

MOLECULAR AND CELLULAR MECHANISMS OF LASER THERAPY

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Low-intensive laser radiation (LILR) has found broad uses in the clinical practice in Russia, other CIS states and several Western countries over the recent decade.

Two major lines of its use are photodynamic therapy of tumours which recruits the destructive effect on LILR on tumour cells (1,2) and therapy of a wide spectrum of inflammatory diseases which employs stimulating effects of LILR (3,4,5).

The level of clinical and photobiological effects of LILR is determined by the wavelength, power, radiation mode (continuous or pulsed) and methods of laser energy delivery to tissues.

Coherence and polarization are specific properties of laser radiation (LR) which make it different from usual radiation, even monochromatic one (with one wavelength). There is a misconception that the specific properties of LR account for reported clinical and photobiological effects (6,7). As LR penetrates body tissues (the skin, organs, blood), its coherence and polarization are retained at 0.2 to 0.3 mm depths and disappear deeper in tissues, while incoherent and almost nonpolarized, monochromatic radiation spreads further (6). Therefore, benefit of LR in a variety of diseases is not related to its special properties, but occurs like effects of usual nonpolarized and incoherent light with a relevant wavelength, as it is suggested by experimental and clinical studies (4,8).

The most common therapeutic modalities of LR delivery to body tissues are

1. Intravenous laser irradiation of blood (ILIB) (9)
2. Extracorporeal blood irradiation (10)
3. LR delivery to an affected site using endoscopes (4)
4. Transcutaneous treatment of a site of tenderness or an organ projection (4)
5. Treatment of acupuncture reflex points and Head zones (4).
6. Noninvasive supravenuous blood irradiation (5)

Each of the delivery methods has its advantages and limitations, but even a brief comparison of clinical efficacy of laser therapy using different delivery suggests that direct exposure of blood components (cells, lipoproteins and proteins) to LR is the most optimal modality. Generalization of therapeutic effects of LR, which is clinically observable regardless of application sites, may be underlied by photomodification of at least part of the circulatory pool of blood cells, in particular leukocytes, because of change in their effector function, i.e., production of signal substances such as cytokines (11). Thus LR delivery into the radial vein using a flexible light guide has been reported to have therapeutic effects in angina pectoris, myocardial infarction and other diseases (9,12).

Numbers of cell targets of low-intensive laser radiation are smaller when it is applied to the skin. Besides, the proportion of laser photons interacting with photoceptors is significantly reduced by reflection, light scattering and reabsorption (5).

However, ILIB has serious limitations:

The invasive nature of this method, or light guide-blood contact, warrants careful disinfection of the skin and the guide, a cumbersome procedure which impairs optical properties of guide fiber and enhances its fragility.

The intravenous treatment is associated with risks of vascular wall injury or fracture of the guide tip into the vessel opening, relatively high prices of guides, and pain and discomfort of the procedure.

These problems are compounded in pediatrics, where the ILIB procedure is a stressful exposure for children.

Successful use of LILR has been reported in therapy of many diseases, including in pediatrics. An overview of the literature suggests that

- laser equipment, radiation spectra, methodologies and dosage regimens of laser treatment are diversified,

- systemic laser therapy most commonly has anti-inflammatory, analgesic, anti-edematous, regenerative, immunocorrective and bactericidal effects (3, 4,20),

- microcirculation improvement has been documented in numerous experimental and clinical studies (2-26),

- laser therapy allows drug dosage reduction or drug withdrawal in a number of diseases and improves the general condition (13-16,17,18, 19,23),

- the most effective LR delivery modalities are ILIB and supravenuous treatment (3,5,9,23).

Laser radiation has extensive clinical applications, including in pediatrics, because primary photochemical exposure elicits biochemical, biophysical and physiological events, while clinical effects of laser therapy are a denominator photobiological response of organ systems (4).

It is conceivable that the genesis of all disease entities has a common constituent which responds to laser therapy, a shared rather than disease-specific mechanism of ILIB action. The most likely denominator process responsive to the above cited laser therapies is inflammation which occurs either as a major pathogenetic factor or as a response.

Microcirculatory disorders, comprising blood rheology impairment, are a major stage in inflammation pathogenesis. Inflammation evolves as an ischemia-reperfusion sequence concurrent with microcirculatory disturbance. Any intervention which curtails the ischemic stage is a boon.

Thus intravenous blood irradiation using the helium-neon (He-Ne) laser in children with acute respiratory failure has been reported to produce organ perfusion improvement, an increase in partial blood oxygen pressure and normalization of blood gases and the acid-base state (23). A study of induced brain ischemia in rabbits has documented microcirculatory disturbance at one minute following a carotid artery occlusion and deterioration of it with progressive ischemia (21). Preliminary He-Ne brain irradiation significantly alleviated microcirculatory disorders and induced a more rapid normalization of small vessel tone. In addition, repeat He-Ne irradiation was seen to improve capillary regeneration and dilation.

This evidence suggests that microcirculation improvement by He-Ne laser treatment is one of mechanisms accounting for therapeutic effects of laser irradiation. An important determinant are leukocytes which mediate both the onset of inflammation and microcirculation regulation because of their ability to produce numerous biologically active substances (24).

It should be taken into account that clinical adoption of LILR is largely empirical. One of the most serious pitfalls is a strong relation of the response to LILR and even of its positive/negative quality to irradiation dosage and to the functional state of the subject. The positive stimulating effect usually occurs in a relatively narrow range of dosages, beyond which it fades or is even replaced by the inhibitory effect (27-29). Since mechanisms of therapeutic effects of LILR in humans and the nature of endogenous chromophores remain obscure, there are no validated criteria for selection of irradiation dosage in low-intensive laser therapy.

Nonetheless, some laser dosage guidelines are available in the clinical practice. Thus it has been elucidated by evaluation of capillary responses (4) that

- microcirculation-enhancing (therapeutic) dosages are within the range of 10 J/sq. cm,
- dosages inducing reversible vascular dysfunctions are 10 to 30 J/sq. cm,
- dosages resulting in irreversible microcirculatory disorders are above 30 J/sq. cm.

The empirical approach to low-intensive laser dosages and regimens can lead to complications of primary diseases (a secondary exacerbation syndrome) in some patient groups (27-29). Thus a study in patients with rheumatoid arthritis treated with intravenous He-Ne laser irradiation has suggested several contraindications such as chronic infection or chronic renal diseases (25,28). The use of a typical protocol of intravenous He-Ne blood irradiation in patients with ischemic heart disease has been associated with clinical improvement in 66.6 percent of the patients, a lack of response in 20.7 percent, and a higher frequency of anginal attacks, lower exercise tolerance and higher required dosage of nitroglycerin in 12.6 percent (27). Therefore, positive stimulating effects of LILR typically occur in a narrow irradiation dosage range, and are lost or even followed by inhibitory effects in heavier exposures (4,26,27,28). This situation is largely determined by a lack of understanding of subtle molecular mechanisms of LILR, and this hinders dosage individualization thus far.

Inferred molecular and cellular workings of LILR remain speculative. Any hypothesis of laser irradiation effects on the body should focus on elucidation of a primary chromophore acceptor to energy of an absorbed laser photon and of a target cell for LILR. Interaction of laser energy with a chromophore follows a basic photochemistry law: only an absorbable quantum is active. Therefore, triggering all further biochemical and physiological responses to laser therapy requires the presence of a chromophore which is able to absorb a specific quantum of laser energy, i.e., one whose absorption spectrum coincides with the wavelength of the laser radiation source.

The He-Ne laser with a wavelength of 632.8 nm has the most extensive use in medicine and biology to date. Its reported red-spectrum chromophores are

- porphyrins and their derivatives (30,31),
- molecules of antioxidant enzymes: superoxide dismutase, catalase and ceruloplasmin (31, 32, 33),
- components of the mitochondrial respiratory chain: flavoproteins and cytochromes (34),
- molecular oxygen (33-35),
- tetrahydrobiopterin (3).

As for photobiological effects of LILR, their presumed mechanisms are

- reactivation of metal-containing antioxidant enzymes (31, 32, 36, 37),
- interaction of laser radiation with components of the mitochondrial electron transport chain (38),
- nonspecific effects on biopolymers (33, 34),
- photoactivation of singlet oxygen production (33, 34),
- nonspecific effects on the water structure (35).

Many of concepts concerning the mechanisms of LILR therapeutic effects have two major fallacies. First, some overlook chromophores in analysis of the effects. It is obvious that delineation of an acceptor to laser irradiation is crucial for understanding its effects. Second, experimental evidence behind some of concepts is lacking or controversial.

The Biophysics Department of the Russian State Medical University had formulated its hypothesis of photodynamic mechanisms underlying effects of LILR (39-42):

- Red-spectrum laser radiation chromophores are endogenous porphyrins which are able to absorb red-spectrum light and are proven photosensitizers. Porphyrin levels in the body are increased in many diseases and abnormalities (43). Targets of laser energy are cells, in particular leukocytes, and porphyrin-containing blood lipoproteins.

- Absorbing the light energy of LILR, porphyrins induce photosensitized free radical reactions which initiate lipid peroxidation in leukocyte membranes and in lipoproteins with the synthesis of

primary and secondary products of lipid peroxidation. Membrane accumulation of lipid peroxidation products such as hydroperoxides enhance permeability to ions, in particular ionized calcium (Ca^{2+}) (44, 45).

- An increase in Ca^{2+} concentration in the leukocyte cytosol triggers Ca^{2+} -dependent processes leading to cell priming (47), which occurs as functional activation of cells, increased production of biologically active substances (nitric oxide, superoxide anion radicals, hypochlorite anions and others). Some of these have bactericidal and microcirculatory effects. Thus nitric oxide is a precursor of the endothelium derived relaxing factor (EDRF) which relaxes the vascular endothelium, causing vasodilatation and microcirculation improvement, a basis of most of positive clinical effects (24).

Inducible nitric oxide synthase (iNO) is responsible for leukocyte nitric oxide synthesis (51). Production of this enzyme can be induced by numerous stimuli (cytokines, lipopolysaccharides and others) concurrently with nitric synthase mRNA. The mechanism of NO synthase production in phagocytes is inadequately understood, but the presence of inducible NO synthase in phagocytes has been reported to result from cell priming (48). In vivo production of NO synthase can occur in phagocytes of affected tissues, e.g., at an inflammation site where cells have been through the priming phase.

Experimental studies have yielded evidence to corroborate the photodynamic hypothesis of LILR action (42-45):

- Laser irradiation of phagocyte suspensions caused cell priming which was seen as an increase in active oxygen production after laser leukocyte stimulation. Effectiveness of leukocyte priming correlated with both irradiation dosage and porphyrin concentrations.

- Priming amounts of laser irradiation of phagocyte suspensions increased ionized calcium concentrations in the cell cytosol.

- Tentative evidence was obtained to indicate that leukocyte laser irradiation is associated with an increase in NO production in some conditions.

- A correlation was shown between initial in vitro sensitivity of leukocytes to laser irradiation and clinical efficacy of laser therapy.

Normal polymorphonuclear (PMN) leukocytes are known to have a low functional activity. However, PMN preincubation with a similar low concentration of a stimulator unable to activate granulocytes, and successive stimulation using the same agent in a higher, activating concentration have been seen to enhance the effector response of phagocytes as compared to controls. This enhancement of phagocyte functional potential by pretreatment is known as priming, i.e., preparation, conversion of cells to a functional condition. The term has been used for phagocytes since 1979-1980 (46, 47).

Extensive experimental evidence has been reported to suggest that phagocyte priming can be induced by numerous endogenous and exogenous factors (primers) comprising major cytokines: interleukins, tumour necrosis factor (TNF- α), gamma-interferon, granulocyte- and granulocyte-macrophage colony-stimulating factors (G-CSF, GM-CSF), lipopolysaccharides, bacterial wall components (muramyl peptide), formil peptides, bacterial necrolysis products, eicosanoids, leukotrienes, platelet aggregating factor (PAF).

In addition, phagocyte priming is inducible by products of phospholipid enzyme hydrolysis: diacyl glycerin, lysophospholipids, free fatty acids, lipid peroxidation products, immune complexes, plasma proteins and others. Phagocyte priming is also initiated in vitro by Ca^{2+} ionophores, phorbol esters of myristic and acetic acids, and by the chemotactic tripeptide formyl methionil leucyl phenylalanine (49, 50).

Research of leukocyte priming has started over ten years ago, but molecular mechanisms of phagocyte priming are far from understood. Functional potentiation of phagocytes by priming is thought to be related to

- modification of transduction of a signal for stimulator-receptor interaction to intracellular enzyme systems with their resultant activation,
- an increase in numbers and affinity of surface receptors (49, 50).

Modification of phagocyte cytosol calcium concentrations has a major role in signal transduction. Higher Ca^{2+} concentrations in the phagocyte cytosol may activate several key systems of priming. These are primarily Ca^{2+} -dependent phospholipases which hydrolyse phospholipids with production of diacyl glycerin, polyunsaturated fatty acids and other substances which together with ionized calcium activate protein kinase C and promote further phosphorylation of several cytosol proteins and their translocation from the cell cytosol to plasma membranes. Association of these phosphorylated cytosol factors with membrane-bound components of NADPH oxidase converts the enzyme to an activated state, with its functioning induced by subsequent stimulation (49, 50).

Therefore, phagocyte priming with its enhancement of cell functional potential may be determined by at least two major mechanisms:

1. Generation of NADPH oxidase complexes which are in active waiting.
2. Receptor expression.

This cluster of events and standard leukocyte stimulation following the priming result in intensified production of prooxidants and biologically active substances (interleukins, leukotrienes, cytokines and others), preparation of macrophages and probably monocytes for inducible nitric oxide synthase, acceleration of chemotaxis and adhesion, potentiation of cytotoxic and bactericidal effects and other functional developments.

Also, the priming-dependent increase in leukocyte cytokine production presents as proliferation and formation of new collateral vessels, a very important effect of laser radiation (51).

In summary, laser-induced photosensitized leukocyte priming causes dilation of congested and formation of new capillary vessels, and hastens reperfusion of an ischemic organ. In addition, blood supply normalization may restore drug delivery to an inflammatory site, earlier hindered by circulatory disorders. This sum of factors explains beneficial effects of low-intensive laser radiation in inflammatory diseases.

CONCLUSIONS

Low-intensive laser radiation causes leukocyte priming which enhances functional potential of cells and production of biologically active substances (the endothelium derived relaxing factor and cytokines), with improvement of microcirculation. Further evaluation of regulatory roles of leukocytes in microcirculation will provide guidelines for LILR dosage individualization and improvement of laser therapeutic modalities.

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