

Low-Level Laser Therapy to the Bone Marrow Ameliorates Neurodegenerative Disease Progression in a Mouse Model of Alzheimer's Disease: A Minireview.

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OBJECTIVE: This communication reviews the ability of low-level laser therapy (LLLT) to stimulate mesenchymal stem cells (MSCs) in autologous bone marrow (BM) to enhance the capacity of MSCs to infiltrate the brain, clear beta-amyloid, and improve cognition. **BACKGROUND:** We recently reported that LLLT applied to the BM enhanced the proliferation of MSCs and their mobilization toward the ischemic heart region, suggesting a possible application of this approach in regenerative medicine and neurodegenerative diseases. It was also shown that circulating monocytes can infiltrate the brain and reduce brain amyloid load in an Alzheimer's disease (AD) mouse model. **METHODS AND RESULTS:** MSCs from wild-type mice stimulated with LLLT demonstrated an increased ability to mature toward a monocyte lineage and to increase phagocytosis of soluble A β in vitro. Furthermore, weekly LLLT for 2 months to the BM, starting at 4 months of age (progressive stage of the disease in these 5XFAD transgenic male mice), improved memory and spatial learning, compared to a sham-treated AD mouse model. Histology revealed a significant reduction in A β brain burden in the laser-treated mice compared to the nonlaser-treated ones. **CONCLUSIONS:** The application of LLLT to the BM is suggested as a therapeutic approach in progressive stages of AD, and its potential role in mediating MSC therapy in brain amyloidogenic disease is implied.

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Low-level laser therapy to the mouse femur enhances the fungicidal response of neutrophils against *Paracoccidioides brasiliensis*.

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Neutrophils (PMN) play a central role in host defense against the neglected fungal infection paracoccidioidomycosis (PCM), which is caused by the dimorphic fungus *Paracoccidioides brasiliensis* (Pb). PCM is of major importance, especially in Latin America, and its treatment relies on the use of antifungal drugs. However, the course of treatment is lengthy, leading to side effects and even development of fungal resistance. The goal of the study was to use low-level laser therapy (LLLT) to stimulate PMN to fight Pb in vivo. Swiss mice with subcutaneous air pouches were inoculated with a virulent strain of Pb or fungal cell wall components (Zymosan), and then received LLLT (780 nm; 50 mW; 12.5 J/cm²; 30 seconds per point, giving a total energy of 0.5 J per point) on alternate days at two points on each hind leg. The aim was to reach the bone marrow in the femur with light. Non-irradiated animals were used as controls. The number and viability of the PMN that migrated to the inoculation site was assessed, as well as their ability to synthesize proteins, produce reactive oxygen species (ROS) and their fungicidal activity. The highly pure PMN populations obtained after 10 days of infection were also subsequently cultured in the presence of Pb for trials of protein production, evaluation of mitochondrial activity, ROS production and quantification of viable fungi growth. PMN from mice that received LLLT were more active metabolically, had higher fungicidal activity against Pb in vivo and also in vitro. The kinetics of neutrophil protein production also correlated with a more activated state. LLLT may be a safe and non-invasive approach to deal with PCM infection.

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Low-Level Laser Therapy to the Bone Marrow Reduces Scarring and Improves Heart Function Post-Acute Myocardial Infarction in the Pig.

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OBJECTIVE: Cell therapy for myocardial repair is one of the most intensely investigated strategies for treating acute myocardial infarction (MI). The aim of the present study was to determine whether low-level laser therapy (LLLT) application to stem cells in the bone marrow (BM) could affect the infarcted porcine heart and reduce scarring following MI. **METHODS:** MI was induced in farm pigs by percutaneous balloon inflation in the left coronary artery for 90 min. Laser was applied to the tibia and iliac bones 30 min, and 2 and 7 days post-induction of MI. Pigs were euthanized 90 days post-MI. The extent of scarring was analyzed by histology and MRI, and heart function was analyzed by echocardiography. **RESULTS:** The number of c-kit+ cells (stem cells) in the circulating blood of the laser-treated (LT) pigs was 2.62- and 2.4-fold higher than in the non-laser-treated (NLT) pigs 24 and 48 h post-MI, respectively. The infarct size [% of scar tissue out of the left ventricle (LV) volume as measured from histology] in the LT pigs was 3.2 +/- 0.82%, significantly lower, 68% (p < 0.05), than that (16.6 +/- 3.7%) in the NLT pigs. The mean density of small blood vessels in the infarcted area was significantly higher [6.5-fold (p < 0.025)], in the LT pigs than in the NLT ones. Echocardiography (ECHO) analysis for heart function revealed the left ventricular ejection fraction in the LT pigs to be significantly higher than in the NLT ones. **CONCLUSIONS:** LLLT application to BM in the porcine model for MI caused a significant reduction in scarring, enhanced angiogenesis and functional improvement both in the acute and long term phase post-MI.

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Autologous bone-marrow stem cells stimulation reverses post-ischemic-reperfusion kidney injury in rats.

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BACKGROUND/AIMS: Low-level laser therapy (LLLT) has been found to modulate biological activity. The aim of the present study was to investigate the possible beneficial effects of LLLT application to stem cells in the bone marrow (BM), on the kidneys of rats that had undergone acute ischemia-reperfusion injury (IRI). **METHODS:** Injury to the kidneys was induced by the excision of the left kidney and 60 min of IRI to the right kidney in each rat. Rats were then divided randomly into 2 groups: non-laser-treated and laser-treated. LLLT was applied to the BM 10 min and 24 h post-IRI and rats were sacrificed 4 days post-IRI. Blood was collected before the sacrifice and the kidney processed for histology. **RESULTS:** Histological evaluation of kidney sections revealed the restored structural integrity of the renal tubules, and a significant reduction of 66% of pathological score in the laser-treated rats as compared to the non-laser-treated ones. C-kit positive cell density in kidneys post-IRI and laser-treatment was ($p = 0.05$) 2.4-fold higher compared to that of the non-laser treated group. Creatinine, blood urea nitrogen, and cystatin-C levels were significantly 55, 48, and 25% lower respectively in the laser-treated rats as compared to non-treated ones. **CONCLUSION:** LLLT application to the BM causes induction of stem cells, which subsequently migrate and home in on the injured kidney. Consequently, a significant reduction in pathological features and improved kidney function post-IRI are evident. The results demonstrate a novel approach in cell-based therapy for acute ischemic injured kidneys. (c) 2014 S. Karger AG, Basel.

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Long-Term Safety of Low-Level Laser Therapy at Different Power Densities and Single or Multiple Applications to the Bone Marrow in Mice.

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Abstract Objective: The purpose of this study was to determine the long-term safety effect of low-level laser therapy (LLLT) to the bone marrow (BM) in mice. **Background data:** LLLT has been shown to have a photobiostimulatory effect on various cellular processes and on stem cells. It was recently shown that applying LLLT to BM in rats post-myocardial infarction caused a marked reduction of scar tissue formation in the heart. **Methods:** Eighty-three mice were divided into five groups: control sham-treated and laser-treated at measured density of either 4, 10, 18, or 40 mW/cm² at the BM level. The laser was applied to the exposed flat medial part of the tibia 8 mm from the knee joint for 100 sec. Mice were monitored for 8 months and then killed, and histopathology was performed on various organs. **Results:** No histological differences were observed in the liver, kidneys, brain or BM of the laser-treated mice as compared with the sham-treated, control mice. Moreover, no neoplastic response in the tissues was observed in the laser-treated groups as compared with the control, sham-treated mice. There were no significant histopathological differences among the same organs under different laser treatment regimes in response to the BM-derived mesenchymal stem cell proliferation following LLLT to the BM. **Conclusions:** LLLT applied multiple times either at the optimal dose (which induces photobiostimulation of stem cells in the BM), or at a higher dose (such as five times the optimal dose), does not cause histopathological changes or neoplastic response in various organs in mice, as examined over a period of 8 months.

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Induction of autologous mesenchymal stem cells in the bone marrow by low-level laser therapy has profound beneficial effects on the infarcted rat heart.

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BACKGROUND AND OBJECTIVES: The adult mammalian heart is known to have a very limited regenerative capacity following acute ischemia. In this study we investigated the hypothesis that photobiostimulation of autologous bone-marrow-derived mesenchymal stem cells (MSCs) by low-level laser therapy (LLLT) applied to the bone marrow (BM), may migrate to the infarcted area and thus attenuate the scarring processes following myocardial infarction (MI). **MATERIALS AND METHODS:** Sprague-Dawley rats underwent experimental MI. LLLT (Ga-Al-As diode laser, power density 10 mW/cm²), for 100 seconds) was then applied to the BM of the exposed tibia at different time intervals post-MI (20 minutes and 4 hours). Sham-operated infarcted rats served as control. **RESULTS:** Infarct size and ventricular dilatation were significantly reduced (76% and 75%, respectively) in the laser-treated rats 20 minutes post-MI as compared to the control-non-treated rats at 3 weeks post-MI. There was also a significant 25-fold increase in cell density of c-kit⁺ cells in the infarcted area of the laser-treated rats (20 minutes post-MI) as compared to the non-laser-treated controls. **CONCLUSION:** The application of LLLT to autologous BM of rats post-MI offers a novel approach to induce BM-derived MSCs, which are consequently recruited from the circulation to the infarcted heart and markedly attenuate the scarring process post-MI. *Lasers Surg. Med.* 43:401-409, 2011. (c) 2011 Wiley-Liss, Inc.

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