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LOW LEVEL LASER THERAPY: THE BASICS FOR RESEARCH AND PRACTISE.

By Malini Chaudhri Ph.D. Lic.Dr.Ac., India, and Jan Tunér DDS, Swedish Medical Laser Society, NAALT Standards Committee member.

ABSTRACT

Low Level laser Therapy is known to be a science with very diverse applications. This paper discusses the fundamental premise of laser interaction with tissue, dosimetry in various clinical applications and research standards for LLLT and Laser acupuncture with reference to the indicators given by the NAALT Standards Committee in the 2003 NAALT Conference in Bethesda, U.S.A.

Low level laser (LLLT) involves the application of monochromatic, coherent photonic energy to biological tissues with the objective of augmenting a therapeutic reaction. Therapeutic lasers may be used for local treatment as well as laser acupuncture. The physiological reaction may be calculated with variables of dosages, frequencies and wavelengths to produce specific, reproducible results on target cells or pathologies. Available literature on laser research is often contradictory and unreliable due to poor standards of study design, and Committees as that of North American Association of Laser Therapy (NAALT), have formed to define Standards for laser research so that scientific evidence is consistent, valid and reproducible.

MECHANISMS

Numerous mechanisms have been suggested for the beneficial influence of low level lasers on tissue, the main ones being that the absorbers of light reside in the organelles within the cells such as the mitochondria or porphyrins, yet another that the absorber is molecular oxygen which produces reactive oxygen species. Singlet oxygen is a free radical which activates cellular ATP. Alterations in the transmembrane transport of various captions, notably Ca^{++}, follow laser radiation which increase cell membrane permeability and trigger the chain of reactions associated with e.g. the release of cytokines, growth factors and shift of ions. Cells in a reduced redox level will respond most favorably to laser energy.

Singlet oxygen is released from fibroblasts following laser exposure. Reactive oxygen species probably modulate mitochondrial redox activity at the respiratory chain level. Singlet oxygen photoproduced by neutral porphyrins or cytochromes may assist with DNA synthesis, redistribution of Ca^{++} within the cell, and promotes the Ca^{++} influx into the cytoplasm, necessary for promoting cell proliferation. Laser light further alters the double lipid layer in the cell membrane through electron polarization of the lipids' electrical dipoles. This alters lipid protein bonds and the cell membrane amplifies the associated processes of ATP production, immunological reactions, enzyme reactions and transport factors.

Bioeffects of laser exposure may be directed towards photo stimulation, photo biomodulation or photo inhibition. Appropriate wavelengths and energy densities may be calculated to have clinical effects on blood vessel dilatation, angiogenesis, edema, T-cell activity, neuropathy, growth factor activity (nitric oxide) and normalization of cell membrane potential. Cellular activity may also be influenced for keratinocytes, lymphocytes, macrophages, fibroblasts, mast cells, osteocytes, endothelial and other cells.

Nerve transmitters as endorphins, bradykinin, serotonin and nerve C fibres have shown to be therapeutically influenced by laser light. Vasodilatation, improved blood circulation and improved nerve conduction are other significant secondary effects.
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The absorbed photo energy will start a cascade of familiar, but controlled biological activities. The photoreaction at the most fundamental level means that a variety of conditions may be influenced, although the therapy itself remains unspecific and the term biomodulation is often used to describe laser effects. An example may be seen in the treatment of rheumatoid arthritis,(Goldman et al .1) where laser is believed to stimulate suppressor T-cells(loss of control of these cells causes pathology) and suppress overactivity of the B-lymphocyte cell line which creates autoimmune antibody production. Autoimmunity is regulated in this pathogenesis through the immunostimulative (T-cells) and immunosuppressive (B-Lymphocytes) reactions of laser through its capacity to biomodulate. The plethora of medical conditions suggested as suitable for laser therapy have aroused some skepticism. However, an understanding of the fundamental mechanisms of the interaction between laser light and tissue make these claims more plausible.

LASER DOSIMETRY

WAVELENGTH AND ENERGY DENSITY

Different wavelengths and parameters of laser light affect different photo acceptors present in the respiratory chain, the result of which may be a stimulatory or inhibitory effect. Every pathology requires a target cell type or neurotransmitter to be treated during therapy and the clinician requires an understanding of wavelength, frequency, and energy density in laser therapy to achieve precise effects. Laser dosimetry has no cookbook formulas and the investigator must rely on existing literature or on personal experience through trial and error. Existing literature of laser therapy research offers a foundation for dosimetry. Generally Helium Neon (632.8 nm) and laser diodes between 633 - 670 nm are absorbed by the mitochondria cytochromes (mainly cytochrome c oxidase) and known to act mainly on superficial epithelial tissue due to the limited penetration of red light. Wavelengths between 800- 940 nm are absorbed by the cell membrane chromophores but both wavelength areas come to the same result after starting the photochemical cascade response. The infrared lasers, however, offer deeper penetration. They are therefore preferred for the treatment of pain and musculoskeletal disorders. Studies comparing light attenuation of HeNe and 904 nm (Enwemeka.2) in skin, muscle, cartilage and tendon tissue in rabbits showed that the 904 nm wavelength better penetrated all tissue except muscle, which HeNe manifested better penetration. However laser therapy for normal tissue is different than for pathological conditions which address the need to understand cellular effects of different wavelengths, energy densities and frequencies of laser light.

The clearest proof of the effectiveness of lasertherapy comes from in vitro studies where cells are exposed and laser energy is readily absorbed. In vivo dosages, observing laser effects in clinical settings, may be at variance with in vitro dosages, owing to reflexion, or the loss of energy according to the depth of target tissue and the type of intervening tissue. Fat is rather transparent, bone fairly transparent and muscle tissue less transparent. Laser science and its practical use in therapy must necessarily evolve through observation of both in vitro and in vivo studies.
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LASERS IN CELLULAR PROLIFERATION

Studies (Ghali, Dyson.3) have shown that endothelial cells when irradiated with 660nm and 820 nm, only 660nm showed higher cell counts, and 660 nm wavelength at 2.16 J/cm sq induced fibroblasts to secrete growth factors, possibly increasing rate of mitosis and/or reducing cell death (4), thereby indicating that 660nm LLL was best indicated for mitosis, promoting cytokines and growth factors necessary in wound healing. Growth factors secreted from macrophages can modify the activity of other cells involved in the repair

process, control bacterial phagocytosis, and promote fibroblast proliferation. Studies on the U 937 cell line exposed to laser light have shown that Ca ions can be absorbed by the cell. This Ca switch seems to operate the major activities of the cell and light treated macrophages are able to offer more growth factor release. Increased calcium uptake rates in macrophages following laser are reported to be wavelength, dose and pulse frequency dependent, the most effective energy density being 4 to 8 J/cm^2 and a peak frequency window of 16 Hz. Beyond this Ca influx into the cell was found to diminish.(5) The wavelengths 660, 820 and 870 nm were found to be stimulatory, whereas 880nm was ineffective on macrophages. Energy densities of 2 $J/cm^2$and 19 J $/cm^2$ were reported to be ineffective (Dyson, Naalt 03. 6). Yamada(7) found that four sessions of HeNe laser exposure on cloned osteoblastic cells (of mouse calvaria) at 1 J/cm^2showed an increase in Ca^{++} concentration by 46 % compared to control group. Noguerol et al(8) discovered that HeNe laser irradiation caused degeneration of osteoblasts at 31 – 52 J/cm^2 and was adverse to bone healing, whereas 10.5 J/cm^2 showed no degeneration. The 870nm wavelength was found to stimulate macrophages and not mast cells and may be employed for more specific therapy. Exposures to all single wavelengths except 880 nm were followed by a significant increase in total number of mast cells. (Dyson, Naalt 03.6)
The importance of laser light on cells is seen when used for treating pathological conditions. Vasodilatation is one of the biological effects of laser interaction with tissue. Sayed, Dyson(9) suggest that this effect is not solely from light interaction with cell receptors but also due to the release of vasodilating tissue metabolites or mediators as those liberated from mast cells after laser exposure. Anti-inflammatory and anti-histamine effects, serotonin, prostaglandins, and enzymes among many others are controlled from laser action on mast cells. Angiogenesis or blood vessel formation is achieved through laser induced proliferation of endothelial cells. Studies from Ghali, Dyson(3) showed that 660 nm exposure to endothelial cells in vitro manifested a significant increase in these cells and at 820 nm cells showed less response. 820 nm at 1 Joule achieved an inhibitory effect. The authors concluded that inhibitive dosages were important in treating pathologies where overgrowth of blood vessels was dominant, whereas stimulative dosages could be given in tissue implantation or wound healing. Myofibroblasts, the main cells needed for contraction in wound healing, were found to respond to frequencies; (Dyson, Young 10) 700 Hz increased contraction whereas 1200 Hz inhibited contraction. In vivo irradiation at energy densities of 3.5J/ cm^2 at 3000 Hz accelerated healing of rat wounds, while a frequency of 1500 did not do so.(11)

In vitro examples, as those cited above, must be treated as a significant step towards reproducing clinical parameters in treating complex mammalian tissues where biological reactions are inter connected with multiple factors as blood, lymph, hormones, nerves, which undergo changes simultaneously with laser irradiation. Highly reactive oxygen species has been found to even damage in vivo tissue when irradiated with inappropriate wavelengths , despite using low energy densities(12,13). It is hoped that future research will refine these laboratory findings with due consideration to wavelength, dose and frequency into reliable clinical data. The Review panel(14) of Laser Therapy Research at Naalt , (which included the FDA standpoint through representative Waynant) emphasized the need for research which shows the capacity of the laser to biomodulate, offers clear clinical proof of efficiency, and focuses on relevant topics for clinical use with due consideration to dosimetry.

LASERS IN TENDONITIS

Laser trials in tendonitis have shown all lasers to be effective although the 904 nm wavelength appears to act best. Although a great deal of research has been done in this area, the Naalt Review panel commended the studies of Bjordal and colleagues from Norway for their evidence of effectiveness and of clear dose response relationship. The studies managed research standards that clearly proved the effects of laser therapy on the pathology. Bjordal (15)summarizes data from literature regarding the treatment of tendonitis:

- A synthesis of dose from 4 laboratory trials on inflamed collagen producing cell cultures cell cultures gives the following dose for optimal reduction of tendon tissue inflammation: Dose 3-8 J/cm^2, Intensity: 5 – 21 mW/cm^2
- A synthesis from 10 laboratory trials investigating collagen proliferation gives the following optimal dose for stimulation of tendon regeneration. Dose 0.2-4 J/ cm^2. Intensity: 2-10 mW/cm^2
- For the treatment of tendonitis an optimal suggested dosage at target location will be: Dose: 0.2-4 J/ cm^2. Intensity 2-10 mW/cm^2
- Treatment should be applied daily for at least five days to reduce inflammation, and for at least 10 days to increase collagen production.

LASERS IN PAIN MANAGEMENT

Laser dosimetry for pain management in human subjects is easier than in wound healing, bone healing or angiogenesis as patients usually communicate when pain is reduced. Verbal pain scores of laser treatment for pain of all etiologies are often taken. Laser has a systemic effect on Na-K-ATPase thereby improving nerve conductivity whereas increased mitochondrial volume and blood supply from laser exposure is believed to reabsorb pain producing transmitters as bradykinin and acetylcholine. Nerve impulses are accompanied by an internal flow of sodium and an external flow of potassium. Studies by Maeda (16) found that nerve fiber Na-K ATPase activity after LLLT irradiation was increased with shorter exposure and decreased with longer exposure. Studies from Rochkind et al(17) found that HeNe laser worked on crushed sciatic nerves of rats better than on normal nerves, and laser treatment revealed a significant increase in the compound action potential of the injured nerves. The poor penetration of HeNe has, however, made 780 nm necessary for most clinical applications.

Important studies with 904 nm wavelength have shown that nitric oxide is involved in the mechanism of laser therapy induced analgesia (Mrowiec. 18). Whereas serotonin increase has been observed with irradiation of lasers in visible and invisible spectrums, there is a need to further understand the mechanisms of pain relief beyond endorphins, bradykinin, acetylcholine and serotonin. GaAlAs laser was shown to suppress pain by blocking the depolarization of C-fibre afferents(19) . Lubart(20) found that 632 nm light had an effect on the Compound Active Potential of the nerve whereas 904 nm failed to produce this effect. In 1984. Sommers and Klein(1984) reported that the CNS contained rhodopsin kinase, an enzyme involved in photosynthesis which possibly explains the validity of the success of laser therapy on pain. Laboratories worldwide support the evidence that the mammalian nervous system is photosensitive.

LASERS IN ACUPUNCTURE

Laser trials in acupuncture are often concerned with reproducing the effects of needles. Research from Bischko(21) and Kroetlinger(22) suggest that laser stimulates through electromagnetic energy, producing similar biochemical changes in the urine with laser and needle stimulation of St 36, and similar changes in skin resistance. Ding Aihua(23) states that the laser is more effective than moxibustion in turning the fetus in breach position, and Gong,(24) using daily treatment of St 36 and CV 20 indicates 93% response on 144 cases of infantile diarrhea. Lowest dosages of effective therapy recorded with HeNe lasers is .047 J/mm sq , with 1 mw output, and the highest recorded dose is 18 J/mm sq with 20 mw (Harrison 89. 25).
HeNe lasers of 3 – 5 mW used by Ren Shouzhong(26) on pediatric enuresis was compared

with a control group receiving needles. There were no significant differences in the laser group and needle group, and a marked improvement of 73.7% was seen. Studies from Wang Zongxue et al(27) on 180 cases of rhinitis, bronchitis, pharyngitis and gingivitis showed an overall effective rate of 95% when treated with 2 mW HeNe laser.
Rindge(28) at Naalt 2003 used 500 mW to irrigate sinuses along the local acupuncture points, thereby using the dual effects of LLLT and laser acupuncture.
Laser acupuncture is a science still in its infant stage which calls for a new language of modern science, physics and dosimetry independent of LLLT and needles. Experts may show individual preferences for shallow beams as He Ne or longer wavelengths as GaAIA. China offers maximum research on He Ne ranging from 1-5 mw, whereas Nogier's group prefer pulsed or superpulsed GaAs. Researchers from the Bahr school have given prominence to GaAIA in 30 – 50 mw with due emphasis on frequencies and anti-frequencies. Harrison(25) found that he had to use a 15 mw GaAIA laser to give him therapeutic effects equivalent to 1 mw of HeNe. Laasko(29) demonstrated no effect of 670nm 10 mw laser at 5 J/cm sq but an effect with the same laser at 1 J/cm sq. Roberta Chow (30)conveys that 830nm at higher doses has found to give effects at higher and lower energy densities. This gives weight to the concept that different wavelengths may also be mediated by different photochemical pathways, and producing different effects. As a solution to dose dilemmas she offers 1 – 4 J/cm sq as the 'gold standard' in the complicated scientific arena of laser acupuncture dosimetry

FREQUENCIES

Frequencies in laser dosimetry is another vast area to be considered. Lasers can be used in continuous mode or pulsed. Pulsed lasers deliver fewer joules than continuous. However, the frequency, or pulses per second, can be used to achieve specific effects. As explained by Dyson(11), the cyclotron resonance theory states that biological effects occur around particular frequencies, and these depend upon the mass and charge of the particles involved. The major activities of the cell, controlled by membrane permeability to ions such as calcium are modified by these frequency windows. Studies by the same author with the same power and energy densities showed 500 Hz to produce inhibition whereas low frequency pulsation as 2 hz produced stimulation. Studies by Ueda et al(32) with GaAlA used continuous and pulsed mode on proliferation of bone cells. Pulsed irradiation stimulated cellular proliferation, bone nodule formation, ALP activity and ALP gene _expression more than continuous irradiation. The author concluded that pulsing is an important factor affection biological response to bone formation.
Bradley at the Naalt 2003 Conference suggested the following frequencies for specific pathologies

2 Hz Nerve regeneration, neurite outgrowth,
7 Hz Bone growth
10 Hz Ligamentous healing
15, 20, 72 Hz. Decreased skin necrosis, stimulation of capillary formation and fibroblast proliferation
2.5 Hz. Endorphin release
200 Hz Serotonin release

David Rindge(32) explains the principles of pulsing which is accommodated with the view that the body's sensitivity to any steady stimulus diminishes over a period of time. Pulsing aligns the rhythms of the cells when correctly used. Pulsing for lasers with a steady power output is different than for the GaAs laser which builds up to a momentary peak that may be 1000 fold greater than its average output.

Tunér/Hode(33) in their book Laser Therapy suggested for superpulsed GaAs lasers

Pain, neuralgia 0 – 100 Hz
General stimulation 700 Hz
Oedema, swellings 1000 Hz
General stimulation 2500 Hz
Inflammations 5000 Hz
Infections 10,000 Hz

The authors emphasize these references on pulsing to be merely empirical, based on inconclusive research from in vitro studies.
Laser acupuncturists are familiar with Nogier and Bahr frequencies for tonification and sedation, entry, exit and source points, and correspondences to mesodermal, endodermal and ectodermal tissue and the biological functions they represent

CALCULATING DOSAGES AND MAINTAINING RESEARCH STANDARDS

For laser dosimetry to be accurately documented it is clear from the above information that laser wavelength, power, duration of exposure and frequency has to be mentioned.
Dosage (J/cm2) = Power (mW) X Time (seconds)

Joules = Watts x Seconds

A formula for more formal calculation of energy density dose is

$$\text{Energy density (J/sq cm)} = \frac{\text{Power(w)} \times \text{time (s)}}{\text{Area(cm2) of spot}}$$

Also to be considered are other factors as mode of delivery (contact mode or distal mode), treatment schedule and frequency, light source (cluster diodes, scanner or single probe), and methodology of treatment (irradiation, TP's or AP's, lymph nodes, or dermatomes), all of which will influence the therapeutic outcome. The movement to establish a correct doctrine for Low level laser science is underway and clinicians, researchers and laser manufacturers are required to conform to the standards listed for acceptable scientific study and practice.

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