

Nerve Regeneration

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Increase of neuronal sprouting and migration using 780 nm laser phototherapy as procedure for cell therapy.

[Rochkind S](#), [El-Ani D](#), [Nevo Z](#), [Shahar A](#).

Division of Peripheral Nerve Reconstruction, Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv 64239, Israel. rochkind@zahav.net.il

BACKGROUND AND OBJECTIVES: The present study focuses on the effect of 780 nm laser irradiation on the growth of embryonic rat brain cultures embedded in NVR-Gel (cross-linked hyaluronic acid with adhesive molecule laminin and several growth factors). Dissociated neuronal cells were first grown in suspension attached to cylindrical microcarriers (MCs). The formed floating cell-MC aggregates were subsequently transferred into stationary cultures in gel and then laser treated. The response of neuronal growth following laser irradiation was investigated. **MATERIALS AND METHODS:** Whole brains were dissected from 16 days Sprague-Dawley rat embryos. Cells were mechanically dissociated, using narrow pipettes, and seeded on positively charged cylindrical MCs. After 4-14 days in suspension, the formed floating cell-MC aggregates were seeded as stationary cultures in NVR-Gel. Single cell-MC aggregates were either irradiated with near-infrared 780 nm laser beam for 1, 4, or 7 minutes, or cultured without irradiation. Laser powers were 10, 30, 50, 110, 160, 200, and 250 mW. **RESULTS:** 780 nm laser irradiation accelerated fiber sprouting and neuronal cell migration from the aggregates. Furthermore, unlike control cultures, the irradiated cultures (mainly after 1 minute irradiation of 50 mW) were already established after a short time of cultivation. They contained a much higher number of large size neurons ($P < 0.01$), which formed dense branched interconnected networks of thick neuronal fibers. **CONCLUSIONS:** 780 nm laser phototherapy of embryonic rat brain cultures embedded in hyaluronic acid-laminin gel and attached to positively charged cylindrical MCs, stimulated migration and fiber sprouting of neuronal cells aggregates, developed large size neurons with dense branched interconnected network of neuronal fibers and, therefore, can be considered as potential procedure for cell therapy of neuronal injury or disease.

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Phototherapy in peripheral nerve regeneration: From basic science to clinical study.

[Rochkind S](#).

Division of Peripheral Nerve Reconstruction, Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel.

Object This review summarizes the continuous study of low-power laser radiation treatment of a severely injured peripheral nerve. Laser phototherapy was applied as a supportive factor for accelerating and enhancing axonal growth and regeneration after injury or a reconstructive peripheral nerve procedure. In nerve cell cultures, laser phototherapy was used to stimulate activation of nerve cells. **Methods** Low-power laser radiation was used for treatment of peripheral nerve injury using a rat sciatic nerve model after crush injury, neuroorrhaphy, or neurotube reconstruction. Nerve cell growth and axonal sprouting were investigated using laser phototherapy on embryonic rat brain cultures. The outcome in animal studies facilitated a clinical double-blind, placebo-controlled, randomized study that measured the effectiveness of 780-nm laser phototherapy on patients suffering from incomplete peripheral nerve injuries for 6 months to several years. **Results** Animal studies showed that laser phototherapy has an immediate protective effect, maintains functional activity of the injured nerve, decreases scar tissue formation at the injury site, decreases degeneration in corresponding motor neurons of the spinal cord, and significantly increases axonal growth and myelination. In cell cultures, laser irradiation accelerates migration, nerve cell growth, and fiber sprouting. A pilot clinical double-blind, placebocontrolled, randomized study showed that in patients with incomplete long-term peripheral nerve injury, 780-nm laser radiation can progressively improve peripheral nerve function, which leads to significant functional recovery. **Conclusions** Using 780-nm laser phototherapy accelerates and enhances axonal growth and regeneration after injury or a reconstructive peripheral nerve procedure. Laser activation of nerve cells, their growth, and axonal sprouting can be considered as potential treatment of neuronal injury. Animal and clinical studies show the promoting action of phototherapy on peripheral nerve regeneration, making it possible to suggest that the time for broader clinical trials has arrived.

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Laser phototherapy (780 nm), a new modality in treatment of long-term incomplete peripheral nerve injury: a randomized double-blind placebo-controlled study.

[Rochkind S](#), [Drory V](#), [Alon M](#), [Nissan M](#), [Ouaknine GE](#).

Division of Peripheral Nerve Reconstruction, Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Tel Aviv University, Israel. rochkind@zahav.net.il

OBJECTIVE: The authors conducted this pilot study to prospectively investigate the effectiveness of low-power laser irradiation (780 nm) in the treatment of patients suffering from incomplete peripheral nerve and brachial plexus injuries for 6 months up to several years. **BACKGROUND DATA:** Injury of a major nerve trunk frequently

results in considerable disability associated with loss of sensory and motor functions. Spontaneous recovery of long-term severe incomplete peripheral nerve injury is often unsatisfactory. **METHODS:** A randomized, double-blind, placebo-controlled trial was performed on 18 patients who were randomly assigned placebo (non-active light: diffused LED lamp) or low-power laser irradiation (wavelength, 780 nm; power, 250 mW). Twenty-one consecutive daily sessions of laser or placebo irradiation were applied transcutaneously for 3 h to the injured peripheral nerve (energy density, 450 J/mm²) and for 2 h to the corresponding segments of the spinal cord (energy density, 300 J/mm²). Clinical and electrophysiological assessments were done at baseline, at the end of the 21 days of treatment, and 3 and 6 months thereafter. **RESULTS:** The laser-irradiated and placebo groups were in clinically similar conditions at baseline. The analysis of motor function during the 6-month follow-up period compared to baseline showed statistically significant improvement ($p = 0.0001$) in the laser-treated group compared to the placebo group. No statistically significant difference was found in sensory function. Electrophysiological analysis also showed statistically significant improvement in recruitment of voluntary muscle activity in the laser-irradiated group ($p = 0.006$), compared to the placebo group. **CONCLUSION:** This pilot study suggests that in patients with long-term peripheral nerve injury noninvasive 780-nm laser phototherapy can progressively improve nerve function, which leads to significant functional recovery.

[Photomed Laser Surg.](#) 2007 Jun;25(3):137-43

Efficacy of 780-nm laser phototherapy on peripheral nerve regeneration after neurotube reconstruction procedure (double-blind randomized study).

[Rochkind S](#), [Leider-Trejo L](#), [Nissan M](#), [Shamir MH](#), [Kharenko O](#), [Alon M](#).

Division of Peripheral Nerve Reconstruction, Tel-Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel. rochkind@zahav.net.il

OBJECTIVE: This pilot double-blind randomized study evaluated the efficacy of 780-nm laser phototherapy on the acceleration of axonal growth and regeneration after peripheral nerve reconstruction by polyglycolic acid (PGA) neurotube. **BACKGROUND DATA:** The use of a guiding tube for the reconstruction of segmental loss of injured peripheral nerve has some advantages over the regular nerve grafting procedure. Experimental studies have shown that laser phototherapy is effective in influencing nerve regeneration. **METHODS:** The right sciatic nerve was transected, and a 0.5-cm nerve segment was removed in 20 rats. A neurotube was placed between the proximal and the distal parts of the nerve for reconnection of nerve defect. Ten of 20 rats received post-operative, transcutaneous, 200-mW, 780-nm laser irradiation for 14 consecutive days to the corresponding segments of the spinal cord (15 min) and to the reconstructed nerve (15 min). **RESULTS:** At 3 months after surgery, positive somato-sensory evoked responses were found in 70% of the irradiated rats ($p = 0.015$), compared to 30% of the non-irradiated rats. The Sciatic Functional Index in the irradiated group was higher than in the

non-irradiated group ($p < 0.05$). Morphologically, the nerves were completely reconnected in both groups, but the laser-treated group showed an increased total number of myelinated axons. **CONCLUSION:** The results of this study suggest that postoperative 780-nm laser phototherapy enhances the regenerative process of the peripheral nerve after reconnection of the nerve defect using a PGA neurotube.

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Promotion of regenerative processes in injured peripheral nerve induced by low-level laser therapy.

[Mohammed IF](#), [Al-Mustawfi N](#), [Kaka LN](#).

Department of Anatomy, Al-Kindy Medical College, Baghdad University, Baghdad, Iraq.
ihshan20042002@yahoo.com

OBJECTIVE: This study aimed to assess in vitro the influence of low-level laser therapy (LLLT) on the regenerative processes of a peripheral nerve after trauma.

BACKGROUND DATA: In peripheral nerve injury initiated after severing due to accident or by a surgeon during operation, photomodulation by light in the red to near-infrared range (530-1000 nm) using low-energy lasers has been shown to accelerate nerve regeneration.

METHOD: Twenty-four New Zealand adult male rabbits were randomly assigned to two equal groups (control and laser-treated). General anesthesia was administered intramuscularly, and exploration of the peroneal nerve was done in the lateral aspect of the left leg. Complete section of the nerve was performed, which was followed by suturing of the neural sheath (epineurium). Irradiation was carried out directly after the operation and for 10 consecutive days. The laser used was diode with wavelength of 901 nm (impulsive) and power of 10 mW; it was a square-shaped window type (16 cm²), and its energy was applied by direct contact of the instrument's window to the site of the operation. Three rabbits from each group were sacrificed at the end of weeks 2, 4, 6, and 8, and specimens were collected from the site of nerve suturing and sent for histopathological examination.

RESULTS: Two important factors were examined via histopathology: diameter of the nerve fibers and individual internodal length. Compared to the control group, significant variations in regeneration were observed, including thicker nerve fibers, more regular myelin layers, clearer nodes of Ranvier with absence of short nodes in the treated group. Variations between the two groups for diameter were significant for the 2nd week ($p < 0.05$), highly significant for the 4th and 6th weeks, respectively ($p < 0.01$), and very highly significant for the 8th week ($p < 0.001$). Variations between the two groups for internodal length were highly significant for the 2nd and 4th weeks ($p < 0.01$), and very highly significant for the 6th and 8th weeks ($p < 0.001$).

CONCLUSION: This experiment affirms the beneficial effect of LLLT on nerve regeneration, since LLLT produced a significant amount of structural and cellular change. The results of the present study suggest that laser therapy may be a viable approach for nerve regeneration, which may be of clinical relevance in scheduled surgery or microsurgery.

Further development of reconstructive and cell tissue-engineering technology for treatment of complete peripheral nerve injury in rats.

[Rochkind S](#), [Astachov L](#), [el-Ani D](#), [Hayon T](#), [Graif M](#), [Barsky L](#), [Alon M](#), [Odvak I](#), [Nevo Z](#), [Shahar A](#).

Department of Neurosurgery, Division of Peripheral Nerve Reconstruction, Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel. rochkind@zahav.net.il

In this work we evaluated the efficacy of biodegradable composite co-polymer guiding neurotube, based on tissue-engineering technology, for the treatment of complete peripheral nerve injury where the nerve defect is significant. The right sciatic nerve of 12 three-month-old rats was completely transected and peripheral nerve segment was removed. A 2.2-cm biodegradable co-polymer neurotube containing viscous gel (NVR-N-Gel) with survival factors, neuroprotective agents and Schwann cells was placed between the proximal and the distal parts of the transected nerve for reconnection a 2-cm nerve defect. The proximal and distal parts of the nerve were fixed into the neurotube using 10-0 sutures. Ultrasound observation showed growth of the axons into the composite neurotube 2 months after the surgery. Electrophysiological study indicated compound muscle action potentials in nine out of 12 rats, 2-4 months after peripheral nerve reconstructive surgery. The postoperative follow-up (up to 4 months) on the operated rats that underwent peripheral nerve reconstruction using composite co-polymer neurotube, showed beginning of re-establishment of active foot movements. The tube was dissolved and nerve showed complete reconnection. Histological observation of the nerve showed growth of myelinated axons into the site where a 2-cm nerve defect replaced by composite co-polymer neurotube and into the distal part of the nerve. In CONCLUSION: (1) an innovative composite neurotube for reconstruction of significant loss of peripheral nerve segment is described; (2) a viscous gel, containing survival factors, neuroprotective agents and Schwann cells served as a regenerative environment for repair. Further investigations of this reconstructive procedure are being conducted.

Phototherapy promotes regeneration and functional recovery of injured peripheral nerve.

[Anders JJ](#), [Geuna S](#), [Rochkind S](#).

Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20854, USA. janders@usuhs.mil

Numerous attempts have been made to enhance and/or accelerate the recovery of injured peripheral nerves. One of the methods studied is the use of phototherapy (low power laser or

light irradiation) to enhance recovery of the injured peripheral nerve. A critical analysis of the literature on the employment of phototherapy for the enhancement of the regeneration process of the rat facial and sciatic nerve (after crush injury or transection followed by surgical reconstruction) is provided, together with the description of some of the most suitable basic biological mechanisms through which laser radiation exerts its action on peripheral nerve regeneration.

[In Vivo](#). 2004 Jul-Aug;18(4):489-95.

Effect of Ga-as laser on the regeneration of injured sciatic nerves in the rat.

[Bae CS](#), [Lim SC](#), [Kim KY](#), [Song CH](#), [Pak S](#), [Kim SG](#), [Jang CH](#).

College of Veterinary Medicine, Biotechnology Research Institute, Chonnam National University, Gwangju, Korea.

Laser irradiation is one of the therapeutic methods for the recovery of degenerated peripheral nerves. The aim of the present study was to determine if low-power laser treatment stimulates the regeneration process of damaged nerves. A standardized crush to the sciatic nerve was applied to cause extensive axonal degeneration. After this procedure, low-power infrared laser irradiation was administered transcutaneously to the injured sciatic nerve, 3 minutes daily to each of four treatment groups for 1, 3, 5 and 7 weeks, respectively. A nerve conduction study was done, and a morphological assessment was performed using both light and electron microscopy. With trauma of the nerve, both amplitude of compound motor action potential and nerve conduction velocity decreased significantly compared to the pre-trauma state. Morphologically, the numbers of myelinated axons and degenerated axons were decreased and increased, respectively, compared with the control. Typical aspects were of onion skin-type lamellation, fragmentation, edematous swelling and rarefaction in the myelin sheath. All these parameters recovered almost to the level of the pre-trauma state with laser irradiation, in direct proportion to the time spent for treatment. These results suggest that low-power infrared laser irradiation can relieve the mechanical damage of sciatic nerves and stimulate the regeneration of peripheral nerves.

LASER THERAPY - A NEW MODALITY IN THE TREATMENT OF PERIPHERAL NERVE INJURIES

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

S. Rochkind, MD Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Tel-Aviv University, Tel Aviv, Israel, E-mail: rochkind@zahav.net.il

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/cm² 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⁺, K⁺ -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 motor function was minimal to poor pre-treatment. 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.

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

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.

[Rochkind S](#), [Shahar A](#), [Amon M](#), [Nevo Z](#).

Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Israel.
rochkind@zahav.net.il

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-operative days, 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 control group 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.

[J Reconstr Microsurg.](#) 2001 Feb;17(2):133-7; discussion 138.

Double-blind randomized study evaluating regeneration of the rat transected sciatic nerve after suturing and postoperative low-power laser treatment.

[Shamir MH](#), [Rochkind S](#), [Sandbank J](#), [Alon M](#).

Koret School of Veterinary Medicine, Hebrew University of Jerusalem.

This double-blind randomized study evaluated the therapeutic effect of low-power laser irradiation (LPLI) on peripheral nerve regeneration, after complete transection and direct anastomosis of the rat sciatic nerve. After this procedure, 13 of 24 rats received

postoperative LPLI, with a wavelength of 780 nm laser, applied transcutaneously, 30 min daily for 21 consecutive days, to corresponding segments of the spinal cord and to the injured sciatic nerve. Positive somatosensory evoked responses were found in 69.2 percent of the irradiated rats ($p = 0.019$), compared to 18.2 percent of the non-irradiated rats. Immunohistochemical staining in the laser-treated group showed an increased total number of axons ($p = 0.026$), and better quality of the regeneration process, due to an increased number of large-diameter axons ($p = 0.021$), compared to the non-irradiated control group. The study suggests that postoperative LPLI enhances the regenerative processes of peripheral nerves after complete transection and anastomosis.

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

No effect of GA-AS (904 nm) laser irradiation on the intact skin of the injured rat sciatic nerve.

[Bagis S](#), [Comelekoglu U](#), [Coskun B](#), [Milcan A](#), [Buyukakilli B](#), [Sahin G](#), [Ozsisik S](#), [Erdogan C](#).

Mersin University, Adana, Turkey. seldabagis@hotmail.com

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 cm², pulse repetition rate 16, 128 and 1000 Hz; total applied energy density 0.31, 2.48 and 19 J/cm²) 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 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/cm²) 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/cm²) 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.

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

An innovative approach to induce regeneration and the repair of spinal cord injury.

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.

Laser Therapy.1997; 9 (4): 151

New hope for patients with spinal cord injuries.

Rochkind S, Shahar A. Nevo Z. An innovative approach to induce regeneration and the repair of spinal cord injury..

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

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J. Käs . PNAS. 2002; 99: 16024-16028

Guiding neuronal growth with light

A. Ehrlicher, T. Betz, B. Stuhmann, D. Koch, V. Milner, M. G. Raizen,

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 an 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)

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

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.

Rochkind S, Shahar A, Amon M, Nevo Z.

Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Israel.
rochkind@zahav.net.il

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-operative days, 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 control group 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.

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

Growth-associated protein-43 is elevated in the injured rat sciatic nerve after low power laser irradiation.

Shin DH, Lee E, Hyun JK, Lee SJ, Chang YP, Kim JW, Choi YS, Kwon BS.

Department of Anatomy, Seoul National University College of Medicine, Seoul, South Korea.

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 axotomy. 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.

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Low-level laser effect on neural regeneration in Gore-Tex tubes.

Miloro M, Halkias LE, Mallery S, Travers S, Rashid RG.

Department of Surgery, Division of Oral and Maxillofacial Surgery, University of Nebraska Medical Center, Omaha 68198-5180, USA.

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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Effect of low-level laser treatment on neurosensory deficits subsequent to sagittal split ramus osteotomy.

[Khullar SM](#), [Emami B](#), [Westermarck A](#), [Haanaes HR](#).

Department of Oral Surgery and Oral Medicine, University of Oslo, Norway.

OBJECTIVES: Low-level laser treatment has been advocated as a possible treatment for patients with paresthesia. An objectively verified improvement in sensory function is relevant if, at the same time, it is perceived as a subjective improvement by the patient. The aim of this double blind clinical study was to see if low-level laser treatment with a GaAlAs laser (820 nm, Rønvig, Denmark) resulted in objectively verified improvement in sensory function and whether this correlated with the patient's subjective evaluation subsequent to treatment. **STUDY DESIGN:** The 13 patients in this study had all

undergone sagittal split ramus osteotomy resulting in either compression or traction of the inferior alveolar nerve as reported by the surgery notes. The material was collected from a consecutive series of patients at the Karolinska Hospital, all of whom had shown reduced sensibility at their final 2-year postoperative checkup. The patients were randomly divided into two groups; one (eight subjects) group received real low-level laser treatment (4 x 6 J per treatment along the distribution of the inferior alveolar nerve, at the following points extraoral: lateral third of lower lip, intraoral; buccally to the apex of the second premolar tooth and the apex of the second molar tooth; lingually in the region of the mandibular foramen; for a total of 20 treatments). The other group received an equivalent placebo treatment. The study was conducted in a double blind fashion for both patient and doctor as the low-level laser equipment had two settings, A and B, one of which was an unknown void setting. The degree of mechanoreceptor neurosensory deficit was assessed by Semmes Weinstein monofilaments (North Coast Medical, USA) and the degree of thermoreceptor neurosensory deficit was assessed by a ThermoTester (Somedic, Sweden). The degree of subjective neurosensory deficit was assessed by means of a visual analogue scale. Both variables and the degree of subjective injury were comparable between the two groups before starting treatment. **RESULTS:** The patients in the real low-level laser treatment group experienced a subjective improvement in both lip ($p = 0.01$) and chin ($p = 0.02$) after completion of the course of treatment. In addition, this group showed a significant decrease in the area of mechanoperception neurosensory deficit ($p = 0.01$) compared with no difference in the placebo group. The real low-level laser treatment group exhibited a strong tendency toward improvement in mechanoreceptor neurosensory deficit in the areas of most damage for both lip and chin. This improvement was especially pronounced in the lip region ($p = 0.06$). No similar tendency was demonstrated in the placebo group. Neither group showed any significant change or tendency to improvement in thermoreception on completion of the course of treatment. **CONCLUSION:** In conclusion GaAlAs low-level laser treatment results in both a subjective and objective improvement in mechanical sensory perception in long-standing neurosensory deficit in the inferior alveolar nerve.