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Increases in Central Retinal Artery Blood Flow in Humans Following Carotid Artery and Stellate Ganglion Irradiation with 0.6 to 1.6 μm Irradiation

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Abstract

The authors applied near-infrared low-level laser irradiation (LLLI) directed to the stellate ganglion (SG) and to the common carotid artery (CCA), and compared the effects on central retinal artery blood flow using color pulse Doppler sonography. In 10 healthy volunteers, LLLI (0.92 W, 1 : 1 duty cycle, 10 min) to both the SG and CCA significantly increased peak systolic blood velocity in the ophthalmic artery ($p<0.001$, each) and central retinal artery ($p<0.001$, each) without changes in vessel resistance. Irradiation to the CCA produced a stronger effect than that to the SG in the ophthalmic artery ($p=0.007$) and central retinal artery ($p=0.031$). These data suggest that LLLI to the SG or to the CCA is a useful therapy for increasing the retrobulbar blood flow, with irradiation directed to the CCA being more effective than that directed to the SG in clinical settings.
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Key words: low-level laser irradiation, stellate ganglion, carotid artery

Introduction

Stellate ganglion (SG) block (SGB) has been used for the treatment of various ophthalmic diseases for more than 50 years[1]. SGB has been reported to be useful for the treatment of acute impairments of visual acuity induced by drug intoxication[2], vessel obstruction[3], or by acute optic neuritis[4]. SGB has been also used for the treatment of acute pain produced by ophthalmic zoster[5] or by ophthalmic surgery[6]. Our previous clinical study found that SGB significantly improves the final visual acuity of patients with retinal vessel obstruction and that early SGB treatment improves prognosis[3]. Therapeutic actions of SGB in patients with retinal vessel obstruction include the improvement of retinal perfusion caused by increased blood flow to the bulbus oculi and an autonomic-mediated decrease in intraocular pressure[7]. Although SGB is a useful tool for increasing retinal blood flow, it is an invasive procedure that is relatively contraindicated in patients with bleeding tendency or those undergoing anticoagulant therapy. An alternative treatment is thus required for such patients.

Low-level laser irradiation (LLLI) to the SG region

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has recently been used instead of SGB to treat many diseases, however, studies of LLLI to the SG have tended to be quite small and limited in power. Several studies have shown that linearly polarized near-infrared (0.6～1.6 μm) light irradiation to the SG produces changes in skin temperature and autonomic function similar to those that occur following traditional anesthetic SGB[8–10]. On the other hand, some studies have claimed that the beneficial effects of irradiation must occur via a non-autonomic mechanism or through the improvement of tissue circulation secondary to dilatation of the vessels around the SG[11,12].

Although LLLI to the SG produces beneficial effects similar to those of conventional SGB, it has not been reported to cause the sympathetic nerve blockade such as Horner's syndrome. The purposes of this study were to identify the effect of near-infrared LLLI on retinal arterial blood flow as measured by non-invasive color pulse Doppler sonography of the central retinal and ophthalmic arteries[13], and to compare the effect of irradiation directed at the SG with that directed at the CCA.

Materials and Methods

Ten healthy volunteers with normal neurologic and ophthalmologic findings other than nearsightedness, and no history of autonomic or neurologic disease were recruited from the staff of our hospital and participated in this study. Informed consent was obtained from all subjects. The subjects comprised 2 women and 8 men aged 26 to 45 years (mean, 32 years). All subjects were instructed to avoid medications or exposure to substances such as alcohol that might interfere with autonomic responses or retinal blood flow. Investigators who treated the subjects and those who performed blood flow measurements were different physicians, and the investigators who performed measurements were not informed of the subjects' treatments.

The subjects were familiarized with the testing procedures and placed in the supine position with the neck slightly extended. They were then told to relax and lie quietly during the data collection period. The sternocleidomastoid was gently retracted and the probe of the treating device was held firmly and perpendicularly against the skin of the target domain. Each subject underwent three different treatment sessions as follows: 1) SG session: irradiation was administered for 10 minutes with a probe contacting the skin at the right SG region (2 to 2.5 cm above the costoclavicular joint in the jugular groove); 2) CCA session: irradiation was administered for 10 minutes with the probe contacting the skin at the right CCA region, immediately lateral to the thyroid cartilage; 3) sham session: the probe was held in contact with the skin at the right SG region for 10 minutes without irradiation. The right side of the neck was used in all sessions. One treatment session was performed per day at intervals of 2 days or more in a randomized cross over manner. All sessions took place between 5 PM and 7 PM in the recovery room of Nippon Medical School main hospital central operating center in a quiet, controlled (23℃, 20% to 50% relative humidity) environment. Pulse rate (PR) and mean arterial pressure (MAP) were measured before and after each treatment.

In the SG and CCA sessions, subjects received 0.6 to 1.6 μm linearly polarized light irradiation generated by a SuperLizer® HA-2200 (Tokyo Iken Co., Ltd., Tokyo, Japan) using a "safety program" attached to the instrument. Polarized light irradiation was administered for 600 seconds via a 7.0-mm-diameter applicator, with 0.92-W output power and 1-second- on/1-second-off duty cycle. In the sham session, subjects did not receive light irradiation. Ten minutes before and immediately after each treatment sessions, blood flow in the ophthalmic artery (OA) and the central retinal artery (CRA) were measured with color pulse Doppler sonography with some modifications to the method described in previous studies[14,15]. The polyethylene film tape (adhesive patch) which is used for the cornea protection during surgery, was attached to the right eyelid after the subject was instructed to close his/her eyes to protect against the echo probe and conductivity gel, and to keep the eyelid closed. During each examination, the patch remained in place and the subject's eyes remained closed. Then the right eye was scanned horizontally

Table 1 Characteristics of subjects

No.	1	2	3	4	5	6	7	8	9	10	Mean	SD ±
Sex	M	M	F	M	M	F	M	M	M	M		
Age (yr)	26	27	26	38	45	27	33	28	34	37	32.1	6.4

Table 2 Effects of each treatment on mean arterial pressure and pulse rate

Group	SG		CA		Sham	
Time	before	after	before	after	before	after
MAP (mmHg)	83.8 ± 13.4	84.1 ± 12.8	83.0 ± 13.3	88.6 ± 16.0	84.3 ± 14.3	82.2 ± 12.2
PR (beats/min)	68 ± 11	69 ± 12	70 ± 12	71 ± 10	70 ± 11	70 ± 12

MAP, mean arterial pressure; PR, pulse rate. Figures indicate mean ± SD in 10 subjects. There were no significant changes in MAP and PR by each treatment.

Table 3 Control Results of three sessions in 10 subjects for Ophthalmic Artery and Central Retinal Artery (n=30)

		Range	Mean	Confidence Limits (P=0.95)		
				SD	Upper	Lower
Ophthalmic artery						
	PSV (cm^{-1})	23.9 ～ 45.4	34.3	5.8	36.5	32.1
	EDV (cm^{-1})	6.2 ～ 12.8	8.6	2.4	9.5	7.7
	RI	62.3 ～ 83.6	75.1	4.8	76.8	73.3
Central retinal artery						
	PSV (cm^{-1})	6.8 ～ 13.2	10.2	1.9	10.9	9.5
	EDV (cm^{-1})	2.7 ～ 4.0	3.1	0.5	3.3	2.9
	RI	64.7 ～ 73.2	69.2	4.1	70.7	67.6

PSV, peak systolic velocity; EDV, end diastolic velocity; RI, resistive index

through the adhesive patch using a 7.5-MHz sector echocardiographic probe (SONOS 2000, Japan Hewlett Packard, Tokyo, Japan) to detect the routes of the OA and CRA with ultrasonic power set to the lowest level to minimize possible damage to the ocular tissues. The arteries were visualized with their courses as parallel to the ultrasonic beam as possible. With the color pulse Doppler method, blood flow waveforms were then recorded. Peak systolic velocity (PSV) and end diastolic velocity (EDV) for the OA and CRA were calculated from the waveform records. The resistive index (RI) was also calculated from the formula (RI=(PSV−EDV)/PSV × 100) to evaluate the changes in vascular resistance of the two vessels.

All data were expressed as mean ± SD. Statistical evaluations of blood flow velocity, RI, PR, and MAP in each session (SG, CCA, and sham) were performed with one-way analysis of variance (ANOVA). Scheffe's test was used to analyze time-dependent changes. Statistical evaluations between sessions were performed with one-way factorial ANOVA using Bonferroni's test to perform multiple comparisons. Differences with $P < 0.05$ were considered statistically significant.

Results

No complications were noted during this study. No subjects had a significant sensation of warmth or showed Horner' syndrome. **Table 1** shows the characteristics of subjects. No relation between age or sex and blood flow was observed in this study. **Figure 1** shows color pulse Doppler sonography of the OA and CRA. **Table 2** shows the effects of each treatment on MAP and PR. No significant changes

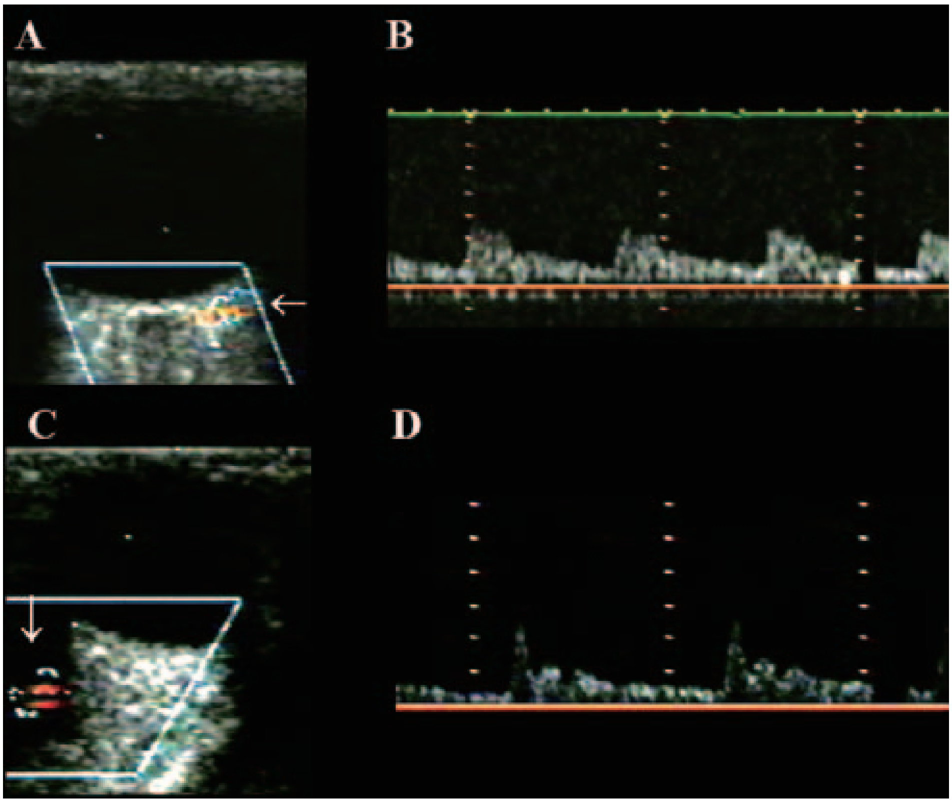

Fig. 1 Color pulse Doppler sonography of the CRA and the OA in a healthy volunteer. Color visualization with color Doppler ultrasonography on a B-mode background is shown on the left (A, B), and spectral waveform with pulsed Doppler is shown on the right (C, D). (**arrow**: sampling position)

in MAP or PR occurred in any of the three sessions.

Table 3 shows the ranges, mean values, and confidence limits of PSV, EDV, and RI in the OA and CRA before each treatment session (control values). **Figure 2** shows changes in PSV, ED, and RI index in the OA during the three sessions. After the SG and CCA sessions, a statistically significant increase in PSV (by 13% and 23% of control values, respectively) was demonstrated (**Fig. 2A**). Treatment of the CCA produced a significantly greater increase in PSV than did treatment of the SG (p=0.045). After the CCA session, a significant increase in EDV (by 21%, p=0.007) was observed (**Fig. 2B**). No significant changes in RI were apparent (**Fig. 2C**).

Figure 3 shows changes in PSV, EDV and RI in the CRA during the three sessions. After the SG and CCA sessions, PSV increased significantly (by 18% and 37% of control values, respectively, p<0.001, each) (**Fig. 3A**). Treatment of the CCA resulted in a significantly greater increase in PSV than did treatment of the SG (p=0.031). After the SG and the CCA sessions, EDV increased significantly (by 21% and 40% of control values, respectively, p<0.001, each) (**Fig. 3B**). Treatment of the CCA produced significantly greater increases in EDV than did treatment of the SG (p=0.049). No significant changes in RI were apparent (**Fig. 3C**).

Discussion

The present study demonstrated that near-infrared LLLI to the CCA or the SG increases OA and CRA blood flow in healthy volunteers without changes in MAP or PR. The eyes of the subjects were closed during the study because photic stimulation affects the OA and CRA blood flow[16]. Irradiation of the CCA produced a stronger effect than irradiation of the SG. The major factor thought to account for increased OA and CRA blood flow is

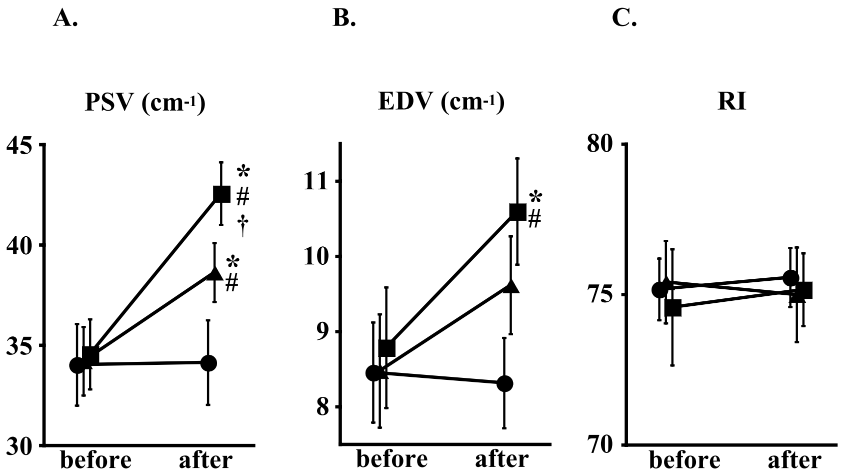

Fig. 2 Changes in PSV (A), EDV (B), and RI (C) for the OA after three treatment sessions. Values are mean ± SD. Circles=sham session (sham); triangles=SG sessions; squares=CCA sessions. *$P<0.05$ compared with control (pretreatment) value. #$P<0.05$ compared with sham sessions. †$P<0.05$ compared with SG session.

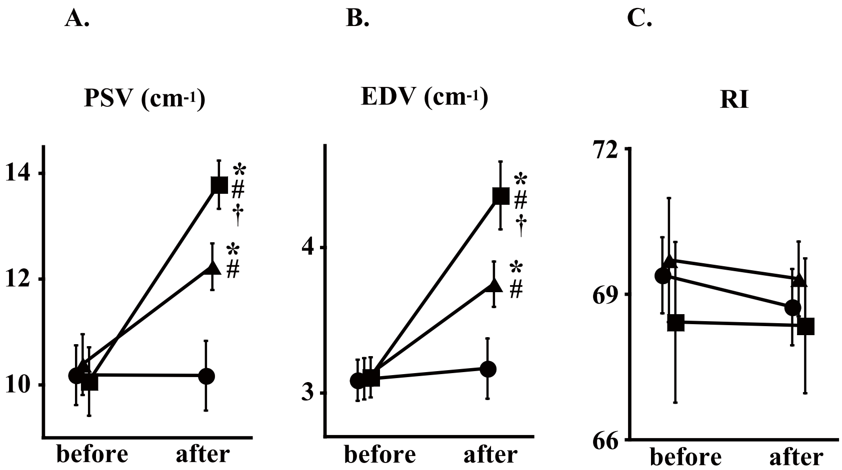

Fig. 3 Changes in PSV (A), EDV (B), and RI (C) for the CRA after three treatment sessions. Values are mean ± SD. Circles=sham session (sham); triangles=SG sessions; squares=CCA sessions. *$P<0.05$ compared with control (pretreatment) value. #$P<0.05$ compared with sham session. †$P<0.05$ compared with SG session.

that LLLI to this region is direct stimulus to the arteries around the SG including the CCA, resulting in increased cranial blood flow. Ultra violet light and visible light irradiation will directly relax vascular smooth muscle (photorelaxation)[17–19] and near-infrared light irradiation dilates arterioles directly by generating light-induced NO[20]. This study suggest that LLLI around the SG causes dilatation of the CCA and increases of retrobulbar blood flow.

LLLI is widely used in clinical situations, influences both the nervous system[21,22] and the immune system[23], and demonstrates many therapeutic effects such as vasodilation[24], analgesia[8,9], and promotion of injury repair[25]. Vasodilation appears to be an important effect of irradiation because the increase in blood flow is a common determinant of the therapeutic effects mentioned above. However, the mechanism of vasodilation is not fully understood. A previous study has demonstrated that near-infrared LLLI increases rat mesenteric microcirculation following dilation of laser-irradiated arterioles, and that the vasodilatory effect is mediated largely by irradiation-induced reduction of the Ca^{2+}concentration in vascular smooth muscle cells, in addition to the involvement of nitric oxide in the initial phase[20].

From the viewpoint of sympathetic nervous blockade, whether LLLI to the SG has the same effect as SGB remains unclear. In neither our previous study[7] nor the present study, did LLLI to the SG affect peripheral blood pressure or a PR. Furthermore, LLLI to the SG did not show the clearly defined effects of sympathetic nerve blockade such as Horner's syndrome and suppression of perspiration. Sympathetic nerves are widely distributed on the retinal artery as far as the lamina cribrosa sclerae[26,27]. Cervical sympathetic nerve blockade[7] and sympathectomy[28] increase retinal artery blood flow by 30% to 50%, perhaps through vasodilation of the retinal artery; however, direct measurement of retinal artery diameter failed to reveal such vasodilatory effects. In the present study, PSV for the OA and CRA increased significantly without changes in vascular resistance after LLLI to the SG. Our data indicate that increased blood flow in the CCA near the SG might account for the increased PSV after LLLI to the SG. It was also suggested that the effects of LLLI on the retrobulbar artery occur by a different mechanism from that seen in SGB.

The present study has several limitations. First, the possible effect of the heat induced by the irradiation could not be evaluated because we could not measure the temperature in the irradiated region. The influence of the heat effect produced by irradiation deserves consideration, although the subjects in this study did not feel heat or any change in the irradiated region. The possibility that the heat affected the sympathetic nervous system cannot be ruled out. Second, there was possible overlap of irradiation areas because of the proximity of the SG and CCA. Although linearly polarized light irradiation was used in this study, the possibility of tissue scattering could not ruled out.

In this study, color pulse Doppler sonography was used to evaluate retrobulbar blood flow[13]. Previous studies have shown the efficacy of this noninvasive method[29,30], and our control data for PSV, EDV, and RI were in agreement with those of a previous study that examined normal ophthalmologic variables. The exact increase in retinal blood flow was not determined in this study, as changes in arterial diameter were not measured. However, as determined in a previous study that evaluated the same variables in response to SGB, the increase in PSV without changes in MAP, PR, or vascular resistance suggest increased retinal blood flow[7]. Our data suggests that LLLI applied to the SG could become a useful alternative to conventional SGB for increasing retrobulbar blood flow. However, further study is necessary to evaluate the duration of the therapeutic effect and complications arising from prolonged treatment.

In conclusion, our results have shown that LLLI to the SG and to CCA increase blood flow velocity in the OA and CRA without changes in vascular resistance. The technique is a useful alternative to conventional SGB for increasing retrobulbar blood flow. In clinical settings, direct irradiation directed to the CCA was more effective for increasing retrobulbar blood flow than that directed to the SG. Further studies are necessary to evaluate the effects of LLLI in patients with impaired OA and CRA blood flow because this study involved only healthy subjects.

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