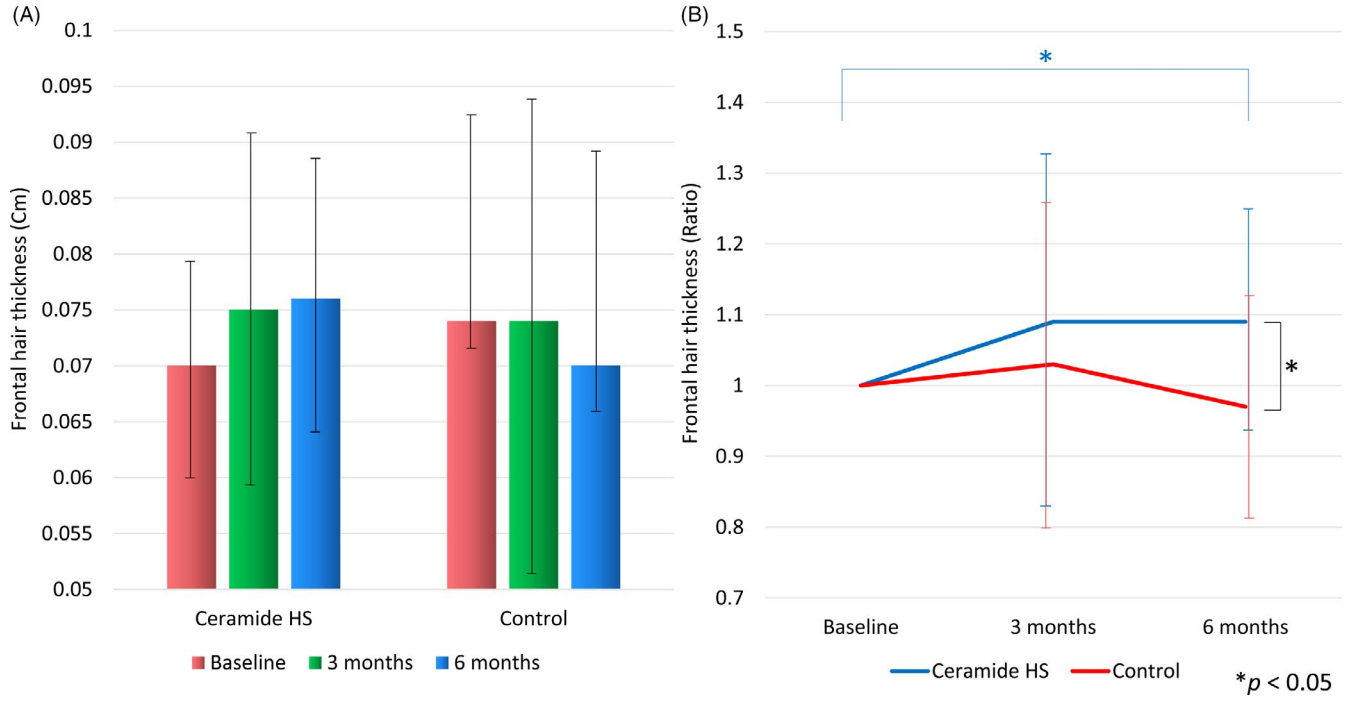

FIGURE 6 A, Frontal hair thickness. The thickness of frontal hair at baseline (0.070 ± 0.009 cm) changed to 0.075 ± 0.016 cm at month 3 and 0.076 ± 0.012 cm at month 6 in the experimental group. The thickness of vertex hair at baseline (0.074 ± 0.011 cm) changed to 0.074 ± 0.010 cm at month 3 and 0.070 ± 0.007 cm at month 6 in the control group. B, Frontal hair thickness ratio. In the experimental group, the frontal hair thickness ratio for month 3 to baseline was 1.09 ± 0.24 and that for month 6 to baseline was 1.09 ± 0.15. In the control group, the vertex hair thickness ratio for month 3 to baseline was 1.03 ± 0.23 and that for month 6 to baseline was 0.97 ± 0.16

month 6 in the experimental group. In the experimental group, the frontal hair density ratio for month 3 to baseline was 1.00 ± 0.36 and that for month 6 to baseline was 1.25 ± 0.34 (Figure 4B). In the control group, the frontal hair density ratio for month 3 to baseline was 1.03 ± 0.23 and that for month 6 to baseline was 1.13 ± 0.29 (Figure 4B). There was a statistically significant difference between baseline and month 6 in the experimental group. In addition, there was a statistically significant difference between the experimental group and the control group at month 6.

3.3 | Hair thickness

The thickness of vertex hair at baseline (0.067 ± 0.012 cm) changed to 0.073 ± 0.012 cm at month 3 and 0.075 ± 0.014 cm at month 6 in the experimental group (Figure 5A). The thickness of vertex hair at baseline (0.072 ± 0.009 cm) changed to 0.074 ± 0.015 cm at month 3 and 0.071 ± 0.013 cm at month 6 in the control group (Figure 5A). There was a statistically significant difference between baseline and each visit in the experimental group. In the experimental group, the vertex hair thickness ratio for month 3 to baseline was 1.11 ± 0.21 and that for month 6 to baseline was 1.13 ± 0.18 (Figure 5B). In the control group, the vertex hair thickness ratio for month 3 to baseline was 1.03 ± 0.15 and that for month 6 to baseline was 0.99 ± 0.12 (Figure 5B). There was a statistically significant difference between baseline and each visit in the experimental group. In addition, there was a statistically significant difference between the experimental group and the control group at month 6.

The thickness of frontal hair at baseline (0.070 ± 0.009 cm) changed to 0.075 ± 0.016 cm at month 3 and 0.076 ± 0.012 cm at month 6 in the experimental group (Figure 6A). The thickness of vertex hair at baseline (0.074 ± 0.011 cm) changed to 0.074 ± 0.010 cm at month 3 and 0.070 ± 0.007 cm at month 6 in the control group (Figure 6A). There was no statistically significant difference between baseline and each visit. In the experimental group, the frontal hair thickness ratio for month 3 to baseline was 1.09 ± 0.24 and that for month 6 to baseline was 1.09 ± 0.15 (Figure 6B). In the control group, the vertex hair thickness ratio for month 3 to baseline was 1.03 ± 0.23 and that for month 6 to baseline was 0.97 ± 0.16 (Figure 6B). There was a statistically significant difference between baseline and month 6 in the experimental group. In addition, there was a statistically significant difference between the experimental group and the control group at month 6.

3.4 | Hair growth

Hair growth for 1 month was 16.17 ± 1.89 mm in the experimental group and 15.79 ± 2.85 mm in the control group (Figure 7). There was no statistically significant difference.

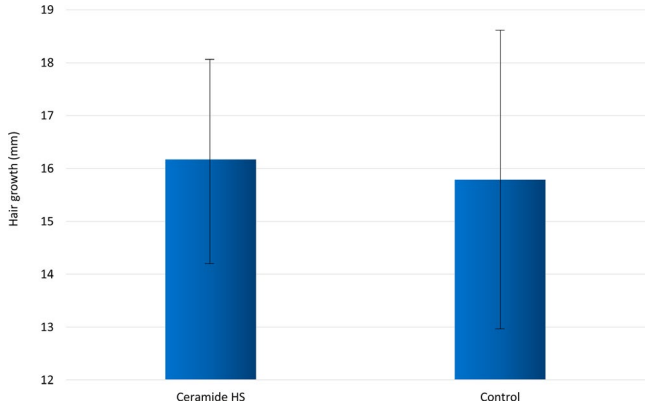

FIGURE 7 Hair growth. Hair growth for 1 mo was 16.17 ± 1.89 mm in the experimental group and 15.79 ± 2.85 mm in the control group

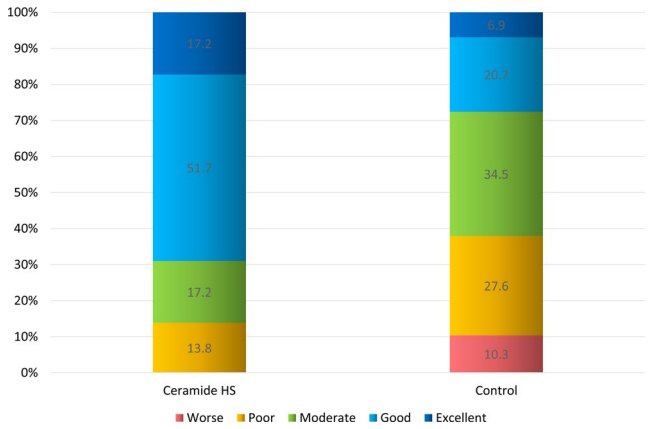

FIGURE 8 Patient satisfaction. Patient satisfaction was assessed at month 6: poor (13.8%), moderate (17.2%), good (51.7%), and excellent (17.2%) in the experimental group; and worse (10.3%), poor (27.6%), moderate (34.5%), good (20.7%), and excellent (6.9%) in the control group

3.5 | Patient satisfaction

Patient satisfaction was assessed at month 6: poor (13.8%), moderate (17.2%), good (51.7%), and excellent (17.2%) in the experimental group; and worse (10.3%), poor (27.6%), moderate (34.5%), good (20.7%), and excellent (6.9%) in the control group (Figure 8). The proportion of good and excellent satisfaction was higher in the experimental group (78.9%) than in the control group (27.6%).

3.6 | Adverse events

There were no serious adverse events. Stickiness was the most common discomfort in using the compound. Twenty-six patients felt sticky in the experimental group. However, 27 patients felt the same discomfort in the control group. In the experimental group, itchy sensations occurred in 2 patients, irritation developed in 2 patients, and folliculitis was seen in 3 patients. In the control group, itchy sensations occurred in 1 patient and folliculitis was seen in 1 patient.

4 | DISCUSSION

Integral hair lipids are composed of fatty acids, phytosphingosine, and ceramide-like epidermal intercellular lipids. These integral hair lipids may act as a barrier against various external aggressors.[21] They may also regulate the hair cycle. Human hair organ culture has shown that inhibition of ceramidase, an enzyme that hydrolyzes ceramide to produce sphingosine, resulted in the retardation of human hair growth and stimulation of anagen-to-catagen transformation.[22] Alkaline ceramidase 1-deficient mice showed aberrant hair shaft cuticle formation and cyclic alopecia.[23] In contrast, inhibition of ceramide synthase 4, an enzyme that catalyzes ceramide biosynthesis, resulted in hair loss.[24] This contradiction may be explained that other sphingolipids produced during de novo synthesis of ceramides, such as sphinganine or sphingosine, regulate hair cycle. Topical application of sphinganine has been reported to reduce human hair loss.[24]

A variety of pseudo-ceramides, structural derivatives of ceramide, have been used as cosmetic ingredients. In addition, pseudo-ceramides are reported as having bioactive characteristics. Pseudo-ceramides can alter enzymatic activities involved in de novo sphingolipid synthesis. Most pseudo-ceramides are synthesized with fully saturated acyl groups, but a pseudo-ceramide with unsaturated acyl groups, BOI, was recently introduced. BOI was reported to stimulate hair growth in cultured human hair follicles and animal models.[20] Bis-oleamide isopropyl alcohol was also reported to induce earlier conversion of telogen hairs into anagen hairs.[20] However, a significant enhancement of growth factor expression and follicular cell proliferation were not observed.[20] However, an increase in sphinganine, sphingosine, and ceramide in dermal papilla cells was observed.[20]

We conducted a clinical trial using BOI. Its application on the scalp resulted in a reduction of hair loss and the promotion of hair growth. Daily hair loss was decreased after treatment with BOI-containing lotion. Hair densities at the vertex and frontal hairline were significantly increased. Hair thickness of vertex frontal hairline was also significantly increased. Hair growth was more prominent in the treated group compared with the control group. Patient satisfaction assessed at six months showed that the proportion of good and excellent satisfaction was higher in the treated group than in the control group. There were no serious adverse events.

In conclusion, the sphingolipid-mimetic compound lotion containing 1% BOI, ceramide HS, is a useful and safe adjunctive modality for the treatment of mild pattern hair loss. More clinical investigation and long-term follow-up will be needed to fully evaluate the efficacy and safety of ceramide HS.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

There was no conflict of interest to declare.

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