Injury of a peripheral nerve frequently results in considerable disability. In an extremity, such lesions may be associated with loss of sensory and motor functions, which leads to severe occupational and social consequences. Surgical repair is the preferred modality of treatment for the complete or severe peripheral nerve injury. In most cases, the repair can be successful if the surgery is performed in the first 6 months after injury, in comparison with long-term cases in which surgical treatment is less successful. Nonetheless, in related literature, there are several publications involving surgical treatment of long-term injuries of the brachial plexus and peripheral nerve. For most patients who suffered from long-term peripheral nerve injuries, the continuation of rehabilitation therapy was recommended, especially in those regions or countries that don’t have specially dedicated peripheral nerve surgeons. Unfortunately, spontaneous recovery of long-term, severe, incomplete peripheral nerve injury is often unsatisfactory.

The usual results after such an injury are degeneration of the axons and retrograde degeneration of the corresponding neurons of the spinal cord, followed by a very slow regeneration. Recovery may eventually occur, but it is slow and frequently incomplete. Understandably, therefore, numerous attempts have been made to enhance and/or accelerate the recovery of injured peripheral nerves. Among the various proposed methods for enhancing nerve repair, phototherapy has received increasing attention over the past 2 decades. The term phototherapy refers to the use of light for producing a therapeutic effect on living tissues. Although a pioneering report of the effects of laser phototherapy on the regeneration of traumatically injured peripheral nerves was published in the late 1970s, it is only since the late 1980s that scientific interest was kindled for this therapeutic approach to neural rehabilitation, leading to the publication of a number of studies that have shown positive effects of phototherapy on peripheral nerve regeneration.

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

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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, neurorrhaphy, 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, placebo-controlled, 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. (DOI: 10.3171/FOC.2009.26.2.E8)

Key Words • axonal sprouting • laser phototherapy • nerve cells • peripheral nerve injury • rat
The possible mechanism of action of phototherapy on the nervous tissue with respect to peripheral nerve regeneration has been provided by in vitro studies, which show that phototherapy induced massive neurite sprouting and outgrowth in cultured neuronal cells as well as Schwann cell proliferation. It has also been suggested that phototherapy may enhance recovery of neurons from injury by altering mitochondrial oxidative metabolism, and guiding neuronal growth cones in vitro, perhaps due to the interaction with cytoplasmic proteins and, in particular, to the enhancement of actin polymerization at the leading axon edge. A possible molecular explanation was provided by demonstrating an increase in growth-associated protein-43 immunoreactivity in the early stages of rat sciatic nerve regeneration after phototherapy. Another study showed that application of phototherapy up-regulates calcitonin gene-related peptide mRNA expression in facial motor nuclei after axotomy. By altering the intensity or temporal pattern of injury-induced calcitonin gene-related peptide expression, phototherapy may thus optimize the rate of regeneration and target innervation and neuronal survival of axotomized neurons. The purpose of this review is to accumulate data pertaining to the effectiveness of 780-nm laser phototherapy in treating a severely injured peripheral nerve, based on our long-term research.

Animal Studies

Experimental Peripheral Nerve Crush Injury

Laser phototherapy significantly improves recovery of the injured peripheral nerve, and in addition, decreases posttraumatic retrograde degeneration of the neurons in the corresponding segments of the spinal cord. Our previous studies investigating the effects of low-power laser irradiation on an injured peripheral nerve in rats have found that it provides: 1) immediate protective effects that increase the functional activity of the injured peripheral nerve; 2) maintenance of functional activity of the injured nerve over time; 3) a decrease or prevention of scar tissue formation at the site of injury (Fig. 1); 4) prevention or decreased regeneration in corresponding motor neurons of the spinal cord (Fig. 2); and 5) an increase in the rate of axonal growth and myelination (Fig. 3).

Moreover, direct laser irradiation of the spinal cord improves recovery of the corresponding injured peripheral nerve. These results suggest that laser phototherapy accelerates and improves the regeneration of the injured peripheral nerve.

Regeneration of the Transected Sciatic Nerve in the Rat After Primary Anastomosis

In acute cases in which a peripheral nerve is completely transected, the treatment of choice is direct anastomosis. The means of enhancing regeneration are essential, because degeneration is always inevitable in severely damaged peripheral nerves.

A double-blind randomized study evaluated the therapeutic effect of 780-nm laser phototherapy on peripheral nerve regeneration after complete transection and direct anastomosis of the rat sciatic nerve. After this procedure, 13 of 24 rats received postoperative transcutaneous laser treatment, for 30 minutes daily on 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% of the laser-treated rats (p = 0.019), compared with 18.2% of the untreated rats. Immunohistochemical staining in the laser-treated group showed a significantly increased total number of
Nerve response to phototherapy

axon (p = 0.026) and better quality of the regeneration process due to more large diameter axons (p = 0.021) compared with the nonlaser-treated group (Fig. 4). This study suggests that postoperative laser phototherapy enhances the regenerative processes of peripheral nerves after complete transection and anastomosis.

Regeneration of the Sciatic Nerve in the Rat After Neurotube Reconstruction

In cases in which the peripheral nerve is injured and complete segmental loss exists, the treatment of choice is nerve reconstruction using an autogenous nerve graft. The use of a regenerating guiding tube for the reconstruction of segmental loss of a peripheral nerve has some advantages compared with the regular nerve grafting procedure.

A pilot study was conducted to evaluate the efficacy of 780-nm laser phototherapy on the acceleration of axonal growth and regeneration after experimental peripheral nerve reconstruction using a guiding tube. The 5-mm segment of the right sciatic nerve was removed and proximal and distal parts were inserted into a bioabsorbable polyglycolic acid neurotube (Fig. 5). The rats were divided into 2 groups (laser-treated and nonlaser-treated).

Postoperative low-power laser irradiation was applied for 30 minutes transcutaneously on the transplanted peripheral nerve area and corresponding segments of the spinal cord on 14 consecutive days. Conductivity of the sciatic nerve was determined by stimulating the sciatic nerve and recording the somatosensory evoked potentials from the scalp. Three months after surgery, somatosensory evoked potentials were found in 70% of the rats in the laser-treated group in comparison with 40% of the rats in the nonlaser-treated group. Morphologically, the previously transected nerve had good reconnection in both groups and the neurotube had dissolved (Fig. 6). The growth of myelinated axons, which crossed through the composite neurotube, was found and the continuation of axonal sprouting through the area of the tube to the distal part of the nerve was recognized. The laser-treated group showed more intensive axonal growth compared with the control group.

Influence of Laser Irradiation on Nerve Cell Growth In Vitro as a Potential Procedure for Neuronal Injury

Neuronal loss and degeneration resulting from peripheral nerve injuries has lead us to explore the possibility of using laser phototherapy on cells as a method of preventing or decreasing this phenomena. In this work, the effect of 780-nm laser phototherapy was investigated on axonal sprouting and cell size of embryonic nerve cells.
rat brain cells on microcarriers embedded in NeuroGel in culture. Whole brains were dissected from 16-day-old Sprague-Dawley rat embryos. After mechanical dissociation, cells were seeded directly in NeuroGel or suspended in positively charged cylindrical microcarriers. Single-cell microcarrier aggregates were either irradiated with the laser within 1 hour after seeding, or cultured without irradiation. Neurogel (hyaluronic acid and laminin) was enriched with growth factors (brain-derived neurotrophic factor and insulin-like growth factor–I).

To optimize energy density for activation of nerve cell culture, 10, 30, 50, 110, 160, 200, and 250 mW laser powers were applied. Dissociated cells or cell microcarrier aggregates embedded in NeuroGel were irradiated for 1, 3, 4, or 7 minutes. Cell cultures were fixed with 4% paraformaldehyde and incubated with antibodies against neural cell markers (mouse anti–rat microtubule-associated protein). Cells were then washed and incubated with Texas Red conjugated goat anti–mouse immunoglobulin.

A rapid sprouting of nerve processes from the irradiated cell microcarrier aggregates was detected within 24 hours after seeding (Fig. 7). The extension of nerve fibers was followed by active neuronal migration. Differences between controls and irradiated stationary dissociated brain cultures became evident at approximately the end of the 1st week of cultivation; several neurons in the irradiated cultures exhibited large perikarya and thick elongated processes (Fig. 8). Furthermore, during the next 2–3 weeks of cultivation, neurons in the irradiated cultures developed a dense, branched, interconnected network of neuronal fibers (Fig. 9).

Clinical Study

Based on the outcome of these animal studies, a clinical double-blind, placebo-controlled, randomized study...
Low-power laser phototherapy in peripheral nerve-injured patients

An extensive review article published in 2005 revealed that most experimental studies showed that phototherapy promoted the recovery of a severely injured peripheral nerve. This review makes it possible to suggest that the time has arrived for broader clinical trials to be conducted. The significance of the experimental and clinical studies is the introduction of new laser technology for treatment of severe nerve injury.

Conclusions

The analysis of the results of this trial in the laser-treated group showed statistically significant improvement in motor function in the previously partially paralyzed limbs compared with the placebo group, whereas no statistical significance in neurological status was found (Fig. 10). Mean motor function of the most influential (functionally dominant) muscle for movement of the affected limb showed a statistically significant improvement in the laser-treated group compared with the placebo group. The function was improved mostly by increasing the power of the dominant muscles and not the intrinsic muscles.

Electrophysiological observation during the study supplied us with important diagnostic information and helped to determine the degree of functional recovery in nerve-injured patients. The electrophysiological analysis also showed statistically significant improvement in recruitment of voluntary muscle activity in the laser-treated group compared with the placebo group (Fig. 11).

This study is not the final judgement regarding 780-nm laser phototherapy in peripheral nerve-injured patients. The disadvantages of this study are the small number of patients, the different nerves treated, and the different causes of injury. Nevertheless, this pilot study suggests that in peripheral nerve-injured patients, 780-nm low-power laser phototherapy can progressively improve peripheral nerve function, which has led us to continue this study in a prospective multicenter trial.

Nerve response to phototherapy

Mean motor function (± SD) of all affected muscles was examined in injured patients using the Medical Research Council (MRC) Grading System. The analysis of the results showed that at baseline the 780-nm laser-treated and placebo groups were in clinically similar conditions (p = 0.887). The analysis of motor function during the 6-month follow-up period compared with baseline showed statistically significant improvement (p = 0.0001) in the laser-treated group compared with the placebo group.

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Disclaimer
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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