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Antinociceptive effect of linear polarized 0.6 to 1.6 μm irradiation of lumbar sympathetic ganglia in chronic constriction injury rats

Hiroshi Muneshige, MD, PhD (deceased);[1] Katsuhiro Toda, MD, PhD;[1*] Dianli Ma, MD, PhD;[2] Hiroaki Kimura, MD, PhD;[1] Tomohiro Asou, MD;[1] Yoshikazu Ikuta, MD, PhD[2]
[1]Department of Rehabilitation, Hiroshima University Hospital, Hiroshima, Japan; [2]Department of Orthopaedic Surgery, Hiroshima University School of Medicine, Hiroshima, Japan

Abstract—Linear polarized near-infrared light created with linear polarized near-infrared light therapy equipment (Super Lizer™ HA-550, Tokyo Iken Co, Ltd, Tokyo, Japan) has been used for the treatment of various painful disorders in Japan. Irradiation near the stellate ganglion with a Super Lizer (ISGL) is an especially notable therapeutic method used with stellate ganglion block (SGB) or substitutes for SGB. ISGL is a safe, simple, well-tolerated, and effective treatment. We examined the effects of irradiation with a Super Lizer applied to an area near the lumbar sympathetic ganglia on the ligated side in a chronic constriction injury (CCI) model, which is believed to be an animal model of complex regional pain syndrome (CRPS). Rats showing thermal hyperalgesia in a radiant heat test 1 wk postoperatively were used in Experiments 1 and 2: (1) Thermal hyperalgesia of irradiation group (n = 11) was less than that of the control or nonirradiation (n = 11) group at 1, 3, and 8 h after irradiation; however, the effect disappeared 12 h after irradiation. (2) Daily irradiation (n = 16) and 1 wk (n = 14) from 7 days after nerve ligation significantly shortened the interval from thermal hyperalgesia until recovery. Rats showing mechanical hyperalgesia in the von Frey hair test 1 wk postoperatively were used in Experiment 3: 1 wk irradiation beginning 7 days after nerve ligation (n = 9) did not promote the recovery from mechanical hyperalgesia. We speculate that repeated ISGL may be more effective than a single ISGL in alleviating pain in CRPS patients. We cannot explain the discrepancy between the results obtained in Experiments 2 and 3. We believe the results of this study are relevant to the effect of ISGL for patients with upper-limb CRPS: irradiation near the lumbar sympathetic ganglia of the rat is effective for thermal but not mechanical pain in CCI.

Key words: chronic constriction injury model, complex regional pain syndrome, control study, ISGL, linear polarized near-infrared light, reflex sympathetic dystrophy, rehabilitation, stellate ganglion block, Super Lizer™.

INTRODUCTION

Complex regional pain syndrome (CRPS) causes intractable chronic pain. CRPS occurs after minor trauma, such as an injection, a drip infusion, or iatrogenic puncture, as well as after surgery or accidental injury. Among many treatments, stellate ganglion block (SGB) is one of the most effective treatments. However, SGB sometimes causes complications such as infection, nerve injury, bleeding, and pneumothorax [1]. Other serious complications such as shock, respiratory arrest, and death [2] can

Abbreviations: CCI = chronic constriction injury, CRPS = complex regional pain syndrome, ISGL = irradiation near the stellate ganglion with a Super Lizer™, PLSD = protected least significant difference, SGB = stellate ganglion block.

***Address all correspondence to Dr. Katsuhiro Toda, Department of Rehabilitation, Hiroshima Prefectural Rehabilitation Center, 295-3 Taguchi, Saijyo, Higashi-Hiroshima, 739-0036, Japan; +81-82-425-1455; fax: +81-82-425-1094. Email: goutattack@yahoo.co.jp**
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occur, although they are uncommon. Furthermore, some patients fear the procedure, which may require emergency treatment equipment and techniques, including intubation. Because of such limitations, only trained anesthesiologists usually perform SGB.

In Japan, linear polarized near-infrared light created with linear polarized near-infrared light therapy equipment (Super Lizer™ HA-550, Tokyo Iken Co, Ltd, Tokyo, Japan) has been used mainly to treat painful disorders. Many open studies and case reports showed that direct irradiation or irradiation near the stellate ganglion with a Super Lizer™ (ISGL) was effective for temporomandibular joint pain, frozen shoulder, osteoarthritis, rheumatoid arthritis, thalamic pain, postherpetic neuralgia, etc. [3–8]. Recently, ISGL has often been used with SGB or substitutes for ISGB to treat patients with upper-limb CRPS [9–11].

Only one small, short-term double-blind study demonstrated the efficacy of the ISGL for patients with CRPS [12]. No long-term double-blind studies have demonstrated its efficacy in these patients. Thus, the present study examined the long-term efficacy of irradiation near the lumbar sympathetic ganglia with a chronic constriction injury (CCI) model [13], which is believed to be an animal model of CRPS [14–15].

METHODS

Linear Polarized Near-Infrared Light Therapy Equipment

The linear polarized near-infrared light therapy equipment [16–17] consists of a power source, light source, light-guiding system, and lens unit. The light source is a 150 W iodine lamp, on which the position of the lens unit can be adjusted with an adjustable arm. The apparatus emits linear polarized near-infrared light between 0.6 and 1.6 µm (**Figure 1**). The light is not a laser because it is not a single wavelength. In all experiments, the animals were irradiated at 80 percent of the maximum power output with cycles of 1 s on and 4 s off for 5 min (60 s of total irradiation time) with a B-type lens unit (1.44 W, 86.4 J). The lumbar sympathetic ganglia of the rat are located between the second and fifth lumbar vertebrae and approximately 1 cm below the skin [18]. In all experiments, the lens unit was positioned to irradiate from approximately 1 cm laterally to the right of the spinal process of the second lumbar vertebra to its lateral aspect.

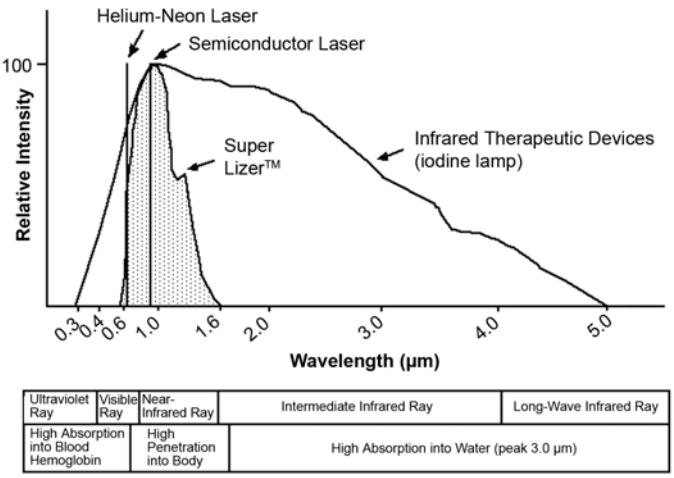

Figure 1.
Properties of wavelengths emitted from phototherapeutic equipment. Wavelengths from 0.6 to 1.6 µm easily reach depths of living tissue. Slanted spectrum ranges from near red to visible red. Reprinted with partial alteration by permission from D. Ma. Permeability of linear polarized near-infrared light. Med J Hiroshima Univ. 1999;47:207–13.

Animals and Operation

The experiments were conducted according to the ethical guidelines for investigations of experimental pain in conscious animals [19]. Male Sprague-Dawley rats weighing between 200 and 250 g upon arrival were habituated to the laboratory for at least 1 week before the experiments began. All rats were housed in transparent plastic cages of which their floors were covered by 3 to 6 cm of sawdust. Following surgery, the rats were housed one per cage for at least 7 days. Food and water were available at all times. For surgical anesthesia, sodium pentobarbital (50 mg/kg, intraperitoneal) was administered. The sciatic nerve was constricted with the procedure described by Bennett and Xie [13]. The right common sciatic nerve was exposed by blunt dissection and four 4-0 chromic gut ligatures were loosely placed approximately 1 mm apart around the right common sciatic nerve. The same procedure was performed on the left side, except that the sutures were omitted (sham procedure).

Measurement of Pain

The same experimenter performed all behavioral measurements in a quiet room. Pain was measured with a radiant heat test and the von Frey hair test. Responses to noxious radiant heat were determined according to the method of Hargreaves et al. [20] with the use of the Ugo Basile Plantar test apparatus. The rats were placed in a

transparent plastic chamber on a glass floor and allowed to acclimate for 10 min. The plastic chamber was 14 cm high × 22 cm wide × 17 cm deep, and the rats were not restrained while measurements were being taken. The radiant heat source was positioned under the glass floor directly beneath the hind paw. Hind paw withdrawal automatically terminated the stimulus and stopped the timer. Withdrawal latencies were defined as the time between the activation of the heat source and hind paw withdrawal. Testing was conducted five times on each side, and the latencies for each side were averaged. The interval between two consecutive stimuli of the same hind paw was at least 5 min.

The von Frey hair test, which resembles the Semmes-Weinstein test, was used for determining a mechanical hyperalgesia. The rats were placed on a metallic plate with a small hole inside a clear plastic chamber for 10 min to acclimate the rats to the environment. The plastic chamber was identical to the one used in the radiant heat test, and the rats were not restrained while the measurements were taken. The sole of the hind paw was stimulated three times within approximately 1 s with each von Frey hair. We applied von Frey monofilaments with increasing force until the rat withdrew the hind paw. The interval between measurement with one filament and the next stiffest filament was at least 10 s. The calculated force in the Semmes-Weinstein test was used for determining the threshold [21]. Testing was performed five times on each side, and the thresholds for each side were averaged.

Difference Scores

We evaluated both the von Frey hair and radiant heat tests by analyzing the difference scores, which we calculated by subtracting the values of the sham-operated side from the values of the ligated side. Negative difference scores in the von Frey hair and radiant heat tests indicate mechanical and thermal hyperalgesia, respectively.

Experiment 1

One week after surgery, we selected for study those rats whose latencies on the ligated side were less than 90 percent of those on the nonligated side in the radiant heat test. The irradiation group (n = 11) was irradiated with linear polarized near-infrared light only once and the radiant heat test was performed at 1, 3, 8, 12, and 24 h postirradiation. The nonirradiation group (n = 11) was restrained for 5 min without irradiation (sham irradiation). Similarly, the radiant heat test was performed at 1, 3, 8, 12, and 24 h after sham irradiation.

Experiment 2

One week after surgery, we selected those rats whose latencies on the ligated side were less than 90 percent of those on the nonligated side in the radiant heat test. The 1-week irradiation group was irradiated once a day for 7 days from 7 to 13 days after nerve ligation (n = 16). The 6-week irradiation group was irradiated once a day for 6 weeks from 7 to 49 days after nerve ligation (n = 14). The nonirradiation group was not irradiated (n = 20). The radiant heat test was performed in all 3 groups at 11, 14, 18, 21, 28, 35, and 49 days after nerve ligation. The radiant heat test was performed at least 22 h after irradiation.

Experiment 3

One week after nerve ligation, we selected those rats whose threshold on the nonligated side was more than four times that of the ligated side in the von Frey hair test [18]. The rats were irradiated once a day for 7 days from 7 to 13 days after nerve ligation (n = 9). The von Frey hair test was conducted at 11, 14, 18, 21, 28, 35, and 49 days after operation. In the group that was not irradiated, the von Frey hair test was conducted at 11, 14, 18, 21, 28, 35, and 49 days after nerve ligation (n = 9). When the von Frey hair test was conducted on the next day after irradiation, the tests were performed at least 22 h after irradiation treatment.

Statistical Method

We analyzed the significant differences between groups (irradiation vs nonirradiation groups) using unpaired t-tests in Experiments 1 and 3. We analyzed the significant differences between groups (1-week irradiation vs 6-week irradiation groups, 1-week irradiation vs nonirradiation group, 6-week irradiation vs nonirradiation group) using a one-way analysis of variance, followed by Fisher's protected least significant difference (PLSD) in Experiment 2. We considered p-values <5 percent significant.

RESULTS

Experiment 1

At 1, 3, and 8 h after irradiation, the difference scores of the irradiation group were greater than those of the nonirradiation group. However, after 12 h, the difference scores of both groups were almost the same. Thus, a single irradiation significantly alleviated thermal hyperalgesia from 1 to 8 h after irradiation; however, the effect disappeared 12 h after irradiation (**Figure 2**).

Experiment 2

In this experiment, the effects on the 1-week daily irradiation group, 6-week daily irradiation group, and nonirradiation group were compared. One week after the operation, the rats showed remarkable thermal hyperalgesia, as indicated by decreased difference scores (**Figure 3**). The thermal hyperalgesia in the nonirradiation group was gradually alleviated. Daily irradiation for 1 week or 6 weeks appeared to have similar effects in the accelerating recovery. Difference scores of the 6-week irradiation and 1-week irradiation groups were significantly greater than those of the nonirradiation group from 11 to 28 days after nerve ligation, indicating that thermal hyperalgesia was significantly relieved from 11 to 28 days after nerve ligation. Difference scores of the 6-week irradiation group were significantly greater than those of the 1-week irradiation group 18 days after the operation (5 days after stopping irradiation in the 1-week irradiation group). Thus, the thermal hyperalgesia of the 1-week irradiation group appeared to be greater than that of the 6-week irradiation group only 18 days after the operation. Both the 6-week irradiation and 1-week irradiation significantly promoted the recovery from thermal hyperalgesia.

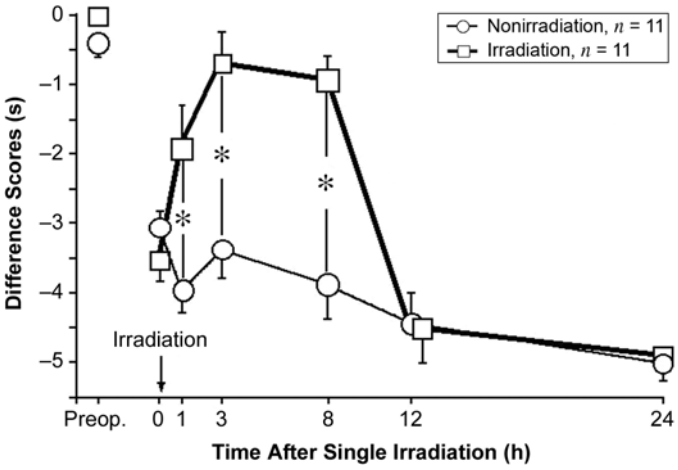

Figure 2.
Analgesic effect of single irradiation with linear polarized near-infrared light on thermal hyperalgesia. Difference scores calculated by subtracting latency on sham-operated side from latency on nerve-injured side. One week after surgery, we selected rats whose latencies on ligated side were <90% of those on nonligated side in radiant heat test. Irradiation performed once (arrow). Difference between irradiation and nonirradiation groups was calculated by unpaired *t*-test. Results were given as mean ± standard error of mean. $^{*}p < 0.05$.

Experiment 3

No difference was found between both groups of rats in responses to the von Frey hair stimuli (**Figure 4**) [18]. Irradiation near the lumbar sympathetic ganglia for 7 days did not promote the recovery from mechanical hyperalgesia.

DISCUSSION

Because the wavelength range of the linear polarized near-infrared light emitted by the linear polarized near-infrared light apparatus is between 0.6 and 1.6 μm, the light is able to reach into the deeper tissue [10,16–17]. Water easily absorbs light in which the wavelength is more than 1.6 μm, and blood easily absorbs light in which the wavelength is less than 0.6 μm (**Figure 1**).

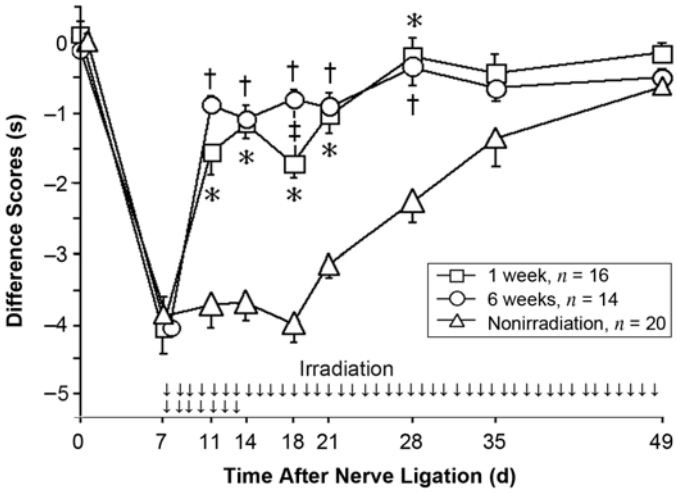

Figure 3.
Analgesic effect of repeated irradiation with linear polarized near-infrared light on thermal hyperalgesia. Difference scores were calculated by subtracting latency on sham-operated side from latency on nerve-injured side. One week after surgery, we selected rats whose latencies on ligated side were <90% of those on nonligated side in radiant heat test. Rats were irradiated with linear polarized near-infrared light once a day for either 1 week or 6 weeks, beginning on postoperative day 7. Difference between 1-week irradiation and nonirradiation groups ($^{*}p < 0.05$), between 6-week irradiation and nonirradiation groups ($^{\dagger}p < 0.05$) and between 6-week irradiation and 1-week irradiation groups ($^{\ddagger}p < 0.05$) was analyzed by one-way analysis of variance followed by Fisher's protected least significant difference. Results were given as mean ± standard error of mean. Down arrows show irradiation.

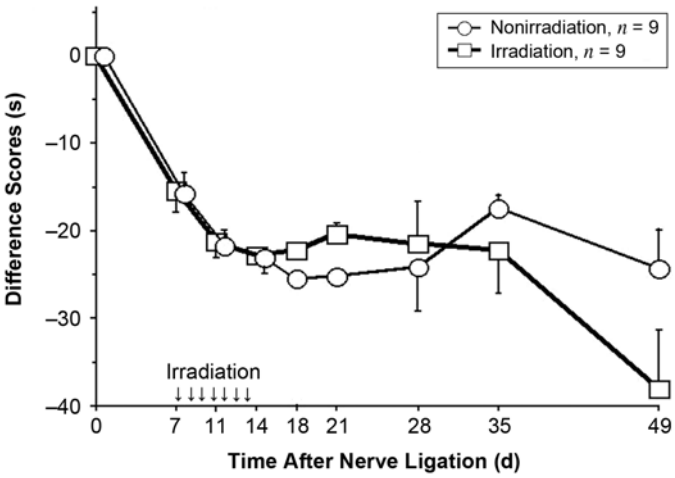

Figure 4.
Analgesic effect of repeated irradiation with linear polarized near-infrared light on mechanical hyperalgesia. Difference scores were calculated by subtracting threshold on sham-operated side from threshold on nerve-injured side. One week after nerve ligation, we selected rats whose threshold on nonligated side was >4 times that on ligated side in von Frey hair test. Rats were irradiated with linear polarized near-infrared light once a day for 1 week, beginning on postoperative day 7. No difference was found between both groups of rats in responses to von Frey hair stimuli. Results were given as mean ± standard error of mean. Down arrows show irradiation.

In Experiment 1, irradiation near the lumbar sympathetic ganglia with linear polarized near-infrared light was effective from 1 to 8 h after the irradiation; however, it was not effective 12 h after the irradiation. In Experiment 2, both the 1-week and 6-week irradiation groups showed a significant reduction in thermal hyperalgesia compared with the nonirradiation group. This observed reduction indicates that the repeated irradiation ameliorated thermal hyperalgesia due to CCI. The results of Experiments 1 and 2 suggest that repeated ISGL may be more effective than a single ISGL in alleviating pain in patients with upper-limb CRPS. A clear effect was not obtained with the von Frey hair test in Experiment 3. Mechanical hyperalgesia increased from 35 to 49 days in both groups of Experiment 3, an unexplained course. This increase may cause the discrepancy between the results obtained in Experiments 2 and 3, but we cannot explain it.

Irradiation near the lumbar sympathetic ganglia in CCI was applied as an animal model of ISGL in upper-limb CRPS. To model ISGL in humans, one should apply irradiation near the cervical sympathetic ganglion in the rat. Because no animal model exists for causing pain in the forepaw, we chose to use irradiation near the lumbar sympathetic ganglia in CCI. Because of the depth of the lumbar sympathetic ganglia in humans, whether near-infrared light can reach such tissue depth is not known. Although the results of this study may not be relevant to the lumbar sympathetic ganglia of humans, we believe they are relevant to the effect of ISGL for patients with upper-limb CRPS because of the relative superficial location of the stellate ganglion in humans.

ISGL has many advantages. First, ISGL is safe. Although theoretically irradiation could possibly cause burn injury to the skin, we have not encountered any such adverse effects in our patients. We usually irradiated patients at 80 percent of the maximum power output with cycles of 1 s on and 4 s off for 10 min. Under these conditions, the possibility of burn is extremely low. If the patient feels heat, the patient can easily terminate the ISGL. Thus, ISGL has double safety controls, i.e., equipment control and personal control. Furthermore, ISGL has been applied in many disorders and none were aggravated in our patients. Also, repeated ISGL does not cause induration, which is sometimes seen after repeated SGB. Second, ISGL is an easy procedure. While only a skilled anesthesiologist can accomplish SGB, any instructed person can easily apply ISGL because it is a safe and simple procedure. Third, ISGL provides bilateral application and daily or more frequent application. Fourth, ISGL does not cause fear. In children, particularly, SGB is often rejected, whereas ISGL is rarely declined. Patients who suffered from CRPS after a procedure involving a needle, such as injection or drip infusion, rarely agreed to SGB but no patient has ever refused ISGL in our hospital. Fifth, ISGL does not cause Horner syndrome, which is inevitable in SGB. Sixth, ISGL requires little preparation and no rest after the procedure. SGB requires more time for preparation and rest after the block than does ISGL. Seventh, the combined treatment with SGB and ISGL may be more effective than treatment with SGB or ISGL alone, as suggested by Suzuki et al. for the treatment of acute herpes zoster-associated pain [22]. Thus, ISGL has been used with SGB or as a substitute for SGB. The disadvantage of ISGL is that ISGL is inferior to SGB in the efficacy of one procedure. Repeated ISGL treatments are usually needed before the desired effect is obtained, whereas a single SGB is often effective immediately. However, ISGL can be performed more frequently than SGB, and ISGL never deteriorates the symptoms. We speculate that the long-term efficacy of ISGL will approach that of SGB.

Suzuki et al. suggested that ISGL is as effective as SGB in acute herpes-associated pain [22].

The mechanisms of the effects of ISGL and direct irradiation are not known. Because the light is partially converted to thermal energy and thus produces a warm sensation in both irradiation methods, we speculate that heat as well as light contributes to the effects. We irradiated a person on the dorsal forearm approximately 2 cm from the wrist for 5 min under conditions identical to this experiment. The skin temperature increased from 32.5 ºC to 35.5 ºC. We could not measure the temperature of the stellate ganglion, located approximately 2 cm deep into the skin; therefore, we do not know the contribution ratio of the photochemical or thermal action in the effect of ISGL on thermal hyperalgesia. The equipment of ISGL irradiates a broad wavelength band, as shown in **Figure 1**. We do not know which wavelengths were effective for thermal hyperalgesia. SGB affects both normal persons and patients with CRPS or Raynaud's syndrome; however, ISGL produces a remarkable change in the patients, yet has no or little effect on normal persons. This difference has been reported in blood flow waves of the upper limb [23–24], skin temperature [25], the electrocardiogram, and heart rate variability [26]. Therefore, we speculate that mechanisms depend on the autonomic nervous system [23,27]. However, further experimental results are needed to clarify the analgesic mechanism of ISGL.

CONCLUSIONS

We used irradiation near the lumbar sympathetic ganglia in rats with CCI as a model for treatment of upper-limb CRPS in humans. A single irradiation near the lumbar sympathetic ganglia in CCI produced an antinociceptive effect on thermal hyperalgesia lasting 8 h. Both 6-week daily irradiation and 1-week daily irradiation beginning 1 week after ligation significantly promoted the recovery from thermal hyperalgesia. However, 1-week daily irradiation did not promote the recovery from mechanical hyperalgesia. We believe the results of this study are relevant to the effect of ISGL for patients with upper-limb CRPS.

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The authors have declared that no competing interests exist.

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