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We are very pleased to have the lead article in this issue by our incoming ISHRS President, Dr. Sharon Keene. This article is the first of her three-part series on low level laser light therapy (LLLT): Part 1, "The Science of LLLT," Part 2, "Regulation of LLLT Devices from a U.S. and International Perspective," and Part 3, "Controlled Trials and Understanding the Methods for Accurate Hair Counts." —RHT

The Science of Light Biostimulation and Low Level Laser Therapy (LLLT)

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The use of light therapy from the sun can be seen illustrated long ago in ancient Egyptian hieroglyphics. Today, the critically important process of photosynthesis, or ability of sunlight to induce chemical changes in plants to consume carbon dioxide and produce water and oxygen, is considered basic science, and taught in elementary school classes. The concept of light-induced cellular chemical reactions is not new—but the acceptance of laser light to induce therapeutic chemical changes in human cells has been slow and gradual.

In the early 1960s, only a few years after their discovery, lasers were first introduced to the medical field for their ability to ablate, dissect, cauterize, or vaporize tissue. It was a serendipitous discovery in 1967 when Dr. Endre Mester, a Hungarian physician and surgeon, first observed the biostimulating or photomodulating effects of low level laser light on tissue. Dr. Mester applied a ruby laser beam of 694nm to the backs of shaved mice, seeking to evaluate potential carcinogenic changes, when he noted instead more rapid regrowth of hair.[1] Since that time, low level laser light has been studied in over 100 randomized, controlled trials and accepted as a therapeutic modality in many human tissues.[2] Ironically, it would take 40 years from the first observation of photostimulated hair growth in mice until the first low level laser therapy (LLLT) device would receive legal clearance in the United States for the treatment of androgenetic alopecia in humans.[3] Since the first device clearance in 2007, other devices utilizing light from laser diodes, as well as light emitting diodes (LED), have been cleared by the FDA and introduced to the U.S. market; similarly, a myriad of devices used in Asia and around the world to treat hair loss have emerged, too.

It should be noted at the outset of this planned series of articles on LLLT to treat hair loss, that many questions remain about its true efficacy, and clinical studies have not addressed some of them. Clearly, there are patients who have tried some of these devices without benefit. The purpose of this series of articles will be to review the science that supports a potential benefit for LLLT to treat hair loss in some patients, as well as the practical limitations of current devices based on variations in hair characteristics and coverage—and certain properties of light in general, as well as device designs or use, in particular. Subsequent articles in this series will delve into what doctors need to know about medical and laser device regulation. In particular, how to determine whether the device your patient is using, or you are selling, is legal in your jurisdiction. Devices that haven't been approved by regulatory agencies may not have met requirements for safety, and may also pose issues of legal liability—which means they are not prudent for consumer use, and neither for a doctor's good reputation. Furthermore, there are now several randomized, controlled trials that support the use of LLLT to treat hair loss, and these will likely be used for marketing purposes, so doctors need to be familiar with them and their reported conclusions. Importantly, some of these studies appear to have substantive flaws in hair counting methodology raising critical questions of their validity and claims, and the correct method to gather and analyze this data will be reviewed. Issues pertaining to dosing or application of particular wavelengths and timing/frequency with a view to encouraging member participation in future clinical trials will also be discussed.

Low Level Laser Light and Mechanisms of Cell Biostimulation

Low level laser light is defined in part by its wavelength which is visible light in the 500nm-1100nm wavelength range, and this determines its properties of tissue absorption. The other characteristic is low power and low power density,

1mW-500mW (5W) and 1mW-500mW/cm^2, respectively, ensure a low thermal output and prevent tissue heating. Studies have shown a minimum of 13 W/cm^2 is required to cause first degree skin burns, and 24 W/

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cm^2 for second degree burns.[4] Maintaining low power in LLLT devices helps avoid thermal injury to tissue and allows the opportunity for photostimulation to occur. The first law of photobiomodulation states that a cell must have a chromophore or photoacceptor that absorbs light photons in order to stimulate a biologic response. The most common photoacceptors in tissue are melanin, hemoglobin (oxyhemoglobin and deoxyhemoglobin), and water. These are well known to doctors who may have lasers for hair removal or other cosmetic uses as these are targets for laser light. However, these chromophores actually have their lowest rate of absorption of light for the above range of wavelengths, thus creating what is referred to as the "optical window," because with minimum absorption by these chromophores, the light wave can be absorbed elsewhere for its biostimulating effects to occur. Studies reveal the cellular organelles involved in low level laser biostimulation are the mitochondria. Specifically, a portion of that organelle's energy and respiratory chain contains a chromophore called cytochrome c oxidase—it is the last step in the electron transport system of the mitochondria. Cytochrome c oxidase is reversibly inhibited by nitric oxide (NO) from performing its functions of electron transport and creating energy for the cell. Photons apparently are able to remove NO from cytochrome c oxidase, liberating it to perform other cellular functions. Among the functions cytochrome c oxidase is associated with are increased ATP production and modulation of reactive oxygen species, which can induce transcription factors that activate genes and produce proteins useful to the cell. The latter can result in increased cell proliferation and migration, production of growth factors (i.e., nerve growth factor), production of inflammatory mediators and cytokines, as well as increases in tissue oxygen.[2,5] There is some evidence to suggest it may even play a role in modulating 5-alpha reductase. Specifically in regard to hair growth, it is postulated these cellular effects result in stimulation of anagen re-entry, prolongation of the anagen phase, proliferation of anagen hair follicles, and prevention of premature catagen.[5]

It has been observed that cells in tissue culture when stimulated with varying wavelengths of low level laser light produced four peaks of DNA production felt to be a reflection of increased cytochrome c oxidase activity. These wavelength ranges (to the nearest single digit) were 614-624nm, 668-684nm, 751-772nm, and 813-846nm.[1,6] Remarkably, none of the published laser device studies to date conform to these wavelengths, raising the question of whether efficacy would be enhanced if they did.

Low Level Light Therapy as Medication and Dose

When considering low level light as medical therapy, it can help to consider the irradiance parameters as "the medicine." The medicine, then, includes the wavelength, which determines which chromophores will offer the greatest absorption; and the irradiance, which in mathematical terms is the power (Watts) administered to a given area, or Watts/cm^2. Keep in mind that in the United States, LLLT devices are part of a laser class that allows a maximum power of 5mW or .005 watts.

The dosing of the "medication" adds in the element of time, or irradiation duration, known as energy. Energy is given by Watts × time (sec) = Joules. Fluence is Joules/cm^2. The dose is also affected by frequency of or interval between therapies.[2,7]

Therefore, when using low level light as a therapy, the wavelength will determine a target for absorption, and the radiant energy that travels with it will determine the level of cellular excitation the light can create—meanwhile duration and interval will determine how long and frequent this excitation must occur for the desired cellular effect and clinical outcome.

Properties of Light Impacting Light Delivery and Effect on Cells

How Light Interacts with Tissue

Light interacts with tissue in the following ways: it can be reflected, transmitted, scattered or absorbed. Light wavelengths help determine the absorption of various chromophores as previously stated, but other tissue properties contribute to interactions that reduce absorption, too.[8] For example, melanin is a known chromophore that absorbs light. Between the two types of melanin in hair, pheomelanin (blonde or red hair) and eumelanin (brown or black hair), the latter has one of the highest light absorption properties of any tissue. In fact, in a published bioengineering study using a computer simulation model to study the effect of hair color on low level laser light transmission (635nm, 5mW) for photodynamic therapy of the scalp, it was concluded that light transmission was reduced between 32-37% depending on hair color—blonde hair allowing greater light transmission than black hair. Importantly, this model assumed a hair length of only 2mm, and therefore did not consider how layering of hair would reduce transmission. Furthermore these numbers assumed a level of transmission into skin to be very superficial, only .08mm deep—less than full depth of the epidermis.[9] When the model assumed greater skin depths of penetration, light transmission was reduced even further. One could assume transmission would be strongly impacted with longer hair lengths and layering of hair on skin—although the latter was not considered for this study. This strongly draws into question the benefit of beaming LLLT onto hair with hoods and helmets—where hair absorbs, reflects, and scatters light. The more hair present, the less likely it is that light will be transmitted to the scalp and absorbed by its intended target, in particular, follicle mitochondria.

The Inverse Square Law & Lamberts Cosine Law Effecting Light Transmission for LLLT devices

One of the physical properties of light that can affect light transmission and irradiance is referred to as the "inverse square law," which states: intensity of radiation varies inversely with the square of the distance from the source, and is described in the equation I = 1/d2. What this means is that light intensity is reduced based on the target's distance from the source. For example, for a target (scalp) that is twice (2cm) the distance from the source, light intensity is reduced to one-fourth the intensity at 1cm, and a target 3 times (3cm) the distance from the source receives only one-ninth the light intensity. The inverse square law, however, assumes the divergent properties of a normal light beam. Laser light is collimated and coherent with substantially less divergence of the beam and when it hits a target has a spot size that influences its power and intensity. Laser diode beams are more oval in shape—and unless controlled by a focusing lens, they will still follow a modified inverse square law so that distance from the source is a factor impacting light intensity and transmission.

LED lights are not collimated or coherent, but provide less

beam divergence than regular light bulbs. Nevertheless, LEDs are more affected by a modified inverse square law effect because of their beam divergence. This means their beam may cover a larger area, distance from the source (light) can be expected to have an impact on intensity at their target (scalp), too. Ultimately, for LLLT devices, distance is a factor when trying to apply light at a particular dose for scalp absorption and therapeutic response.[10] Devices (such as hoods or overhead apparatus) that beam light from a distance cannot claim comparable dosing, even when using the same wavelengths and treatment frequency, as a similar device that touches, or nearly touches, the skin.

Lamberts Cosine law of light states that a beam perpendicular to its target provides 100% irradiance, but is reduced at oblique angles as a cosine of the incident angle, because the light is spread over a wider area. The cosine law indicates that off angle beams at the most oblique angle can end up being completely reflected. Off angle light from hoods and overhead apparatus will results in reduced irradiance—presumably below therapeutic doses if calculated on the assumption of a perpendicular beam—especially one that touches the skin.[10]

Collimated and Coherent (Laser) vs. Non-coherent Light (LED)

Normal light bulbs, as previously noted, beam light in a variety of colors and wavelengths in all directions, which results in ambient lighting. This is remarkably different than laser light where each beam of light produced is monochromatic (same color and wavelength) and collimated and coherent, so that light waves move parallel to one another and in the same direction forming a "spot" at the target—described as "spot size" for purposes of calculating power density.

LED light, while also a largely monochromatic beam, may vary slightly in wavelength and is much more divergent (non-coherent) than laser light, as previously noted. Furthermore, it is not collimated, so LED beams do not run parallel to each other. LED light illuminates a larger area, but results in much lower light intensity than laser light. LED light in the visible/NIR spectrum has been deemed a non-significant risk by the U.S. FDA and cleared for human use.[11]

The Arndt-Schultz Law or Biphasic Dose Response for LLLT

A biphasic dose response means that when low level laser light is applied at a wavelength and dose that is too low, no tissue response will occur. If it is applied at a dose that is too high, it can inhibit a tissue response. There is, for a given biostimulus, an optimal dose (timing and interval) where a maximal response is obtained. This has been seen in studies of wound healing where too low a dose did not have an impact, and too high a dose prolonged wound healing—while the optimal dose resulted in faster healing.[2]

The clinical significance of this property is important because until we study sufficient variations of dosing and wavelength, it may be difficult to know if we are actually in the peak dosing range. Furthermore, it begs the question as to whether there is a point at which the same effective dose and timing will achieve a maximal response, and then begin to cause an inhibitory response. Thus far, most clinical trials have lasted for only 6 months or less. There is no long-term follow-up data to indicate if tachyphylaxis or inhibition could or does occur.

References

1. Hamblin, M.R. Mechanisms of laser induced hair regrowth. Source: Wellman Center for Photomedicine. biomediclaser.org. March/April 2006, pp. 28-33.
2. Huang, Y.Y., et al. Biphasic dose response in LLLT. Dose Response. 2009; 7(4):358-383.
3. Lexington International, LLC Laser Comb, 510(K) summary, K060305, 18 January 2007, fda.gov.
4. University of Calgary. Laser Safety Manual, 2008. http://www.ucalgary.ca/safety/system/files/uofclasersafetymanual.pdf.
5. Avci, P., et al. LLLT for treatment of hair loss. Lasers in Surgery and Medicine. 2013; 9999:1.
6. Hamblin, M.R. Mechanisms of LLLT. 2008 (Aug). www.photobiology.info/Hamblin.html
7. Chung, H., et al. The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng. 2012(Feb); 40(2):516-533.
8. Steiner, R. Laser tissue interactions. *Laser and IPL Technology in Dermatology and Aesthetic Medicine.* 2011; 23-36.
9. Mustafa, F.H., M.S. Jaafar, and A. Ismail. Influence of hair color on photodynamic dose activation in PDT for scalp disease. *IFMBE Proceedings.* 2011; vol 35.
10. Ryer, A. Basic Principles, Light Measurement Handbook. 1998; pp. 25-27. www.intl-light.com/handbook/.
11. Barolet, D. Light emitting diodes (LEDs) in dermatology. *Seminars in Cutaneous Medicine and Surgery.* 2008; 27:227-238.

Part 2 of this series will deal with regulation of LLLT devices from both a U.S. and international perspective. This portion of the article will look at medical device categories and regulation worldwide, as well as laser device categories and regulation—and why they should/do exist for patient's safety. However, the effect of regulation on cost of device development, and how this may both impact and impede device innovation, will also be discussed. For those who wish to view an abbreviated review and update of LLLT as provided in a PowerPoint presentation at the 2014 ISHRS Annual Scientific Meeting in Kuala Lumpur, a copy of the recorded lecture can be accessed at the ISHRS website.◆