Intravenous Laser Irradiation of Blood: current state and future perspectives.

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Summary

Lasers are widely used in the modern medicine as important parts of different types of equipment. Laser beams of different powers, wavelengths and optical properties are used in surgery, cosmetology, therapy, diagnostics and number of other medical areas (1-4). One of the most controversial applications of laser light is its application for the therapy of different disorders, therapy method, commonly known as low level (power) laser therapy (LLLT). Unlike laser surgery, for laser therapy low power laser light is used, which cannot cause significant thermal effects or damage irradiated tissues. Usually red and infrared laser light is used for laser therapy (5-8). Recently blue, violet, green and ultraviolet laser based therapy system were introduced (9-14).

For LLLT laser light is usually applied superficially onto surface of body (skin and mucosa). In some cases laser light is delivered through special light-guides inside the body (stomach, intestine, blood). Laser beam can activate microcirculation, improve oxygen and nutrients supply to tissues, balance immune system, influence hormonal, nervous system and as a result support faster recovery. It is generally considered that influence on blood, including blood cells and serum, is one of the most important components of laser therapy. That is why laser irradiation of blood (LBI) is one of the most fascinating versions of LLLT (15-17).

Keywords

Low Level Laser Therapy, superficial laser, intravenous laser, red, green, blue, violet, ultraviolet laser

Zusammenfassung

Laser haben in der modernen Medizin weite Verbreitung gefunden, wobei unterschiedliche Gerätetypen zur Anwendung kommen. Laserstrahlung mit verschiedenen Leistungen, Wellenlängen und optischen Eigenschaften werden in der Chirurgie, Kosmetologie zur Diagnostik und vielen weiteren medizinischen Gebieten angewendet (1-4). Eine oft kontrovers diskutierte Anwendung von Laserlicht ist die Methode der Niederleistungslasertherapie (low level laser therapy, LLLT). Im Gegensatz zur chirurgischen Anwendung entfalten low power Laser eine thermischen Effekte und somit keine Gewebeschädigung durch die Bestrahlung.
Normalerweise wird bei der Niederleistungslasertherapie das Laserlicht auf die Körperoberfläche appliziert (Haut oder Schleimhäute). In einigen Fällen wird der Laser über einen Lichtleiter in den Körper geleitet (Magen, Darm, Blut). Der Laserstrahl kann die Mikrozirkulation aktivieren, die Sauerstoff- und Nährstoffversorgung des Gewebes verbessern, das Immunsystem regulieren, das Nerven- und hormonelle System regulieren, was zu einer rascheren Erholung führt. Es wird generell angenommen, dass die Einfluss auf das Blut- eingeschlossen Blutzellen und -serum und- eine der wichtigsten Komponenten der Lasertherapie darstellt.
Dies ist der Grund warum die intravenöse Laserblutbestrahlung eine der faszinierendsten Versionen der low power Laser Therapie darstellt.

Keywords
Low Level Laser Therapie, Niederleistungslaser, oberflächlicher Laser, intravenöser Laser, rote, grüne, blaue, violette und ultraviolette Laser

Recent studies demonstrated that not only laser light can have beneficial therapy effects. LED light, as well as filtered light of bulbs or other light sources, even natural light of Sun can treat (11, 18, 19). Therefore, different versions of laser therapy (together with LBI) belong to phototherapy methods.

Laser blood irradiation therapy employs modification of blood under influence of laser light to support faster and better recovery.

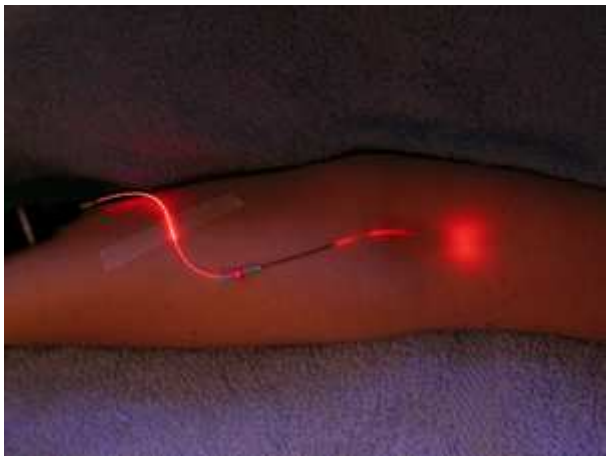
There are direct and indirect methods of laser irradiation of blood. Direct methods are invasive and require immediate contact of light with blood, while indirect ones are non-invasive.

Light can be delivered to blood indirectly, passing through different layers of skin or mucous, as well as number of other tissues (adipose tissues, connective tissues and other tissues depending area of irradiation) before reaching veins, arteries and capillaries. During that journey laser light is partially loosing some of its laser properties (coherency, collimation). Some of laser light is reflected from the body surface, some of light is absorbed by skin or other tissues. Thus indirect methods of blood irradiation (through skin and mucosa) are delivering light not only to blood, but mainly to different tissues in the area of irradiation. Transcutaneous laser blood irradiation is used most commonly by irradiating areas of skin having access to big blood vessels, like cubital and popliteal fossae.

For direct laser irradiation of blood laser light should contact directly with blood. There are 2 main versions of direct laser irradiation of blood. For extracorporeal blood irradiation some volume of blood (usually no more than 250 ml) is withdrawn from the vein in sterile container, and after irradiation blood is returned into the same vein. Extracorporeal laser blood irradiation is technically difficult to perform, it requires specially trained personnel, sterile conditions, and has higher risk of local complications that intravenous laser blood irradiation (IV LBI). Currently IV LBI is the most commonly used version of invasive LBI (10).

For intravenous laser blood irradiation thin sterile single-use light-guide is inserted into the lumen of the vein through injection needle or catheter. Other end of the light-guide is connected to laser therapy system. In this way blood in the vein, while passing near distal end of light-guide, is exposed to laser light. Laser light is absorbed by different blood components, including erythrocytes, blood platelets, leukocytes, lymphocytes, blood proteins and so on. It is considered, that modification of function of blood cells after laser irradiation is resulting with higher anti-infection immunity, improved blood microcirculation and other advantages for body changes. Other methods of direct blood irradiation, such as intra-arterial or intracardiac irradiation with insertion of light-guide into lumen of artery or one of the ventricles of heart are also known. Those techniques can be used in case of arterial thromboses, but they are not widely applied. Some researchers advocate irradiation of blood components or stored blood before transfusion (7, 20).

IV LBI with red helium-neon (HeNe) laser was developed in experiment (1978) and introduced for clinical use in 1981 by soviet scientists E.N. Meshalkin and V.S. Sergievskiy. IV LBI is closely related with older phototherapy technique, with extracorporeal ultraviolet blood irradiation. In 1923 Dr. Emmet Knott (Seattle, USA) began to experiment with ways to irradiate the blood to treat sepsis. The first treatment occurred in 1928. Despite its success, ultraviolet blood irradiation was forgotten after introduction of antibiotics and hormonal medication. After development of laser and more advanced light emitting tools, idea of irradiation of blood with light was reinvented (17, 21).



IV LBI is an invasive procedure. It is preferable to perform in sterile environment, but it can be done also in outpatients rooms, in ambulances and other areas. Originally long relatively thick quartz light-guides were used to perform IV LBI. It was a difficult task to sterilize those light-guides. They were also fragile. Due to large diameter of light-guides (about 1 mm) it was possible to apply IV LBI only to patients who had large cubital veins; otherwise blood circulation in the vein around tip of light-guide was altered. Development of thin (0.4 and 0.5 mm in diameter) single-use sterile plastic light-guides solved those problems and made the therapy much easier and safer (2252048 RU). Nevertheless, it is still difficult to perform IV LBI to individuals with very small veins.

HeNe laser (632.8 nm) or semiconductor laser diodes (633, 635 nm) are usually used to perform the IV LBI. Recently red (660 nm), green (532 nm), blue (441 nm), violet (405 nm) and ultraviolet (337 nm) lasers, as well as red (630 nm), blue (450 nm, 455 nm), violet (405 nm), ultraviolet (365 nm) LEDs were introduced for blood irradiation therapy. Infrared lasers are usually not used for IV LBI due to high penetration ability of light in infrared band.
Different treatment protocols are available for treatment of different disorders. The most common one suggests irradiation of blood with red laser light of 1-3 mW optical power at the end of the light-guide in the vein and with exposure of 20 - 30 minutes. Procedures can be performed on a daily base or every second day, from 3 up to 10 sessions.

Originally the method was applied in the treatment of cardiovascular pathologies. But by 1989 there were published results of research trials conducted in Soviet Union reporting successful application of HeNe laser IV LBI in dentistry, endocrinology, urology, cardiosurgery, surgery, neurosurgery, pulmonology, gastroenterology, oncology and other areas of medicine. In the same year “Influence of low power laser irradiation on blood” conference was organized in Kiev (Soviet Union). Results of that conference stimulated further development and wider application of IV LBI in clinical use. It was then mentioned, that application of IV LBI can shorten period of hospitalization of patients, increase remission period, decrease amount of surgery related complications and so on. A group of scientists

received State Prise of Soviet Union for the development and application of IV LBI in cardiology. The treatment is not expensive, laser equipment can work without special services for several years, and price of single-use light-guides in mass production is very low. IV LBI can be performed outside of hospitals, which then can prevent spreading of hospital infections (22).

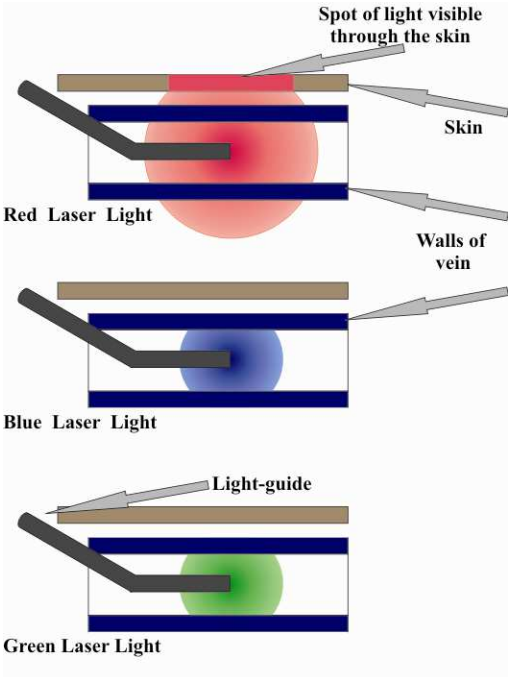
Phototherapy methods of intravenous laser blood irradiation and extracorporeal ultraviolet blood irradiation had similar pattern of development and clinical applications last 30 years. A lot of similarity is found in the mechanisms of action and treatment results. At the same time each of them has its advantages and disadvantages. For example, it is safer and easier to insert a single-use intravenous catheter, that to apply more complicated and expensive blood transfusion set together with sterile quartz blood irradiation chamber. Intravenous treatment is more comfortable for patient, as well as it requires less medical attention and supervision, than extracorporeal version. At the same time it is quite a difficult task to calculate exact values of laser irradiation delivered to volume of blood due to difficulties of assessing speed and volume of blood flow. That means results of IV LBI are difficult to control scientifically and replicate. In case of extracorporeal irradiation known volume of blood is passing through irradiation chamber with certain geometry and given speed. That is why parameters of blood irradiation are easy to control. Both methods have limited value for patients with small or fragile veins, even though there are reports of using central (subclavial) catheters for blood irradiation together with other treatments. Transcutaneous irradiation is a better choice in the majority of similar cases.

IV LBI is a safe therapy method. As any other invasive method connected with catheterization of veins, sporadically it can cause vain damage during catheterization of the vein due to human mistakes. Number of studies performed by Zhukov B.N. and Lisov N.A proved that laser irradiation is safe for veins and surrounding tissues. Vena cava of experimental rats was catheterized and quartz light-guide (0.6 mm in diameter) was inserted. Then HeNe laser light 0.1 mW (group 1) and 20 mW (at the end of light-guide inside the vein) was used with duration of 10 min. Irradiated vena reported, and no damage was visible after laser irradiation. Histological studies of wall of v. cava, aorta and surrounding tissues were preformed after completing laser irradiation. No difference was recorded between application of 0.1 and 20 mW of laser power and non-irradiated control group. No endothelial cell damage, no damage of vessel wall, no damaged in the cells of surrounding fat tissues, no fibrin deposits inside of vessels was found (7). In the other study same authors studied effects of 0.5 mW 10 min HeNe laser IV blood irradiation on aggregation ability of blood platelets. Blood tests were done before insertion of light-guides, after 10 min (at the end of laser irradiation), as well as after 15 and 30 min after finishing laser irradiation of blood. Control animals had higher platelet aggregation and decreased fibrinolytic activity of blood, while test group animals showed opposite trend immediately after completing laser irradiation as well as after 15 and 30 min.

IV LBI is widely used in modern Russia. Several models of IV LBI equipment from different companies are available there. Some of the units are special units to perform IV LBI only, others are designed as modules of general purpose laser therapy systems. Some systems are based on HeNe lasers, but majority are using semiconductor laser diodes. There are systems for LED based blood irradiation using same single-use light-guides. All the systems for laser therapy, including systems for IV LBI, should pass state medical and technical certification before putting into market. Treatment expenses connected to IV LBI are covered by medical insurance.

Unfortunately method of IV LBI is not used much in the countries outside of the former Soviet Union. IV LBI producers from Russia are not working in European markets. Even though there are producers of equipment for IV LBI in Europe, laser therapy methods are not used much in hospitals. In the majority of countries laser therapy is not covered by medical insurance.

It is necessary to mention, that term “blood” irradiation in case of intravenous irradiation is misleading. In the same way like in case of transcutaneous LBI, laser light is absorbed not only by blood, but also endothelium and other tissues of walls of veins, adipose tissues, muscles, even skin. As it is shown on the fig. 2, red light during IV LBI is not completely absorbed by blood. It is penetrating walls of vein and skin and it is visible as a light spot in cubial area. Prof Brill (23) considered the term Intravenous Laser Irradiation as more appropriate. Current reality is that the term IV LBI is still widely used both by producers of equipment and medical professionals.



There are several reports about successful application of IV LBI in the treatment of different disorders and diseases. They have shown that laser light can stimulate microcirculation, increase oxygen and nutrients supply to tissues and so activate reparation of damaged tissues or limit damage caused by subsequently applied ionizing radiation, hypoxia, bacterial toxins or cytostatic medications. Other mechanisms of action are related to activation and balancing of immune system. That is why IV LBI can be applied together with other therapy methods in the treatment of inflammations, infections, autoimmune diseases, allergy and cancer. Laser light can also influence the level and activity of number of hormones, so additional application of IV LBI can improve treatment results of diabetes, hypothyroidism, and other hormonal disorders (24-26).

IV LBI is widely used in the treatment of cardiovascular disorders. As it was already mentioned, IV LBI was developed and first applied in cardio-surgery, as well as I. Korochkin with colleagues received State Prize of Soviet Union for application of that method in cardiology. Ability of IV LBI to improve rheological properties of blood and microcirculation is usually considered the main reason of anti-ischemic and pain killing effects of invasive laser therapy (27-29). It has been reported that patients after IV LBI need smaller amount of medications, especially nitrates. IV LBI supported faster and better recovery after myocardial infarction. Animal studies on dogs with acute myocardial ischemia have demonstrated that HeNe laser IV LBI (1 mW, 30 min) causes increase of pO2 in arterial blood and arterial-venous difference of pO2, which serves as evidence of improvement of oxygenation of tissues (30). The improvement of microcirculation and utilization of oxygen in tissues as a result of IV LBI is intimately linked with positive influence on metabolism: higher level of oxidation of energy-carrying molecules of glucose, pyruvate, and other substances.

The improvement of microcirculation after IV LBI can be detected in all structures of the central nervous system. This effect is strongest in the vascular system hypothalamus. The capillaries of the hypothalamus are remarkable for high permeability for macro-molecular proteins. That can further amplify influence of the irradiated blood to subthalamic nuclei. It is assumed, that IV LBI can increase the functional activity of hypothalamus and all limbic system, which then can cause the activation of energetic, metabolism, immune and vegetative responses, mobilization of adaptive responses of the body.

Protection of tissues from ischemia and restoration of microcirculation in tissue are important issues in anaesthesiology and intensive care. Despite of the normal values of pulse and blood pressure and total volume of blood during surgical anaesthesia, tissues in a certain region or all over the body may experience hypoxia due to opening of shunts between the arterial and venous system. Similar process is also happening during shock. Shvetsky F.M. et al. (31) found out impairment of tissue microcirculation even before surgery. Using methods of computerized cappilaroscopy, laser Doppler flowmetry, polarogrphic monitoring of level of oxygen tension in tissues and reovasography authors demonstrated the worsening of tissue microcirculation due to surgery. Significant improvement was achieved after applying multiple sessions of HeNe laser IV LBI before and during surgery. The first session (10 mW, 30 min) was performed 24 hours before surgery, next one (20 mW, 15 min) was stared immediately after starting anaesthesia, next one (20 mW, 15 min) during the most traumatic part of surgery and the last one (20 mW, 15 min) before completing surgery. Positive effects of IV LBI including improvement of tissue trophics together with restoration of neurological regulation of microcirculation, together with more than 11% increase of oxygen tension in tissues are demonstrating stress limiting ability of laser irradiation.

Derbenev V.A. et al (32) reported faster recovery with better results for patients with burn injuries who received IV LBI as part of treatment in military hospital. IV LBI (635 nm, 2 mW, 20 min, 7-10 sessions) was applied starting the third or fourth day after injury together with conventional methods of treatment. Laser irradiation supported faster recovery due to faster healing of burn wounds, better outcomes of skin grafting with fewer rejections. In average, for patients who received IV LBI time period for wound healing was almost 9 days shorter. All the patients were under further observation (1 to 3 years). Patients in laser group had soft scars, and control group 20% of patients had ulcerations or skin hypertrophy.

At the same time there are reports about limited effects of IV LBI for the treatment of ischemic heart disease, especially stable angina pectoris. Some patients have stronger pain syndrome after number of sessions of IV LBI, as well as after transcutaneous application of red HeNe laser light. In the placebo controlled randomized studies positive effect of IV LBI was recorded in 43% of patients, while 21% of patients had stronger pains during physical exercise after laser therapy. Researchers found that patients with positive results after applying IV LBI exhibited weaker response for nitrates. Also such patients had higher triglyceride levels and longer duration of the disease. At the same time nitrates did not help much to the patients, which reacted negatively to IV LBI. It was concluded that IV LBI mimics action of nitrates on coronary arteries by possibly supporting higher production of nitric oxide by laser irradiated leucocytes. Other possible explanation of positive effects of IV LBI is known ability of laser light to limit production on thromboxane A2 by blood platelets (А.И.Коряков Е.Д.Рождественская)

Activation of mechanisms of cellular immunity is other important action of laser light. IV LBI can activate anti-bactericidal activity of the serum of the blood and complement, decrease levels of C-reactive protein (CRP), amounts of middle molecules and toxicity of plasma, levels of circulating immune complexes and increase the concentration of IgA, IgM and IgG in the serum of the blood. Laser light can stimulate phagocytic activity of macrophages causing bigger amount of bacteria captured as well as destroyed (34).

The immunological effect of IV LBI can be explained by normalization of intercellular relationships within the subpopulation of T-lymphocytes and increasing the amount of immune cells in a blood. It increases the function activity of B-lymphocytes, strengthens the immune response, reduces the degree of intoxication and as a result improves the general condition of patients (35).

IV LBI can be successfully applied with conventional methods for antimicrobial treatments. Ihsan M.F.R. (2008) reported about significantly higher concentration of Genetamicin in plasma of experimental animals when after intramuscular injection of medication IV LBI (904 nm, 10 mW) was performed.

Kosenko I.A. et al. (36) studied results of different protocols of IV LBI (670 nm, 1.5 mW) in the therapy of patients with cancer of uterus. Control group patients received conventional therapy only, including surgery, chemotherapy and radiotherapy. Patients of 3 test groups received in addition different number of laser sessions. It was found, that the number of patients with metastases after 5 years was the lowest and survival rate was the highest after receiving 10 sessions of IV LBI. Smaller number of laser therapy sessions was associated with less favourable treatment results.

Ailioaie C. et al. (37) reported about experience of treatment of chronic joint pain in children Juvenile Idiopathic Arthritis (JIA) with IV LBI. 72 children between 8 and 16 years of age were included in the study. Test group patients received conventional therapy together with IV LBI (3 mW, CW, 630 nm, 15 minutes each session, 7 consecutive days). Control group patients received placebo irradiations together with conventional therapy. Authors reported that patients in laser therapy group displayed a noticeable diminution of the pain parameters and also, of the SDAI score, so reducing the classification level of the disease activity from severe to moderate, with a statistically significant difference from the control group ($p<0.05$).

Experience of intravenous blood irradiation with lasers or LEDs of other colours than red is rather limited. Red HeNe laser were widely available in the clinics and research centres in USSR and some other countries, while lasers of blue, ultraviolet or other colour were rare. Nerveless, some studies were done in 1980s and 1990s, but the number of studies started to grow after recent development of diode based green and violet lasers.

Babadjanov B.R et al. (2001) applied ultraviolet intravenous laser blood irradiation (337 nm, 3 mW in the vein, 25 min per treatment session, 4-5 sessions) for the treatment of purulent complications of diabetes. Faster improvement of general condition (temperature, pulse, blood pressure), detoxication effect, improvement of microcirculation and fluidity rate, activation of phagocytic activity of neutrophils was recorded. Blood samples contained smaller amounts of both aerobic and anaerobic bacteria after laser treatments.

IV LBI was successfully applied in the treatment of tinnitus. Improvements of microcirculation, higher oxygenation of tissues, together with lower aggregation of blood platelets are important components for the treatment, which can be achieved by laser light. Gasparyan L. (11) was comparing effects of applying red laser (633 nm) IV LBI and blue light (440-460 nm) IV blood irradiation for patients with of hearing loss and tinnitus. Positive results were recorded after application of both, red laser and blue light blood irradiation, but results were better after applying blue light.

Numbers of clinical trials for the treatment of different diseases with application of red, green and violet lasers have been performed in Germany (Weber M, 2006-2008). Positive results were obtained for the treatment of diabetes, ischemic heart disease, Parkinson disease and some other disorders. Hypoglycaemic effect of green laser light was recorded (13). Makela A. (39, 40) discussed the biochemical background of positive influence of blue light in case of diabetes mellitus and some other conditions. She examined several molecules which can act as primary photo acceptors for blue light and some other molecules which can participate in blue light action. Blue light appears to also have nerve growth factor influencing effects thought the regulation of Agrin release as well as other neurologically important molecules.

Clinical trials showed positive effects of application of IV LBI of red and green laser light for athletes during training (41)

First encouraging trials of IV LBI with red (632 nm) and violet (405 nm) for treatment of horses were recently presented (42).

As one can see from the text above, IV LBI can be applied in the treatment of wide variety of disorders. The long term effects of low level laser therapy can involve treatment mechanisms connected with activation of stem cells. During recent years attention of scientific community was concentrated on the study of biology stem cells and development of methods of autologous stem cell therapy. Studies demonstrated important role of stem cells in naturally occurred recovery and regeneration processes, following tissue hypoxia and injury. The three clinically important steps in this natural process are mobilization of stem cells from the bone marrow or other tissues, homing of these cells to the site of injury, and finally differentiation of the stem cells into functional cells of the injured tissue.

The possible therapeutic applications of laser therapy and stem cell therapy are very similar to each other. Therefore, earlier Gasparyan et.al (2005) proposed hypotheses that one of the mechanisms of laser therapy is connected with action of stem cells, acceleration of tissue repair due to better mobilization of stem cells to the spot of injury, as well as activation of stem cells in damaged tissues due to laser irradiation (43). It was demonstrated that red and infrared laser light can activate stem cell motility as well as migration in vitro towards gradient of potent chemo attractor cytokine stromal cell-derived factor-1α (SDF-1α). Authors suggested that ability of stem cells to react to laser light can be one of the factors of laser therapy, because normally small number of hematopoietic stem cells is available in blood circulation. Amount of stem cells increases after significant damages to body or some acute diseases. Authors suggested that circulating stem cells may receive laser irradiation during IV LBI with consecutive activation of migration towards spot of injury. It was demonstrated protective effect of direct laser irradiation of ischemic myocardium (44). Oron U., et al. (45) reported higher ATP levels in ischemic myocardium after direct laser irradiation and better regeneration with smaller scarification of myocardium after injection of laser irradiated stem cells into ischemic myocardial tissues.

It was discovered, that vascular endothelial growth factor (VEGF), as well as granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF) and some cytokines have the ability to increase the number of circulating hematopoietic stem cells (HSC) and endothelial progenitor cells (EPCs) by mobilizing them from the bone marrow (46). EPCs may then be recruited to areas of neovascularization. EPCs that are capable of contributing to in vitro capillary formation can be derived from bone marrow cells (47).

Recent discovery that laser irradiation of different cell types can induce VEGF secretion can be a clue to better understanding of mechanisms of laser therapy. N. Kipshidze et al. (48) demonstrated that laser irradiation increases production of VEGF by smooth muscle cells, fibroblasts, and cardiac myocytes and stimulates human endothelial cells growth in culture. Authors observed that low level laser irradiation of vascular and cardiac cells results in a statistically significant increase of VEGF secretion in culture and are dose dependent. Also significant stimulation of endothelial cell growth was obtained with laser-treated conditioned medium of smooth muscle cells. Direct HeNe laser irradiation increases myocardial capillary permeability and the production of VEGF in myocardial microvessels and in myocardium. Zhang W.G., et al. (49) provided experimental morphological evidence that myocardial microcirculation can be improved using HeNe laser irradiation. Red laser light can induce angiogenesis in vitro and in vivo. Moreover, Gasparyan L (2005) reported that laser light can enhance angiogenic effects of VEGF in vitro (50).

Kaplan M.A. and Makela A.M. (51) researched and collated information from different research papers about direct and indirect effects of laser irradiation on different blood cells. It was demonstrated that laser light can trigger different treatment mechanisms depending the condition of the body. Laser light irradiation can cause very fast changes in the body, visible even within 15-20 minutes. Kaplan M.A. and Makela A.M. examined different blood cells and substances, which can be released or produced de novo after laser irradiation. Neutrophils, for example, after laser influence can produce IL-2, IL-3, IL-6, IL-8, G-CSF, GM-CSF, M-CSF and Interferon. Among some of the important substrates released by macrophages are: neutral proteases like collagenase and elastase which break down connective tissue (scars); plasminogen activator, which activates fibrinolytic plasmin; chemotactic substances for leukocytes; growth factors for fibroblasts, veins and bone marrow; different cytokines such as IL-1, TNF (Tumour Necrotic Factor) and PAF (Platelet Activating Factor). Monocytes contain and release PA17‑factor, which in turn causes the release of serotonin and histamine (49). That can explain number of clinical observations, like, for example, feeling of sleepiness or drowsiness during IV LBI and relaxation together with being well rested after therapy session, which was reported by Gasparyan L.V (16). That may be related to release of serotonin triggered by activation of monocytes.

As a conclusion, IV LBI is a non-expensive method for treatment, which can be widely applied in the treatment of variety of conditions. It can be successfully combined with conventional methods of therapy to accelerate recovery and decrease overall therapy costs.

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