Chapter 69
LLLT: Does It Work?

Shigeki Inui

69.1 LLLT and Paradoxical Hypertrichosis

In 1968 Mester et al. examined the carcinogenic potential of a low-power ruby laser (694 nm) using mice. Although there was no carcinogenesis, incidentally finding of hair growth was noted [1]. More recently in humans, undesirable hair growth was observed around treated areas after the laser-assisted hair removal, and this phenomenon has been known as "paradoxical hypertrichosis" [2]. This fact suggested the potential photobiostimulation of hair growth by low-level laser therapy (LLLT). Many basic and clinical studies of LLLT on hair growth have been reported, and several LLLT devices have received FDA 510 (k) clearance [3, 4]. In spite of this clearance for safety and efficacy, LLLT effect on hair loss diseases is still a matter of controversy especially for male pattern hair loss or androgenetic alopecia (MPHL) and female patter hair loss (FPHL). In this review, the randomized controlled trials (RCTs) are surveyed, and the question "Does LLLT work?" is discussed.

69.2 Clinical Trials of LLLT for Hair Loss Diseases

As of the date of this publication, five RCTs of LLLT use for MPHL have been published. Two utilized a comb device [3, 5] and three used a helmet/cap [6–8].

S. Inui, M.D., Ph.D.
S Inui Clinic, Minami-Senba 3–5-11, Chuo-ku, Osaka 542-0081, Japan
e-mail: inui@inuihifuka.com

D. Pathomvanich, K. Imagawa (eds.), *Practical Aspects of Hair Transplantation in Asians*, https://doi.org/10.1007/978-4-431-56547-5_69

69.2.1 Effect of LLLT on Hair Density and Thickness

Jimenez et al. [5] designed the largest study of LLLT thus far. Four multicenter prospective randomized, double-blinded studies were performed. In the trials #1 and #2, FPHL patients were treated with a 9-beam (655 nm) (#1, $n = 53$; sham = 25) or a dual 12-beam (6–655 nm, 6–635 nm) (#2, $n = 42$; sham = 21). In the trials #3 and #4, MPHL patients were treated with a 7-beam (655 nm) (#3, $n = 33$; sham = 16) or a 9- (655 nm) or 12-beam (6–655 nm, 6–635 nm) (#4, 9-beam, $n = 25$; 12-beam, $n = 28$; sham = 26) laser combs. The subjects applied the device three times a week. The irradiation periods were 15 min for the 7-beam, 11 min for the 9-beam, and 8 min for the 12-beam device. The treatment was continued for 26 weeks. Scalp assessment, global and macro digital imaging after hair clipping, and computer-aided hair counts were carried out. All four studies showed significant terminal hair density increase by LLLT compared with the sham treatments. Global photographs to show hair volume increase were provided only in a female subject. The result of self-assessment did not always reach statistical significance. Laser comb-related adverse events were dry skin (5.1%), pruritus (2.5%), scalp tenderness (1.3%), irritation (1.3%), and a warm sensation at the treated site (1.3%). However, there were no serious adverse events that resulted in discontinuation of the treatments.

Leavitt et al. [3] reported similar results by comparing the laser comb ($n = 71$) and sham device ($n = 39$). The LLLT showed significant terminal hair density increase compared with the sham after 26 weeks.

Kim et al. [6] evaluated a helmet-type LLLT device consisting of LEDs (630 nm) and laser diodes (650 nm) for MPHL and FPHL at two research centers. Treatments were performed once a day for 24 weeks. The duration of each treatment was 18 minutes, and its irradiation energy was 47.90 J/cm^2. LLLT significantly increased hair density and thickness ($n = 15$) compared with the sham treatment ($n = 14$). The investigator global assessment (excellent, good, slight, no change, worse) was good or excellent in 26.7% in the treatment group, but no sham group subjects were rated good or excellent, demonstrating significant positive effect on hair appearance ($p = 0.002$, Wilcoxon ran sum test). However, the global photographs were not provided.

Similarly, two other trials reported by the same author showed significant hair growth in MPHL [7] and FPHL [8] by the helmet/cap devices containing laser diodes and LEDs (both, 655 nm).

Together, these five RCTs demonstrated significant hair regrowth by LLLT. Therefore, LLLT is a well-evidenced and safe treatment for MPHL and FPHL. These evaluations primarily examined precise objective hair parameters such as density and width. However, the subjective effect on hair appearance was demonstrated only by global photographs of one case by Jimenez et al. [5] and by global point assessment by Kim et al. [6]. Moreover, no study compared LLLT and conventional drugs such as topical minoxidil [9, 10], oral finasteride [11, 12], and dutasteride [13]. Therefore, at present, LLLT should be considered as an adjunctive therapy to these treatments. Further, if patients dislike currently available medical treatments, LLLT may be offered as an alternative method.

69.3 Potential Mechanism of LLLT/LED Effect

For LLLT to be effective, light must penetrate the skin and reach hair follicles. Therefore, red or near-infrared lights (600–950 nm) are appropriate for hair treatments. In general, light must reach receptors in the cells, known as photoacceptors or chromophores [14]. Cytochrome C oxidase, which catalyzes the final step in the mitochondrial electron transfer chain, is a potential photoacceptor of red or near-infrared lights [15]. However, the mechanism downstream from the photoacceptor is not clear, and the search continues for potential mediators to exert the biological functions of red or near-infrared lights, particularly using LED [16]. First, to examine effect of LED light on hair growth, the dorsa hairs of 7-week-old female BL-6 mice were shaved off. Starting the next day (day 1), red LED light (638 nm/1.0 J/cm^2) was irradiated for 20 minutes three times a week. Thereafter, we took photos of the dorsa skin and measured the percentage of hair regrowth. No LED light was irradiated elsewhere for a control. At days 18 and 22, hair regrowth areas were significantly increased by red LED light irradiation when compared to controls. In addition, the dorsa skin of the red LED irradiation group at day 22 was colored black, indicating anagen induction. Furthermore, we searched molecular mechanisms of LED stimulation on hair growth using cultured normal human dermal papilla cells irradiated with red (638 nm/1.5 J/cm^2) LED. RNA samples were extracted from the cells and subjected to semiquantitative RT-PCR for various growth factors and cytokines. Analysis revealed mRNA of HGF, leptin, and VEGF-A was increased. Then, we confirmed the enhanced production of these factors by red LED light at the protein level from cultured normal human dermal papilla. The conditioned media of dermal papilla cells irradiated with red LED were harvested and used to measure the protein levels of the cytokines by ELISA. We found that HGF, leptin, and VEGF-A were significantly increased, agreeing with previous observations: (1) upregulation of HGF reportedly accelerates hair growth and retards entry to catagen in hair cycling [17, 18], (2) leptin induces the anagen phase of hair cycle [19], and (3) VEGF-A induces perifollicular angiogenesis, accelerating hair regrowth [20].

Recently, the wavelength-dependent effects of hair growth were examined using laser diodes with wavelengths of 632, 670, 785, and 830 nm in Sprague-Dawley rats. Results revealed that LLLT with a 830-nm wavelength induced greater stimulation of hair growth than the other wavelengths examined [21]. Accordingly, LLLT of longer wavelengths than utilized today may have more potent effects on hair growth.

69.4 Conclusion

The stimulatory effect of LLLT/LED has been convincingly demonstrated by several RCTs, but its potency has not been definitively established. At present, LLLT should be considered as an adjunctive or alternative therapy to conventional treatments. Therefore, further basic and clinical studies are needed for refinement of the devices and light sources.

References

1. Mester E, Ludany G, Sellyei M, Szende B, Gyenes G, Tota GJ. Studies on the inhibiting and activating effects of laser beams. Langenbecks Arch Chir. 1968;322:1022–7.
2. Lolis MS, Marmur ES. Paradoxical effects of hair removal systems: a review. J Cosmet Dermatol. 2006;5(4):274–6. https://doi.org/10.1111/j.1473-2165.2006.00269.x.
3. Leavitt M, Charles G, Heyman E, Michaels D. HairMax LaserComb laser phototherapy device in the treatment of male androgenetic alopecia: a randomized, double-blind, sham device-controlled, multicentre trial. Clin Drug Investig. 2009;29(5):283–92. https://doi.org/10.2165/00044011-200929050-00001.
4. Afifi L, Maranda EL, Zarei M, Delcanto GM, Falto-Aizpurua L, Kluijfhout WP, et al. Low-level laser therapy as a treatment for androgenetic alopecia. Lasers Surg Med. 2017;49(1):27–39. https://doi.org/10.1002/lsm.22512.
5. Jimenez JJ, Wikramanayake TC, Bergfeld W, Hordinsky M, Hickman JG, Hamblin MR, et al. Efficacy and safety of a low-level laser device in the treatment of male and female pattern hair loss: a multicenter, randomized, sham device-controlled, double-blind study. Am J Clin Dermatol. 2014;15(2):115–27. https://doi.org/10.1007/s40257-013-0060-6.
6. Kim H, Choi JW, Kim JY, Shin JW, Lee SJ, Huh CH. Low-level light therapy for androgenetic alopecia: a 24-week, randomized, double-blind, sham device-controlled multicenter trial. Dermatol Surg. 2013;39(8):1177–83. https://doi.org/10.1111/dsu.12200.
7. Lanzafame RJ, Blanche RR, Bodian AB, Chiacchierini RP, Fernandez-Obregon A, Kazmirek ER. The growth of human scalp hair mediated by visible red light laser and LED sources in males. Lasers Surg Med. 2013;45(8):487–95. https://doi.org/10.1002/lsm.22173.
8. Lanzafame RJ, Blanche RR, Chiacchierini RP, Kazmirek ER, Sklar JA. The growth of human scalp hair in females using visible red light laser and LED sources. Lasers Surg Med. 2014;46(8):601–7. https://doi.org/10.1002/lsm.22277.
9. Olsen EA, DeLong ER, Weiner MS. Long-term follow-up of men with male pattern baldness treated with topical minoxidil. J Am Acad Dermatol. 1987;16(3 Pt 2):688–95.
10. Olsen EA, Weiner MS, Delong ER, Pinnell SR. Topical minoxidil in early male pattern baldness. J Am Acad Dermatol. 1985;13(2 Pt 1):185–92.
11. Kaufman KD, Olsen EA, Whiting D, Savin R, DeVillez R, Bergfeld W, et al. Finasteride in the treatment of men with androgenetic alopecia. Finasteride male pattern hair loss study group. J Am Acad Dermatol. 1998;39(4 Pt 1):578–89.
12. Leyden J, Dunlap F, Miller B, Winters P, Lebwohl M, Hecker D, et al. Finasteride in the treatment of men with frontal male pattern hair loss. J Am Acad Dermatol. 1999;40(6 Pt 1):930–7.
13. Gubelin Harcha W, Barboza Martinez J, Tsai TF, Katsuoka K, Kawashima M, Tsuboi R, et al. A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia. J Am Acad Dermatol. 2014;70(3):489–498. e3. https://doi.org/10.1016/j.jaad.2013.10.049.
14. Sutherland JC. Biological effects of polychromatic light. Photochem Photobiol. 2002;76(2):164–70.
15. Karu TI. Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation. IUBMB Life. 2010;62(8):607–10. https://doi.org/10.1002/iub.359.
16. Fushimi T, Inui S, Ogasawara M, Nakajima T, Hosokawa K, Itami S. Narrow-band red LED light promotes mouse hair growth through paracrine growth factors from dermal papilla. J Dermatol Sci. 2011;64(3):246–8. https://doi.org/10.1016/j.jdermsci.2011.09.004.
17. Lee YR, Yamazaki M, Mitsui S, Tsuboi R, Ogawa H. Hepatocyte growth factor (HGF) activator expressed in hair follicles is involved in in vitro HGF-dependent hair follicle elongation. J Dermatol Sci. 2001;25(2):156–63.
18. Yamazaki M, Tsuboi R, Lee YR, Ishidoh K, Mitsui S, Ogawa H. Hair cycle-dependent expression of hepatocyte growth factor (HGF) activator, other proteinases, and proteinase inhibitors

correlates with the expression of HGF in rat hair follicles. J Investig Dermatol Symp Proc. 1999;4(3):312–5.
19. Sumikawa Y, Inui S, Nakajima T, Itami S. Hair cycle control by leptin as a new anagen inducer. Exp Dermatol. 2014;23(1):27–32. https://doi.org/10.1111/exd.12286.
20. Yano K, Brown LF, Detmar M. Control of hair growth and follicle size by VEGF-mediated angiogenesis. J Clin Invest. 2001;107(4):409–17. https://doi.org/10.1172/JCI11317.
21. Kim TH, Kim NJ, Youn JI. Evaluation of wavelength-dependent hair growth effects on low-level laser therapy: an experimental animal study. Lasers Med Sci. 2015;30(6):1703–9. https://doi.org/10.1007/s10103-015-1775-9.