

### **Laser Therapy - A New Modality In The Treatment Of Peripheral Nerve Injuries**

(Twenty-five years experience from basic science to clinical studies)

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Since our first publication (Rochkind 1978), we have been studying and testing low power laser irradiation as a means to treat peripheral nerves, using both in vitro and in vivo methods. We have reached the clinical stage and are treating a variety of peripheral nerve injuries. This study is a review of my personal experience over the last twenty-five years in the use of laser therapy in treating these conditions.

#### **I. Influence of Low Power Laser Irradiation on Nerve Cells**

A study was done using direct 632.8nm HeNe laser irradiation to determine the effect of focused laser beams on aggregates of rat fetal brain cells and rat adult brain. The direct HeNe laser irradiation 3.6J/cm<sup>2</sup> caused a significant amount of sprouting of cellular processes outgrowth in aggregates, compared to small amounts produced by non-irradiated controls. This observation suggests that low power laser irradiation applied to the area of an experimentally injured nerve may induce axonal processes sprouting, thereby improving nerve tissue recovery. The mechanism of low power laser on nerve tissue is not completely understood, but some studies partially explain the photochemical effect of laser irradiation on the biological system. Cytochromes are affected, thereby stimulating redox activity in the cellular respiratory chain, thereby causing increases in ATP production which activates Na<sup>+</sup>, K<sup>+</sup> -ATPase and other ion carriers, thereby increasing cell activation.

#### **II. Animal Studies - Influence Of Laser Therapy On The Severely Injured Peripheral Nerve**

A radiation method for treating lesions in both the peripheral and central nervous systems was proposed in 1978 by Rochkind and modified over the years. The model used in this work was the rat sciatic nerve. Low power laser irradiation then was delivered to the crushed nerve either transcutaneously or directly. The effects of this laser therapy were measured both in the short-term, i.e. minutes and in the long-term, i.e. days and months. Short-term model: direct irradiation of the nerve was done through the open wound directly to the crushed injured nerve and the compound nerve action potential was measured. A variety of wavelengths and powers were applied and 540nm, 632.8nm and 780nm were found most effective (p=0.01). Long-term model: We found electrophysiological activity dropped as expected in the non-irradiated nerves following the crush injury, but the use of low power laser irradiation prevented or decreased this phenomenon (p=0.001), both immediately after the crush and in the long term.

Furthermore, this investigation showed that when laser treatment was delivered to both the crushed nerve and the corresponding segments of the spinal cord, the recovery time and the quality of regeneration of the crushed sciatic nerve improved, compared to the application of irradiation to the nerve alone. Histological studies supported the electrophysiological findings: low power laser irradiation was found to prevent or decrease scar tissue formation in the injured area. Laser irradiation enhanced axonal sprouting in the crush-injured sciatic nerve, thus accelerating recovery of the severely injured peripheral nerve. In addition, a beneficial effect of low power laser irradiation was found not only in the laser-treated nerve, but in the corresponding segments of the spinal cord as well. Such laser treatment has been found to decrease significantly the degenerative changes in the corresponding neurons of the spinal cord and induce proliferation of neuroglia, both in astrocytes and oligodendrocytes. This suggests a higher metabolism in neurons and a better ability to produce myelin under the influence of laser treatment. Also, low power laser irradiation exerts pronounced systemic effects on severely injured peripheral nerves and corresponding regions of the spinal cord.

#### **III. Double-Blind Randomized Study Evaluating Regeneration of the Rat Sciatic Nerve after Suturing and Post-Operative Laser Therapy**

The therapeutic effect of low power laser irradiation on peripheral nerve regeneration after complete transection and direct anastomosis of the rat sciatic nerve was studied recently. A

780nm laser wavelength was applied transcutaneously 30 minutes daily for 21 consecutive days to corresponding segments of the spinal cord and to the injured sciatic nerve immediately after closing the wound. Positive somato-sensory evoked responses were found in 55% of the irradiated rats and in 11% of the non-irradiated rats. Immuno-histochemical staining in the laser-treated group showed more intensive axonal growth and better quality of the regenerative process due to an increased number of large and medium diameter axons. IV. Clinical Pilot Studies The group of patients who were treated in the Department of Neurosurgery at Tel Aviv Sourasky Medical Center had been suffering from severe peripheral nerve and brachial plexus injuries for more than two years. Each of the 59 patients received laser treatment CW, 780nm, five hours daily for 21 consecutive days with the use of a laser system specially developed for our treatment method. Criterion for laser treatment in these cases was as follows: patients who suffered from partial motor and sensory disturbances and where surgery was not indicated. Fifty-six percent of the laser-treated patients showed good to excellent results in their motor function. V. Clinical Double-Blind Placebo-Controlled, Randomized Study of Low Power Laser in the Treatment of Peripheral Nerve Injuries Since our previous pilot clinical results were positive, a final evaluation of the response to treatment was in order. Therefore, we performed a double-blind, placebo-controlled randomized study of patients who had been suffering from incomplete peripheral nerve and brachial plexus injuries from 6 months up to several years after injury. The protocol of this study was done with the permission of the Helsinki Committee of the Tel Aviv Sourasky Medical Center and with the approval of the Ministry of Health of Israel and by a grant from the Rehabilitation Department of the Ministry of Defence of Israel. The study evaluated the functional recovery of these patients after undergoing low power laser or placebo treatment. Recovery was classified by comparing each of the deficits present before and after surgery. The post-laser or post-placebo grade was determined by the change in strength compared to the pretreatment levels. In almost all cases, the level of motorfunction was minimal to poor pretreatment. In the laser-treated group, statistically significant improvement was found in motor functional activity  $P=0.0001$ , compared to the placebo group). The electrophysiological findings also showed statistically significant improvement in the laser-treated group. Our twenty-five years of experience indicates that Laser Therapy is a low-cost, non-invasive method and will be recognized as standard additional treatment for improving the functional recovery of patients with peripheral nerve and brachial plexus injuries. According to our clinical experience, the main advantages of Laser Therapy are the enhancement and acceleration of the recovery of injured nerve tissue. The therapeutic results show that an objective progressive improvement appears in nerve function, leading to a significant and earlier recovery.

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### **An Innovative Approach To Induce Regeneration And The Repair Of Spinal Cord Injury**

Laser Therapy.1997; 9 (4): 151.

Rochkind S, Shahar A. Nevo Z.

An Israeli research group has investigated an innovative method of repairing injured spinal cords. In a rat model the spinal cords were transected in 31 animals (between T7/T8). In vitro constructed composite implants were used in the transected area. These implants contained embryonal spinal cord neuronal cells dissociated from rat fetuses, cultured on biodegradable microcarriers. After being embedded in hyaluronic acid the implants were ready to be placed into the injured area. The whole lesion area was covered with a thin coagulated fibrin-based membrane. Control animals underwent the same laminectomy but did not receive any implant. In all animals the wound was closed normally. Laser therapy was started immediately after surgery. It was continued daily for two weeks using 780 nm, 200 mW, 30 minutes daily. One group received the implant but no laser. During the 3-6 months follow up, 14 of the 15 animals that received laser (A) showed different degrees of active movements in one or both legs, compared to 4 of 9 animals in the group who had received implants but no laser (B). In the group receiving no implant and no laser (C), 1 out of 7 showed some motor movements in one leg. Somatosensory evoked potentials were elicited in 10 of the 15 rats in group A at three months,

and on one side in one animal in group B. Axon sprouting was observed as soon as three days post surgery, in group A only.

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**New Hope For Patients With Spinal Cord Injuries**

**An Innovative Approach To Induce Regeneration And The Repair Of Spinal Cord Injury**

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**Guiding Neuronal Growth With Light**

A. Ehrlicher, T. Betz, B. Stuhmann, D. Koch, V. Milner, M. G. Raizen,  
J. Käs . PNAS. 2002; 99: 16024-16028

We have shown experimentally that we can use weak optical forces to guide the direction taken by the leading edge, or growth cone, of a nerve cell. In actively extending growth cones, we place a laser spot in front of a chosen area of the nerve's leading edge, promoting growth into the beam focus. This allows us to guide neuronal turns as well as enhance growth. The power of our laser has been selected so that the resulting gradient forces are sufficiently powerful to bias the actin polymerization-driven lamellipodia extension, but too weak to hold and move the growth cone. We are therefore using light to control a natural biological process, in sharp contrast to the established technique of optical tweezers, which uses large optical forces to manipulate entire structures. Our results therefore open a new avenue to controlling neuronal growth in vitro and in vivo with a simple, non-contact technique. Currently we have been using 800nm with continuous application of powers ranging from 20 to 130 mW over a circular area of 1 to 4 um in radius. Recently we've developed and active feedback mechanism to trace the contour of the growth cone and subsequently raster the beam image upon that, instead of the pure beam profile we had used previously.

(Abstract supplied by Allen Ehrlicher, main author)

**Transplantation Of Embryonal Spinal Cord Nerve Cells Cultured On Biodegradable Microcarriers Followed By Low Power Laser Irradiation For The Treatment Of Traumatic Paraplegia In Rats**

Neurol Res. 2002 Jun;24(4):355-60.

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This pilot study examined the effects of composite implants of cultured embryonal nerve cells and laser irradiation on the regeneration and repair of the completely transected spinal cord. Embryonal spinal cord nerve cells dissociated from rat fetuses and cultured on biodegradable microcarriers and embedded in hyaluronic acid were implanted in the completely transected spinal cords of 24 adult rats. For 14 consecutive post-operativedays, 15 rats underwent low power laser irradiation (780 nm, 250 mW), 30 min daily.

Eleven of the 15 (73%) showed different degrees of active leg movements and gait performance, compared to 4 (44%) of the 9 rats with implantation alone. In a controlgroup of seven rats with spinal cord transection and no transplantation or laser, six (86%) remained completely paralyzed. Three months after transection, implantation and laser irradiation, SSEPs were elicited in 69% of rats ( $p = 0.0237$ ) compared to 37.5% in the nonirradiated group. The control group had no SSEPs response. Intensive axonal sprouting occurred in the group with implantation and laser. In the control group, the transected area contained proliferating fibroblasts and blood capillaries only.

This suggests: 1. These in vitro composite implants are a regenerative and reparative source for reconstructing the transected spinal cord. 2. Post-operative low power laser irradiation enhances axonal sprouting and spinal cord repair.

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**Growth-Associated Protein-43 Is Elevated In The Injured Rat Sciatic Nerve After Low Power Laser Irradiation**

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Neurosci Lett. 2003 Jun 26;344(2):71-4.

Low power laser irradiation (LPLI) has been used in the treatment of peripheral nerve injury. In this study, we verified its therapeutic effect on neuronal regeneration by finding elevated immunoreactivities (IRs) of growth-associated protein-43 (GAP-43), which is up-regulated during neuronal regeneration. Twenty Sprague-Dawley rats received a standardized crush injury of the sciatic nerve, mimicking the clinical situations accompanying partial axonotmesis. The injured nerve received calculated LPLI therapy immediately after injury and for 4 consecutive days thereafter. The walking movements of the animals were scored using the sciatic functional index (SFI). In the laser treated rats, the SFI level was higher in the laser treated animals at 3-4 weeks while the SFIs of the laser treated and untreated rats reached normal levels at 5 weeks after surgery. In immunocytochemical study, although GAP-43 IRs increased both in the untreated control and the LPLI treated groups after injury, the number of GAP-43 IR nerve fibers was much more increased in the LPLI group than those in the control group. The elevated numbers of GAP-43 IR nerve fibers reached a peak 3 weeks after injury, and then declined in both the untreated control and the LPLI groups at 5 weeks, with no differences in the numbers of GAP-43 IR nerve fibers of the two groups at this stage. This immunocytochemical study using GAP-43 antibody study shows for the first time that LPLI has an effect on the early stages of the nerve recovery process following sciatic nerve injury.

**Low-Level Laser Effect On Neural Regeneration In Gore-Tex Tubes**

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Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002 Jan;93(1):27-34.

**PURPOSE:** The purpose of this investigation was to determine the effects of low-level laser (LLL) irradiation on neural regeneration in surgically created defects in the rabbit inferior alveolar nerve.

**STUDY DESIGN:** Five adult female New Zealand White rabbits underwent bilateral exposure of the inferior alveolar nerve. A 6-mm segment of nerve was resected, and the nerve gap was repaired via entubulation by using a Gore-Tex conduit. The experimental side received 10 postoperative LLL treatments with a 70-mW gallium-aluminum-arsenide diode at 4 sites per treatment. At 15 weeks after surgery, the nerve segments were harvested bilaterally and prepared for light microscopy. Basic fuchsin and toluidine blue were used to highlight myelinated axons. The segments were examined histomorphometrically by using computer analysis to determine mean axonal diameter, total fascicular surface area, and axonal density along the repair sites.

**RESULTS:** Gross examination of all nerves showed intact neural bundles with variable degrees of osseous remodeling. Light microscopic evaluation revealed organized regenerated neural tissue in both groups with more intrafascicular perineural tissue in the control group. Histomorphometric evaluation revealed increased axonal density in the laser treated group as compared with the control.

**CONCLUSIONS:** LLL irradiation may be a useful noninvasive adjunct to promote neuronal wound healing in surgically created defects repaired with expanded polytetrafluoroethylene entubulation.

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**No Effect Of GA-AS (904 Nm) Laser Irradiation On The Intact Skin Of The Injured Rat Sciatic Nerve**

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Lasers Med Sci. 2003;18(2):83-8.

We evaluated the electrophysiological and histopathological effects of low-energy gallium arsenide (904 nm) laser irradiation on the intact skin injured rat sciatic nerve. Twenty-four male Wistar rats were divided into three groups (n=8 each). At the level of proximal third of the femur the sciatic nerve was crushed bilaterally with an aneurysm clip (Aesculap FE 751, Tuttingen, Germany) for half a second. A gallium arsenide laser (wavelength 904 nm, pulse duration 220 ns, peak power per pulse 27 W, spot size 0.28 cm<sup>2</sup>, pulse repetition rate 16, 128 and 1000 Hz; total applied energy density 0.31, 2.48 and 19 J/cm<sup>2</sup>) was applied to the right sciatic nerve for 15 min daily at the same time on 7 consecutive days. The same procedure was performed on the left sciatic nerve of same animal, but without radiation emission, and this was accepted as control. Compound muscle action potentials were recorded from right and left sides in all three groups before surgery, just at the end of injury, at the 24th hour and on the 14th and 21st days of injury in all rats using a BIOPAC MP 100 Acquisition System Version 3.5.7 (Santa Barbara, USA). BIOPAC Acknowledge Analysis Software (ACK 100 W) was used to measure CMAP amplitude, area, proximal and distal latency, total duration and conduction velocity. Twenty-one days after injury, the rats were sacrificed. The sciatic nerves of the operated parts were harvested from the right and left sides. Histopathological evaluation was performed by light microscopy. Statistical evaluation was done using analysis of variance for two factors (right and left sides) repeated-measures (CMAP variables within groups) and the Tukey-Kramer Honestly Significant Difference

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test (CMAP variables between laser groups). The significance was set at  $p < 0.05$ . No statistically significant difference ( $p > 0.05$ ) was found regarding the amplitude, area, duration and conduction velocity of CMAP for each applied dose (0.31, 2.48 and 19 J/cm<sup>2</sup>) on the irradiated (right) side and the control (left) side, or between irradiated groups. Twenty-one days after injury there were no qualitative differences in the morphological pattern of the regenerated nerve fibres in either irradiated (0.31, 2.48 and 19 J/cm<sup>2</sup>) or control nerves when evaluated by light microscopy. This study showed that low-energy GaAs irradiation did not have any effect on the injured rat sciatic nerve.

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