Comparison of 1470 nm Laser and Radial 2ring Fiber with 980 nm Laser and Bare-Tip Fiber in Endovenous Laser Ablation of Saphenous Varicose Veins: A Multicenter, Prospective, Randomized, Non-Blind Study

Masayuki Hirokawa, MD, PhD, 1 Tomohiro Ogawa, MD, PhD, 2 Hiromitsu Sugawara, MD, PhD, 3 Shintaro Shokoku, MD, PhD, 4 and Shoji Sato, MD, PhD 5

Objective: The aim of this study is to compare the clinical efficacy and safety of two laser wavelengths and fiber types in endovenous laser ablation (EVLA) of saphenous varicose veins of the lower limb. Design: Multi-center prospective randomized non-blind clinical trial.

Patients and Methods: From January 2007 to December 2011, 113 patients (113 limbs) with primary varicose veins were randomized into two groups. They were treated with radial 2ring fiber and 1470 nm laser in Group I (57 limbs) and bare-tip fiber and 980 nm laser in Group E (56 limbs) in order to ablate the saphenous vein. Vein occlusion rates at 12 weeks and pain in treated region were recorded as primary endpoint. Visual analogue scale (VAS) for assessment of pain, rates of bruising, complications and equipment failure were recorded as secondary endpoint of safety.

Results: Occlusion rates at 12 weeks were 100% in both groups. Rates of pain (0% vs. 25.0%) and bruising (7.0% vs. 57.1%) were significantly lower in Group I (p <0.0001). VAS of pain was significantly lower on postoperative day 1, day 5 and 2nd week in Group I.

Conclusion: Treatment of saphenous varicose veins by EVLA using a 1470 nm laser and a radial 2ring fiber resulted in comparable occlusion rates at 12 weeks and less postoperative pain and bruising than EVLA with a 980 nm laser and a bare-tip fiber. (This article is a translation of Jpn J Vasc Surg 2014; 23: 964–971.)

Keywords: varicose vein, 1470 nm laser, radial 2ring fiber, endovenous laser ablation, VAS score

Introduction

In Japan, a minimally invasive treatment for varicose veins of the lower limbs, endovenous laser ablation (EVLA), has been routinely performed since it became covered by national health insurance in 2011. However, after surgery, pain along the treated veins, bruising, induration, and a pulling sensation have often been reported. 1,2) In a clinical trial with a 980-nm laser, the incidences of postoperative bruising and pain were 56.5% and 37.1%, respectively. 3) To decrease the incidences of these complications, various wavelengths (810 to 2000 nm) of laser have been used for EVLA. 4) These are classified into two types: water-specific laser wavelengths (WSLW: 1000 nm or greater), which are specifically absorbed in water, and hemoglobin-specific laser wavelengths (HSLW), which are specifically absorbed in hemoglobin. 5) Recently, the usefulness of a laser at a WSLW of 1470 nm has been emphasized. 6–8)

Furthermore, various types of optical fiber, such as jacket-tip, 9) diffusion, 10) and radial 11) fibers, have been developed. Among these, radial fibers are optical fibers that reflect the laser beam by means of a prism, and the laser energy is emitted in a 360-degree manner, thus allowing homogeneous irradiation of the vein wall and making it possible to prevent perforation. It has been reported that the combined use of radial fibers with a 1470-nm laser reduces postoperative bruising and pain. 12–16) However, sticking of the fiber to the vein wall may reduce manipulations, and when such adhesions are removed, there is a possibility of moving the fiber more than necessary, resulting in insufficient laser irradiation of the vein wall. To prevent this, the
Comparison of 1470 and 980 nm Laser in EVLA

radial 2ring fiber was developed. The basic concept of the radial 2ring fiber is that the vein is contracted in advance by the proximal irradiation component of the laser fiber, followed by reliable ablation of the vein wall by the distant irradiation component. Moreover, as the laser irradiation is divided between two irradiation components, the laser energy density is approximately half of that of conventional radial fibers, thus preventing vein wall adhesion.

To evaluate the efficacy and safety of EVLA of varicose veins of the lower limbs using a 1470-nm laser and radial 2ring fiber, this clinical trial was conducted as a multicenter, prospective, randomized, non-blind clinical study, establishing a control group treated using a 980-nm laser and conventional bare-tip fiber.

**Subjects and Methods**

This clinical trial (Protocol No.: INT, Study Title: “Controlled Clinical Study of INT02 in Patients with Primary Varicose Veins of the Lower Extremities”, Sponsor: Integral Corporation) was approved by the Pharmaceuticals and Medical Devices Agency in Japan and performed in accordance with the Helsinki Declaration and Good Clinical Practice (GCP), adopted by the Ministry of Health, Labour and Welfare. After explaining the purpose of this clinical trial, methods, and expected disadvantages to patients, written informed consent regarding free will-based trial participation was obtained.

**Subjects**

The present study was conducted from September 2012 to March 2013 at five medical centers (Ochanomizu Vascular and Vein Clinic, Fukushima Daiichi Hospital, Sendai Hospital of the East Japan Railway Company, Shokoku Shintaro Clinic, and Keiyu-kai Tsukuba Vascular Center). Among patients who consulted each medical center, the subjects were outpatients with primary saphenous varicose veins (great or small saphenous varicose veins measuring 20 mm or smaller in maximum diameter) from whom written informed consent could be obtained, with an age of 20 years or older. Patients meeting one of the exclusion criteria (Table 1) were excluded.

**Laser equipment**

As study equipment, we used a 1470-nm diode laser (Ceralas E1470/15W, CeramOptec GmbH, Germany) and radial 2ring fiber (ELVeS Radial 2ring™ fiber, CeramOptec GmbH, Germany). The radial 2ring fiber is an optical fiber, 1850 μm in external diameter, provides laser irradiation from the lateral surface over the entire circumference of 360° by two
prisms, 6 mm apart from each other at the tip (Fig. 1). As control equipment, we used a 980-nm diode laser approved for clinical use in Japan (Ceralas E Model 15 W/980 nm, CeramOptec GmbH, Germany) and bare-tip fiber, 1100 µm in external diameter (600 µm in core diameter).

**Patient registration and assignment**

The subjects were assigned to undergo EVLA with the 1470-nm laser (Group I) or EVLA with the 980-nm laser (Group E). Based on the number of patients required to verify the efficacy of the study equipment in comparison with the control equipment, the target number of patients was 55 per group (total: 110). After pretesting patients from whom written informed consent regarding trial participation could be obtained at each institution, their case registration forms were sent to the registration center. At the center, only patients who were considered eligible based on inclusion and exclusion criteria were enrolled. The investigator in charge of study equipment assignment randomly assigned them in the order of enrollment at the respective institutions.

**Surgical procedures**

Surgical treatment consisted only of EVLA of the veins to be treated, with no concomitant phlebectomy, stripping, high ligation, or sclerotherapy. Prior to surgery, the course of the saphenous vein to be treated was marked on the skin under ultrasound guidance. The basic method was to access the vein segment via an ultrasound-guided percutaneous approach from the distal portion of the saphenous vein. A guidewire and introducer sheath were inserted into the saphenous vein, and tumescent local anesthesia (TLA) was infiltrated into the perivenous space around the sheath under ultrasound guidance. TLA solution was prepared by mixing epinephrine-containing lidocaine and sodium bicarbonate with physiological saline. After TLA, the radial 2-ring or bare-tip fiber was inserted into the sheath. In Group I, the sheath was completely removed from the site of insertion. In Group E, the fiber was connected to the sheath. The fiber tip was positioned 1 to 2 cm distal to the sapheno-femoral or -popliteal junction, and laser irradiation was performed in both groups under duplex guidance, with a laser power setting of 10 W, while pulling back the fiber manually to achieve a linear endovenous energy density (LEED) of 70 to 85 J/cm. Irradiation was conducted only once. When additional irradiation was considered necessary, this clinical trial was discontinued.

After surgery, the treatment area was covered with gauze, and the patients wore thigh high compression stockings. The gauze was removed the day after surgery. The patients were instructed to use the compression stockings until 5 days after surgery. From 6th day to 4th week, the patients wore below knee compression stockings. As an analgesic drug, 60 mg of loxoprofen sodium was administered three times a day for 2 days.

**Endpoints**

1) **Primary endpoints**

   The primary efficacy endpoint was the occlusion rate of the treated vein 12 weeks after surgery. Duplex ultrasonography was performed 1 and 5 days, as well as 2, 4, and 12 weeks, after surgery to evaluate vein occlusion. Based on the results at 12 weeks, occlusion rates in the two groups were calculated. The primary safety endpoint was the incidence of pain during the postoperative observation period. Patients were examined 1 and 5 days, as well as 2, 4, and 12 weeks, after surgery to evaluate pain. Patients with pain at least once during the observation period were regarded as having pain.

2) **Secondary endpoints**

   The secondary safety endpoints were pain on the visual analog scale (VAS), bruising, adverse events, and study equipment failure during surgery. The VAS was measured 1 and 5 days, as well as 2, 4, and 12 weeks, after surgery, and the maximum VAS during the observation period was
assessed. The presence or absence of bruising was evaluated based on photographs of the lower extremities at 1 and 5 days, as well as at 2 and 4 weeks. Patients with bruising at least once during the observation period were regarded as having bruising. The presence or absence of adverse events was evaluated by physicians on the day of surgery, after 1 and 5 days, and after 2, 4, and 12 weeks.

**Evaluation methods**

(1) Efficacy

Occlusion of the treated vein was evaluated by observing the entire ablated vein using duplex ultrasonography in a standing position. Vein occlusion was defined as incompressibility with an ultrasound transducer and compressibility with absence of blood flow induced by calf squeezing or presence of blood flow, but the extent was 5 cm or less.\(^{17–19}\)

(2) Safety

For pain assessment, patients without pain and with tolerable pain requiring no additional analgesics were regarded as having no pain, and those requiring an additional analgesics or topical cooling or those in whom pain affected their activities of daily life were regarded as having pain. The VAS was evaluated using a VAS scale measuring 100 mm in length. On consultation, each subject was instructed to indicate the grade of pain using the VAS scale. The left end of the VAS scale (0 mm) indicates “no pain”, and its right end (100 mm) indicates “the severest pain that can be imagined”. The distance from the left end to the position indicated by each subject (mm) was determined, and recorded as the VAS score. Bruising was evaluated based on photographs by three physicians who were not involved with the study institutions. Patients with specific-color or darker bruising involving 20% or more of the treated area or those with markedly dark bruising involving 20% or less of the treated area were regarded as having bruising. The results of evaluation for which two or more physicians' opinions were consistent were adopted as those of each photograph.

**Statistical analysis**

For statistical analysis, the unpaired t-test or Wilcoxon’s test was used to compare the results between the two groups. To compare proportions between the two groups, the chi-square or Fisher’s exact tests were used. A p-value of 0.05 was regarded as significant. For occlusion rates, in cases of non-inferiority in which the two-sided 95% confidence interval of intergroup differences in occlusion rates showed a non-inferiority margin of –12% or above, Group I was deemed to show noninferiority in efficacy with respect to Group E.

**Results**

**Patient background**

Of the 124 patients from whom informed consent regarding trial participation could be obtained, 113 with primary varicose veins of the lower extremities were enrolled in this clinical trial, excluding nine meeting exclusion criteria and two who withdrew from this trial. Fifty-seven patients were assigned to Group I, and 56 to Group E (Fig. 2). All subjects completed this trial, and were included in the analysis. Concerning the patient background, there were no significant differences in the mean age, sex, treated veins, vein diameter, or the clinical, etiologic, anatomic and pathophysiologic (CEAP) classification between the two groups (Table 2).

**Efficacy assessment**

In the two groups, the occlusion rates during the observation period, involving 12 weeks after surgery, were 100% (Table 3). Therefore, it was impossible to calculate the difference between the two groups, and so we calculated the 95% confidence interval of the intergroup difference.
assuming that the treated vein was not occluded in one patient in Group I. As a result, the difference between the two groups was −1.8%, and its 95% confidence interval ranged from −5.2 to 1.7%. Despite a treatment disadvantage for Group I, the lower limit of the 95% confidence interval exceeded the noninferiority limit (−12%), suggesting the noninferiority of efficacy in Group I in comparison with Group E.

**Safety assessment**

(1) Primary endpoints

Pain at the treated site was noted in 14 patients (25.0%) in Group E, but not in Group I (0%). In Group I, the incidence of pain was significantly lower than in Group E (p < 0.0001) (Table 3).

(2) Secondary endpoints

1. VAS for pain
The maximum VAS scores (mean ± standard deviation) in Groups I and E were 6.3 ± 9.6 and 22.8 ± 19.0, respectively, showing a significant difference (p < 0.0001) (Table 3). The mean VAS scores in the two groups 1 and 5 days after surgery and after 2, 4, and 12 weeks were 2.8 ± 5.6 vs. 12.4 ± 17.2 (p = 0.0007), 2.5 ± 5.9 vs. 18.1 ± 17.9 (p < 0.0001), 3.0 ± 7.9 vs. 6.7 ± 11.0 (p = 0.0022), 0.7 ± 2.3 vs. 1.0 ± 3.5 (p = 0.7407), and 0.3 ± 1.8 vs. 0.0 ± 0.0 (p = 0.1656), respectively. In Group E, there was a peak 5 days after surgery though there were no marked changes in Group I in which VAS scores 1 and 5 days after surgery and after 2 weeks were significantly lower than in Group E (Fig. 3).

2. Bruising

Postoperative bruising was observed in 4 patients (7.0%) in Group I and 32 (57.1%) in Group E. Incidence of bruising was significantly lower in Group I than in Group E (p < 0.0001) (Table 3).

3. Complications (Table 4)

Adverse events of which the relationship with the study equipment could not be ruled out were noted in 45 patients. Induration was observed in four patients (7.0%) in Group I and 8 (14.3%) in Group E. Tenderness was noted in four patients (7.1%) in Group E (Group I: 0 (0%)). Sclerosis was observed in one patient (1.8%) in Group I and 3 (5.4%) in Group E. A pulling sensation was noted in two patients (3.6%) in Group E (Group I: 0 (0%)). Paresthesia was observed in one patient (1.8%) in Group E (Group I: 0 (0%)). Although the incidences of these adverse events were higher in Group E, there were no significant differences. Concerning thrombotic complications, class 2 endovenous heat-induced thrombus (EHIT) were observed in one patient (1.8%) in Group I and 2 (3.6%) in Group E, and class 3 EHIT in one patient (1.8%) in Group I and 1 (1.8%) in Group E. Thrombophlebitis was noted in one patient (1.8%) in Group I (Group E: 0 (0%)). Thrombi in the vein were observed in one patient (1.8%) in Group I and 7 (12.5%) in Group E.

4. Intraoperative failure of the study equipment

There was no failure of the study equipment during surgery.

**Discussion**

The efficacy of endovenous ablation, such as EVLA, radiofrequency ablation (RFA), and sclerotherapy is evaluated
Based on occlusion of the entire length of the treated vein. Venous occlusion is assessed based on the absence of venous compressibility and blood flow using duplex ultrasound.\(^{17}\) However, after EVLA with a radial fiber, a partial patency, in which compressibility is present, but there is no blood flow, is often observed in a portion of the treated vein.\(^{16}\) Furthermore, there is a patency with blood flow measuring 3 cm or less at the saphenous junction after endovenous ablation; therefore, most patients with a patency measuring 5 cm or more are regarded as showing unsuccessful results.\(^{18,19}\) Based on these findings, in this clinical trial, when there was no blood flow despite compressibility, including cases in which the area of blood flow measured 5 cm or less, the efficacy was evaluated, regarding it as occlusion. Twelve weeks after surgery, there was no patient with compressibility or blood flow at sites other than the saphenous junction in either group. The occlusion rate was 100%. In Group I, the primary efficacy endpoint, the occlusion rate 12 weeks after surgery, was similar to that in Group E. Although the interval from surgery was relatively short (12 weeks), the efficacy of EVLA with the study equipment was similar to that of EVLA with the control equipment. A laser at a wavelength of 1470 nm is strongly absorbed by water in the tissue, and the absorption coefficient is about nine times higher than that of a laser at a wavelength of 980 nm in the human venous wall.\(^{20}\) Therefore, when a vein is directly irradiated, the optical energy of the 1470-nm laser is efficiently absorbed, and its thermal degeneration is stronger than that of the 980-nm laser. Even when blood is present in the vein, the laser is absorbed by the water contained in the blood, facilitating indirect venous ablation. Therefore, the 1470-nm laser may cause more marked vein wall damage compared to the laser at an HSLW, 980 nm. To date, no study has reported any wavelength-related difference in the venous occlusion rate. Several studies indicated that the venous occlusion rate after EVLA with a 1470-nm laser and radial fiber was 99.6% to 100%,\(^{8,12-16}\) being similar to that after EVLA with a 980-nm laser (88.0 to 100%).\(^{21,22}\)

The primary safety endpoint, the incidence of pain, and secondary endpoint, the maximum VAS score for pain, were significantly lower in Group I. In this group, the changes in the VAS score were also significantly lower than in the control group until 2 weeks after surgery. Pain at the treated site was observed in approximately 30% of patients after EVLA.\(^{23}\) There was no difference between EVLA with a conventional HSLW laser and stripping.\(^{24}\) The incidence of pain was higher than after RFA, an endovenous ablation procedure.\(^{25}\) However, several studies reported that the use of a laser at a WSLW, 1470 nm, decreased the incidence of pain after EVLA,\(^{7,14,15}\) and that the laser in combination with a radial fiber more markedly decreased it compared to that in combination with a bare-tipped fiber.\(^{8,12,16}\) Doganci et al.\(^{13}\) conducted a prospective, randomized, comparative study of EVLA with a 1470-nm laser and radial fiber using EVLA with a 980-nm laser and bare-tip fiber as a control procedure, as described for this clinical trial, and reported that the duration of pain after EVLA and use of analgesics were significantly lower in the 1470-nm laser group. Our study demonstrated that a radial fiber combined with a 1470-nm laser reduced postoperative pain, facilitating minimally invasive treatment, as indicated for the radial fiber.

Generally, bruising at the treated site was observed in all patients after EVLA, including those with slight bruising, although it disappears within 2 to 3 weeks, and there are no sequelae.\(^{23}\) However, bruising is primarily associated with laser-related perforation of the vein wall; therefore, its frequency reflects whether or not the vein is adequately ablated. In patients with varicose veins of the lower extremities, which are more frequent in females, the development of bruising may lead to postoperative restriction of normal activity, decreasing the quality of life. The incidence of bruising varies considerably depending on its definition. In order to objectively evaluate bruising, the treated site was photographed, and assessed by several physicians other than attending physicians later in this trial. The results showed that the incidence of bruising in the study

### Table 4 Complications

<table>
<thead>
<tr>
<th>Complication, number of limbs (%)</th>
<th>Group I (n = 57)</th>
<th>Group E (n = 56)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induration</td>
<td>4 (7.0)</td>
<td>8 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Tenderness</td>
<td>0</td>
<td>4 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Sclerosis</td>
<td>1 (1.8)</td>
<td>3 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Pulling sensation</td>
<td>0</td>
<td>2 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>1 (1.8)</td>
<td>NS</td>
</tr>
<tr>
<td>EHT Class 2</td>
<td>1 (1.8)</td>
<td>2 (3.6)</td>
<td></td>
</tr>
<tr>
<td>EHT Class 3</td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>1 (1.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Thrombus in the vein</td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>7 (12.3)</td>
<td>7 (12.5)</td>
<td></td>
</tr>
</tbody>
</table>

EHIT: endovenous heat-induced thrombus; NS: not significant; χ² test or Fisher’s exact test.
equipment group was significantly lower than in the control group (7.0 vs. 57.1%, respectively, p < 0.0001). Interestingly, the incidence in the control group was similar to that in a previous clinical trial of a 980-nm laser (56.5%). When a 1470-nm laser is used to directly irradiate a vein, the mean energy density for perforation is lower than after irradiation with a 980-nm laser.20 However, the occurrence of bruising depends on the shape of optical fibers rather than differences in the laser wavelength. According to several studies, after EVLA with a 1470-nm laser and bare-tip fiber, bruising was noted in 60% or more of patients,7 whereas the incidence of bruising after EVLA with a 1470-nm laser and radial fiber was significantly lower than after EVLA with a 980-nm or 1470-nm laser and bare-tip fiber. When a radial fiber is used, laser irradiation is from the lateral side of the fiber to an extensive area, and the irradiation energy per unit area (fluence) is 1/5 to 1/9 of the normal value; perforation of the vein wall may not occur.11 The fluence of the radial 2ring fiber is much lower than that of the radial fiber, and the former facilitates uniform cauterization of the vein over its entire circumference; this may have contributed to the prevention of perforation and a low incidence of bruising.

Generally, pain after EVLA is more marked than after RFA, and the incidence of bruising is higher. However, in this study, the results of EVLA with the study equipment were similar to those of RFA. In the RECOVERY study using a ClosureFAST™ catheter,27 the maximum pain value on a 10-point VAS was 0.7 forty-eight hours after surgery. In this study, the mean maximum value during the observation period was 6.3 (10-point conversion: 0.63) and 2.8 (10-point conversion: 0.28) the day after surgery. The incidence of bruising over an area of 25% or greater after 6 days after surgery developed to class 3 thirteen days after surgery. In the control group, the class 2 EHIT noted 6 days after surgery developed to class 3 thirteen days after surgery. The continuation of this clinical trial was approved through a review at the Institutional Review Board, and observation was performed until 12 weeks after surgery for this case. In these patients with EHIT, there were no symptoms suggestive of pulmonary embolism, and the investigation of pulmonary embolism was not conducted; therefore, the possibility of concomitant asymptomatic pulmonary embolism cannot be ruled out. However, in the two patients, disappearance of the thrombus was confirmed by the anticoagulant therapy during the trial period. There were no significant differences in the incidences of other adverse events between the study equipment and control groups, suggesting that the safety is similar.

Conclusion

The primary efficacy endpoint in this clinical trial, the occlusion rate 12 weeks after surgery, in the study equipment group was similar to that in the control group. The primary safety endpoint, the incidence of pain, was significantly lower in the study equipment group. In this group, secondary endpoints, the maximum VAS score for pain and incidence of bruising, were also significantly lower than in the control group. There were no differences in the incidences of complications between the two groups, and there was no equipment failure. Thus, EVLA with a 1470-nm laser and radial 2ring fiber have the similar efficacy with EVLA with a conventional 980-nm laser and bare-tip fiber and significantly decreased the incidences of postoperative pain and bruising; it may be a safe, minimally invasive treatment procedure.

Acknowledgments

We thank Dr. Mano (Shokoku Shintaro Clinic), Dr. Kume (Tsukuba Vascular Center, Moriyakeiyu Hospital), and Drs. Kurihara, Mitsuoka, and Ban (Ochanomizu Vascular and Vein Clinic) for their cooperation.

Disclosure Statement

This study was designed and funded by Integral Corporation. The first author (Masayuki Hirokawa) is a consultant for Integral Corporation. Shintaro Shokoku received a lecture fee from Integral Corporation. There are no conflicts of interest for Tomohiro Ogawa, Hiromitsu Sugawara, and Shoji Sato.

References


