Laser Phototherapy (780 nm), a New Modality in Treatment of Long-Term Incomplete Peripheral Nerve Injury: A Randomized Double-Blind Placebo-Controlled Study

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ABSTRACT

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.

INTRODUCTION

Injury of a major nerve trunk 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 brachial plexus and peripheral nerve injury.1-4

In most cases, results can be successful if the surgery is performed in the first 6 months after injury, compared to long-term cases in whom surgical management is less successful. Even so, several publications report surgical treatment of long-term injuries of the brachial plexus and peripheral nerve.5-7 For most patients who suffer from long-term peripheral nerve injuries, the continuation of rehabilitation therapy is recommended, especially in those regions or countries that do not have specially dedicated peripheral nerve surgeons. Unfortunately, spontaneous recovery of long-term severe incomplete peripheral nerve injury is often unsatisfactory. The usual results of 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 accel-
ate the recovery of injured peripheral nerves. One of the methods studied is the use of different wavelengths of low-power laser irradiation to enhance the recovery of injured peripheral nerve. Studies that evaluated the effects of 632.8-nm and 780-nm laser energy on Schwann and nerve cell cultures and injured peripheral nerves of animals have shown positive results. Low-power laser irradiation induces Schwann cell proliferation, affects nerve cell metabolism, and increases the rate of cellular processes.

Animal studies indicate that laser phototherapy of injured peripheral nerves significantly improves nerve recovery and in addition, low-power laser irradiation (632.8 and 780 nm) decreases retrograde degeneration of the neurons in the corresponding segments of the spinal cord after peripheral nerve injury. Since our animal studies showed positive therapeutic effect, an evaluation of the response to 780-nm laser phototherapy was appropriate. Therefore, a clinical randomized double-blind, placebo-controlled study was performed to measure the effectiveness of 780-nm low-power laser irradiation on patients who had been suffering from incomplete peripheral nerve and brachial plexus injuries for 6 months up to several years, most of whom were discharged by orthopedics, neurosurgeons, and plastic surgeons without further treatment.

**MATERIALS AND METHODS**

**Patient population**

Eighteen patients with clinical signs and symptoms of peripheral nerve or brachial plexus injury were selected. The entry criteria were as follows: patients of either gender, at least 18 years of age, and with a diagnosis of traumatic peripheral nerve injury that had occurred at least 6 months prior to inclusion; and patients who suffered from incomplete injury with motor deficit in a stable stage or those undergoing slow neu-

### Table 1. Description of Patients in the Placebo Group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Injured nerve</th>
<th>Side</th>
<th>Dominant muscle</th>
<th>Etiology</th>
<th>Months after injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>37</td>
<td>Peroneal</td>
<td>R</td>
<td>Tibialis anterior</td>
<td>Traction</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>46</td>
<td>Brachial plexus</td>
<td>R</td>
<td>Biceps</td>
<td>Traction</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>74</td>
<td>Peroneal</td>
<td>L</td>
<td>Tibialis anterior</td>
<td>Traction/compression</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>60</td>
<td>Peroneal</td>
<td>L</td>
<td>Tibialis anterior</td>
<td>Traction</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>29</td>
<td>Peroneal</td>
<td>L</td>
<td>Tibialis anterior</td>
<td>Traction</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>60</td>
<td>Axillary</td>
<td>R</td>
<td>Deltoid</td>
<td>Traction</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>25</td>
<td>Sciatic</td>
<td>L</td>
<td>Deltoid</td>
<td>Traction</td>
<td>236*</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>65</td>
<td>Axillary</td>
<td>L</td>
<td>Deltoid</td>
<td>Traction</td>
<td>11</td>
</tr>
</tbody>
</table>

Median age = 49.5 (SD = 17.93); median months after injury = 11.5 (SD = 79.14).

*This patient had a very long-standing disease but his neurological and electrophysiological changes were similar to the group’s average.

### Table 2. Description of Patients in the Laser-Treated Group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Injured nerve</th>
<th>Side</th>
<th>Dominant muscle</th>
<th>Etiology</th>
<th>Months after injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>47</td>
<td>Peroneal</td>
<td>L</td>
<td>Tibialis anterior</td>
<td>Traction</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>22</td>
<td>Brachial plexus (upper trunk)</td>
<td>R</td>
<td>Biceps</td>
<td>Stab</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>18</td>
<td>Axillary suprascapular</td>
<td>L</td>
<td>Deltoid</td>
<td>Traction</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>78</td>
<td>Brachial plexus (upper trunk)</td>
<td>R</td>
<td>Deltoid</td>
<td>Traction</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>24</td>
<td>Peroneal</td>
<td>L</td>
<td>Tibialis anterior</td>
<td>Traction</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>56</td>
<td>Axillary suprascapular</td>
<td>R</td>
<td>Deltoid</td>
<td>Traction</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>59</td>
<td>Peroneal</td>
<td>R</td>
<td>Deltoid</td>
<td>Traction</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>24</td>
<td>Median, ulnar, radial</td>
<td>L</td>
<td>Flexor carpi radialis</td>
<td>Traction/compression</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>27</td>
<td>Axillary</td>
<td>L</td>
<td>Deltoid</td>
<td>Traction</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>24</td>
<td>Median</td>
<td>L</td>
<td>Flexor carpi radialis</td>
<td>Gunshot</td>
<td>30</td>
</tr>
</tbody>
</table>

Median age = 37.9 (SD = 20.58); median months after injury = 7 (SD = 8.73).
Laser or placebo treatment

Either 780-nm low-power laser or placebo irradiation was applied transcutaneously, each day for 21 consecutive days, 5 h daily (3 hours to the injured area of the peripheral nerve and 2 h to the corresponding segments of the spinal cord). With the patient lying in bed, the laser was placed approximately 40 cm from the skin-treated point, focused on the injured area of the peripheral nerve or corresponding level of the spine (the area of corresponding segments of the spinal cord). The equipment was under the supervision of the investigator and was used only by appropriately trained personnel.

### Laser Dosage

Spinal cord area: laser irradiation was performed transcutaneously directly above the projection of the corresponding segments of the spinal cord, which was divided into two intrathecal levels. Each level was irradiated for 60 min a day (150 J/mm²), totaling 120 min a day (300 J/mm²).

Peripheral nerve area: Laser irradiation was performed transcutaneously directly above the projection of the injured nerve, which was divided into three parts: proximal, injured area, and distal. Each section was irradiated for 60 min a day (150 J/mm²), totaling 180 min a day (450 J/mm²). The irradiating spot size was 3 × 2 mm (6 mm²).

### Clinical, Neurological, and Electrophysiological Assessment

Clinical status was monitored and recorded at baseline, at the end of treatment (after 21 days), and 3 and 6 months later. At each stage, patients were examined by a qualified neurologist and a specialist in neurophysiology.

The physicians were blind to the type of treatment administered. Recovery was assessed by comparing each of the deficits present before and after treatment. Records of diagnostic tests, clinical notes, and patient’s medical records were kept in each patient’s file as original source documents for study.

The neurological examination included motor and sensory status and functional abilities of the patient. The results of the treatment on motor function were evaluated using the Medical Research Council’s (MRC) Grading System with grades of 0 to 5 given to evaluate each affected muscle (Table 3).

In the injured limb, up to five weak muscles innervated by the affected nerve were examined. Two separate analyses were done, using as evaluation parameters the mean MRC grade of all affected muscles corresponding to the injured nerve, as well as the MRC grade of the most influential (functionally dominant) muscle for movement of the affected limb (Tables 1 and 2).

### Table 3. Medical Research Council’s (MRC) Grading System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Total paralysis</td>
</tr>
<tr>
<td>1</td>
<td>Muscle flicker</td>
</tr>
<tr>
<td>2</td>
<td>Moves with gravity eliminated</td>
</tr>
<tr>
<td>3</td>
<td>Moves against gravity but not resistance</td>
</tr>
<tr>
<td>4</td>
<td>Slight movement against resistance</td>
</tr>
<tr>
<td>4+</td>
<td>Moderate movement against resistance</td>
</tr>
<tr>
<td>5</td>
<td>Submaximal movement against resistance</td>
</tr>
<tr>
<td>---</td>
<td>Normal power (compared to the other side)</td>
</tr>
</tbody>
</table>

The randomization was computer generated and each new patient received a code with the assignment to group A (placebo) or group B (laser-treated). None of the investigators were aware of the type of treatment given to each group. Clinicians from the hospital and a representative physician from the Ministry of Health recruited the required number of patients and evaluated patients for clinical and electrophysiological responses.

### Laser Apparatus and Placebo Device

The laser apparatus used was a polarized diode laser (wavelength 780 nm, power 250 mW, continuous wave, with a power supply control unit) (Medi-Robot Ltd., Tel Aviv, Israel). The placebo device (wavelength 637 nm, power <15 mW, diffused LED lamps) (HLMP-3300 series) (Siemens, Germany) was fully identical to the laser device. Neither the investigator nor the operator were able to distinguish between the laser and placebo equipment. The power produced by the placebo device was negligible and had no detectable biological effect. There was no external physical difference between the laser or placebo device except that each bore the letter “A” or “B.”

### Laser or Placebo Treatment

Either 780-nm low-power laser or placebo irradiation was applied transcutaneously, each day for 21 consecutive days, 5 h daily (3 hours to the injured area of the peripheral nerve and 2 h to the corresponding segments of the spinal cord). With the patient lying in bed, the laser was placed approximately 40 cm from the skin-treated point, focused on the injured area of the peripheral nerve or corresponding level of the spine (the area of corresponding segments of the spinal cord). The equipment was under the supervision of the investigator and was used only by appropriately trained personnel.

### Table 4. Louisiana State University Medical Center System Used to Assess Sensory Deficit

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent: No response to touch, pinprick, or pressure</td>
</tr>
<tr>
<td>1</td>
<td>Bad: Testing gives hypesthesia or paresthesia; deep pain recovery in autonomous zones</td>
</tr>
<tr>
<td>2</td>
<td>Poor: Sensory response sufficient for grip and slow protection; sensory stimuli mislocalized with over-response</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Response to touch and pin in autonomous zones; sensation mislocalized and not normal with some over-response</td>
</tr>
<tr>
<td>4</td>
<td>Good: Response to touch and pin in autonomous zones; response localized but not normal; no over-response</td>
</tr>
<tr>
<td>5</td>
<td>Excellent: Normal response to touch and pinprick in entire field, including autonomous zones</td>
</tr>
</tbody>
</table>
2). The influence of the treatment on the sensory deficit was assessed by the Louisiana State University Medical Center System (LSUMC; Table 4).16

Electrophysiological studies provide useful information on the functional integrity of the injured peripheral nerve or brachial plexus and consisted of motor and sensory nerve conduction tests, as well as EMG studies, performed on appropriate nerves and muscles. The neurophysiologist was blind to the type of treatment administered. All electrophysiological examinations were done using Medelec (Teca, Surrey, UK) Sapphire 4ME equipment. Special attention was taken to minimize artifacts (e.g., limb temperature).

Nerve conduction tests were done in a standard manner on all affected nerves. The selection of nerves for examination was based on clinical findings. For each nerve, the following parameters were measured: motor distal latency, amplitude of compound muscle action potential (CMAP), and when appropriate, nerve conduction velocity and F-wave latency. CMAP amplitude was measured baseline to peak. Qualitative needle electromyography was done using concentric needle electrodes on different muscles. For each muscle, the presence of spontaneous activity, the amplitude and duration of motor units, and voluntary motor unit recruitment were measured. Motor unit recruitment was graded as follows: 0, absent; 1, firing of a single motor unit; 2, firing of a few motor units; 3, partial; 4, slightly reduced; and 5, full. Only CMAP amplitude and muscle recruitment data were used for statistical analysis, as these parameters are expected to change in response to nerve fiber regeneration and are not significantly affected by late pathophysiological processes related to the nerve injury itself. If more than one nerve was examined, calculated mean CMAP amplitude of all examined nerves was used for statistical purposes, as well as the CMAP amplitude of the functionally most important (dominant) nerve. Similarly, if more than one muscle was examined, a calculated mean recruitment grade of all examined muscles, as well as the recruitment grade of the functionally most important (dominant) muscle—that the same muscle that was evaluated clinically (Tables 1 and 2)—was used for statistical purposes.

Statistical analysis

The statistical evaluation included all data available from all patients entering the study. Clinical and electrophysiological data of each patient at baseline were compared to the patient’s data at follow-up examinations (at end of 21 days of treatment, and 3 and 6 months later). Statistical analyses were performed using univariate analysis, parametric or nonparametric, as needed. Analyses of variance with repeated measures were performed in order to compare the two groups after the four examinations. The patients were evaluated at each scheduled interval (baseline, at the end of 21 days of treatment, and 3 and 6 months later).

RESULTS

In the laser-irradiated group, 34 muscles were examined; mean muscles per patient were 3.4. In the placebo group, 14 muscles were examined; mean muscles per patient were 1.75. More patients with brachial plexus injuries were assigned to the laser-irradiated group, and therefore more muscles per patient were studied in this group.

FIG. 1. Mean motor function (±SD) of all affected muscles examined (p = 0.0001).

FIG. 2. Mean motor function (±SD) of the most influential (functionally dominant) muscle for movement of the affected limb (p = 0.002).

FIG. 3. Sensory function (±SD) (p = NS).
Mean motor function of all affected muscles examined

The analysis of the results showed that at baseline the 780-nm laser-irradiated and placebo groups were in clinically similar conditions ($p = 0.887$). 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-irradiated group compared to the placebo group (Fig. 1).

Mean motor function of the most influential (functionally dominant) muscle

For movement of the affected limb, the laser-irradiated and placebo groups were in clinically similar conditions at baseline ($p = 0.942$). In the laser-treated group, statistically significant improvement ($p = 0.002$) was found in motor function during the 6-month follow-up, compared to the placebo group (Fig. 2).

Sensory function

The laser-irradiated and placebo groups were in clinically similar conditions at baseline ($p = 0.733$). In the laser-irradiated group, no statistical significance ($p = 0.550$) was found in sensory function during the 6-month follow-up, compared to the placebo group. However, in the laser-treated group, statistically significant improvement ($p = 0.035$) was found in sensory function at the end of the 6-month follow-up period, compared to baseline (Fig. 3). In the placebo group, no statistical change ($p = 0.356$) was found in sensory function at the end of the 6-month follow-up period, compared to baseline.

Mean amplitude of examined compound muscle action potentials (CMAP)

The 780-nm laser-irradiated and placebo groups were in similar conditions at baseline ($p = 0.873$). In the laser-irradiated group, no statistical significance ($p = 0.067$) was found in CMAP amplitude during the 6-month follow-up, compared to the placebo group.

Motor unit recruitment, mean of all examined muscles

The 780-nm laser-irradiated and placebo groups were in similar conditions at baseline ($p = 0.934$). In the laser-irradiated group, statistically significant improvement ($p = 0.006$) was found in motor unit recruitment during the 6-month follow-up period, compared to the placebo group (Fig. 5).

Motor unit recruitment, mean of the most influential (functionally dominant) muscle

The laser-irradiated and placebo groups were in similar conditions at baseline ($p = 0.457$). In the laser-irradiated group, statistically significant improvement ($p = 0.006$) was found in motor unit recruitment during the 6-month follow-up, compared to the placebo group (Fig. 6).

DISCUSSION

This trial was designed to determine the value of low-power laser irradiation in the treatment of long-term incomplete peripheral nerve and brachial plexus injuries. This study evaluated the functional recovery of patients undergoing 780-nm
laser or placebo (non-active light) irradiation, who had been suffering from incomplete injury for 6 months up to several years.

Our previous studies investigating the effects of low-power laser irradiation (632.8 and 780 nm) on injured peripheral nerves of rats have found: protective immediate effects that increase the functional activity of the injured peripheral nerve,1,17 maintenance of functional activity of the injured nerve over time,11 decrease or prevention of scar tissue formation at the injured site,11,18 prevention or decreased degeneration in corresponding motor neurons of the spinal cord,12 and increases in the rates of axonal growth and myelinization11,14 resulting in accelerated and improved regeneration of the injured nerve. Moreover, direct laser irradiation of the spinal cord improves recovery of the corresponding injured peripheral nerve.14,18 These animal experimental studies and the present clinical investigation of laser irradiation of incomplete peripheral nerve injury suggest that continuous improvement of nerve function is related to the acceleration of nerve conductivity, followed by increased myelinization in existing nerve fibers, and most probably partial re-growth of new axons and new synaptic connections. The extensive review article suggesting a potential mechanism of action of phototherapy published in Muscle and Nerve in 2005,19 revealed that all experimental studies but two20–21 showed phototherapy to promote the recovery of the severely injured peripheral nerve.10,11,13,14,22–27

CONCLUSION

In the present study, 18 patients with a history of traumatic peripheral nerve /brachial plexus injury (at least 6 months after the injury), with a stable neurological defect and significant weakness were randomized to receive either 780-nm laser or placebo (non-active light) irradiation. The analysis of the results of this trial in the laser-irradiated group showed statistically significant improvement in motor function in the previously partially paralyzed limbs, compared to the placebo group, in whom no statistically significant change in neurological status was found. Electrophysiological studies during the trial 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-irradiated group, compared to the placebo group. This study shows that in long-term peripheral nerve injured patients 780-nm low-power laser irradiation can progressively improve peripheral nerve function, which leads to significant functional recovery.

ACKNOWLEDGMENTS

We would like to thank Prof. Emeritus Kendrick Smith from Stanford University for his constructive review of this manuscript.

We also thank Dr. Y. Sosnov, Mrs. T. Packer, Dr. V. Davidson, and Dr. M. Khaigrekht for helpful assistance with this study, and Mrs. Arleen Kline and Ms. Ilana Aronson for assistance in preparation of this manuscript.

The study was supported by a grant from the Rehabilitation Department of the Ministry of Defense, State of Israel.

REFERENCES


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