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ORIGINAL ARTICLE

Effects of 1064-nm Nd:YAG long-pulse laser on polidocanol microfoam injected for varicose vein treatment: a controlled observational study of 404 legs, after 5-year-long treatment

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Abstract

Sclerotherapy continues to be the treatment of choice for varicose veins in the legs. However, isolated treatment using microfoam or lasers requires a high number of sessions to eliminate them. In 2013, we published results about the efficacy and safety 3 years after the combined treatment with microfoam injections and subsequent application of Nd:YAG laser. The aim of this paper is to clinically evaluate the treatment of varices in a control visit after 5 years, when polidocanol microfoam is used and is immediately irradiated in the tissue with 1064-nm Nd:YAG laser beam. The outcome persistence after 5 years was studied in the legs that had received combined treatment and had been studied 3 years after treatment. Patients were contacted by phone, interviewed, and examined with echo-Doppler. Out of the 259 patients who were contacted, 221 agreed to make the appointment, although in the end, only 202 came, which meant analysing 404 legs. At 5 years, the clearance rates were very high: patients were included in class CEAP C1 showing vessels of from 0.5 to 3 mm diameter. The patients showed a high level of satisfaction. Regarding adverse effects, only 4 cases of hypopigmentation described in the previous publication persisted. Although the action mechanisms between the microfoam and the Nd:YAG laser must still be elucidated, it is notable that combining microfoam with laser exposure obtained a complete, effective treatment of legs in only 2 sessions, with high clearance rates and high level of satisfaction among patients.

Keywords Sclerotherapy · Varicose veins · Spider veins · Reticular veins · Microfoam polidocanol · Nd:YAG laser

Introduction

According to the majority of authors, sclerotherapy continues to be the benchmark treatment for the chronic venous disorders included in C1 group of CEAP classification: telangiectasias (class I), venulectasias (class II), and reticular veins (class III) lower than 4 mm [1–4]. However, although the injections of polidocanol (POL) are effective in microfoam form, they require a high number of sessions to eliminate varicose veins. On the other hand, treatment only with Nd:YAG long-pulse lasers is successful, but the application is painful and it does not lack adverse effects. This prevents laser treatment from reaching the same high levels of popularity as microfoam [5–11]. However, other therapeutic options are possible to obtain success in treating varicose veins with fewer sessions and fewer side effects [7, 11]. In 2013, we published an article concerning the results of varicose vein treatment in which we confirmed the efficacy and safety 3 years after treatment [7]. In that study, POL microfoam was injected while a Nd:YAG laser beam was applied transcutaneously immediately afterwards, the fluence of the laser beam being lower than of the laser alone treatment. This method achieved a high clearance level for the varicose veins, while also earning a high level of satisfaction among patients. Furthermore, the positive results persisted throughout

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the study control period [7]. Before proceeding to evaluate the obtained results, the action mechanisms and physical interactions which take place between POL microfoam and the Nd:YAG laser were investigated to explain the synergistic action observed when both procedures are used nearly simultaneously. The studies confirmed that POL physical-chemical properties, as well as the effect and thermal propagation of the energy supplied by Nd:YAG laser, varied in the conditions in which they were used to treat varicose veins [8–10]. In accordance with these observations, microfoam presence inside the vessel makes it possible to use lower therapeutic laser fluences than those proposed by other authors when applying laser as the sole treatment [4, 5, 11].

Furthermore, a previous study evaluated the efficacy of this combination of treatments for varicose veins in the legs with a diameter lower than 1.5 mm in patients with phototype IV [10]. The results of using combined POL and laser therapy were compared with those obtained when POL microfoam or Nd:YAG laser was used separately. The combined treatment obtained a considerable clearance of vessels in short term (3 months), in comparison with POL injection technique alone or when only laser was used. However, follow-up of results was relatively short and it did not elucidate if they could be maintained in long term [10].

The goal of this paper is to present a synthesis of the clinical assessment of the treatment of reticular veins and telangiectasias (classes I to III) with a control 5 years after using POL microfoam and irradiating immediately thereafter along the course of the vein with a 1064-nm Nd:YAG long-pulse laser beam.

Material and methods

This is a longitudinal, observational, controlled, and retrospective study, performed 5 years after treatment and proposed to evaluate the efficacy, safety, and persistence of the results obtained 3 years after having treated patients with POL and Nd:YAG laser beam, whose evaluations were published in Phlebology [7]. For this purpose, 5 years after having conducted the treatment, the patients were contacted to objectively and subjectively confirm the quality of the results; this is a very long-term follow-up. The patients who agreed to conduct a visit were clearly explained by phone the objectives of the study. That is, patients were informed that they would be interviewed and examined using duplex ultrasound (Siemens® Soniline 050®, Issaqua, Japan), to rule out refluxes in the deep venous system at the saphenofemoral and/or saphenopopliteal junctions, or in some of the perforating veins. Patients with reflux of major veins were excluded and only patients without major venous pathology were included in the study. No micro-surgical interventions were made.

The patients who stated by phone that they were dissatisfied with the treatment and who refused to personally come to evaluate the results were not included in the study.

The results were evaluated based on photographs taken with the same camera used in the previously published study. The photographs were taken at a constant distance of 18 cm in standard lighting conditions, focusing on the same treated areas aiming to obtain comparative images. The varicosities presented by patients were analysed in detail. As in the study 3 years after treatment [7], each patient completed an evaluation questionnaire identical to the previous ones to determine the level of satisfaction with the results. The adverse effects of the treatment after 5 years were also included in the questionnaire according to each patient's opinion.

The interview and study methodology were approved by the Ethics Committee of the Fundación Antoni de Gimbernat, and all patients who agreed to participate at control visit for evaluation of the results signed an informed consent form.

Out of the 259 patients who received the combined treatment whose results at 3 years had already been published [7] and who could be contacted, 221 agreed to carry out the review visit 5 years after the treatment, although finally, only 202 attended, which meant analysing 404 legs.

The varicose veins monitored 5 years after treatment corresponded to class I, red telangiectasias lower than 0.5-mm calibre; class II, blue-red venulectasias with 0.5–1.5-mm calibre, and class III, blue-coloured reticular veins and 1.5 –4-mm calibre. The majority of patients had been treated due to presenting varicose patterns with different degrees of expression from each class. All had received treatment for the entire legs (5 years before), from the ankle to the groin [7]. Each patient had received two treatment sessions. The two treatments had been carried out with a 3-week interval. The second session was considered as reinforcement for the first treatment. In the study of the efficacy of results after 3 years, an evaluation was also performed after 3 months and 2 years. In all control periods, adverse effects of the procedures were taken into account and treatment had been carried out by the same physician [7].

Data about experimental procedures

The treatment was performed with POL microfoam obtained using 2 luer-lock syringes of 10 ml volume (Omnifix®, B-Braun, Melsungen, Germany). The syringes were connected through a three-way stopcock, which in turn was joined to a microfilter connected to a 15-G calibre needle to load the sclerosant and saline solution. In order to obtain a 0.3% concentration of POL, 1.6 ml of Aethoxysklerol® (Kreussler Pharma, Wiesbaden, Germany) was diluted with 0.4 ml of

saline solution at 0.5% concentration (Grifols Movaco, Paret del Vallés, Barcelona, Spain). Microfoam was obtained by combining 2 ml of 0.3% POL mixture with 8 ml of ambient air taken through the microfilter and pumped between 15 and 20 times from one syringe to another, following the Tessari technique [12–15]. Resulting microfoam is rich in nitrogen, a gas with low solubility in organic fluids which gives rise to irregular-sized, but highly cohesive bubbles [15].

For treatment, the entire leg was disinfected with hydrogen peroxide. Later, POL microfoam was injected with 30-G needles, using a 2 ml syringe (Omnifix®, B-Braun, Melsungen, Germany). In general, the amount injected in each leg was lower than 10 ml. After injection, vessel whitening was observed which, between approximately 1 and 3 min changed to a slightly pink colour. Immediately after POL sclerosing microfoam injection, the leg was irradiated with a laser beam so that the successive pulses covered the entire course of the vein.

After treatment, the patient was indicated to wear graduated compression stockings with 15–21 mmHg (140 DEN: high compression) compression pressure for 2 weeks. The stockings were used only during the day. In average, the treatment for both legs lasted less than 1 h.

The 1064-nm Nd:YAG long-pulse (10–100 ms, dependent on the spot size) laser was used (Laserscope Lyra-i®, Laserscope, San José, CA, USA). This laser is equipped with a glass chamber adapted to the tip of the handpiece nozzle to cool the skin. In order to enhance the cooling of the skin, cold air at 4 °C was applied (Zimmer Cryo 5, Zimmer Medizin Systeme, Neu-Ulm, Germany), directed toward the surface where laser pulses were applied.

For treatment, a spot equal to or slightly larger than the vein diameter was selected, generally between 2 and 5 mm. The energy per pulse was established based on the spot used. For 2-mm spot, 9.42 J beam energy was used, while for a 5-mm spot, 11.77 J was used. Laser pulses were 30 ms for classes I and II varicose veins, and 50 ms for class III varicose veins; pulse repetition rate was 5 Hz for class I and class II varicose veins and 2 Hz for class III varicose veins.

Assessment of results

In the determination of clearance level of vessels 5 years after treatment, photographs were taken to compare them with those taken before treatment and with those showing results obtained 3 years after treatment [7]. The photographs were taken with the same camera from the previously published study (Canon EOS 400D, with a lens Sea & Sea Flash Macro DRF 14, Canon Inc., Tokyo, Japan). The photographs were taken at a constant distance of 18 cm in standard lighting conditions, focusing on the same areas treated in order to obtain comparative images.

The clearing scale was established using 6 points: 0, no changes or worsening of the initial condition; 1, 20% clearing; 2, 40%; 3, 60%; 4, 80%; and 5, 100% or full clearing of the veins. In the results 3 years after treatment, scoring was awarded by three independent medical evaluators, who were nevertheless familiar with the technique.

We have done the same in the 5-year follow-up visit for this study.

Clearance rates were established separately for each class of varicose vein classifications (I, II, and III). The average obtained from each evaluator's ratings was used for statistical analysis.

In order to evaluate results, the varicosities presented by patients were analysed again in detail. Subjective reports on the post-treatment outcome were evaluated using the Global Aesthetic Improvement Scale (GAIS). More, as in the first study (3 years after treatment [7]), each patient completed an evaluation questionnaire identical to the previous ones to determine the level of satisfaction with the results, such as very dissatisfied, dissatisfied, somewhat satisfied, satisfied, and very satisfied. The adverse effects of the treatment after 5 years were also included in the questionnaire according to each patient's opinion.

Statistical analysis

To process the data, SPSS v. 22 program for Windows was used. As in the previous study, descriptive statistical data have been expressed as arithmetic mean (m) ± standard deviation (SD), including also median (M), range (r), and percentage (%). The main statistical procedure has been the estimation of percentages based on a semi-quantitative numerical scale. The agreement between evaluators has been assessed by using Cohen's Kappa test. The groups of treated varicose veins were compared, according to each class on each follow-up date, using the Mann-Whitney U test for their evaluation. A value of $p < 0.05$ was deemed to be statistically significant.

Results

Out of the 320 patients from the first study, 22 did not complete treatment, some for reasons external to the research and others due to not attending follow-up visits. Out of the remaining 298 patients, only 259 were treated with POL and Nd:YAG laser, totalling 518 legs. After 5 years, the 259 patients who had received combined treatment were contacted. An appointment was made with 221 of them, of whom 202 attended, which meant analysing 404 legs 5 years after having finished the second treatment.

Table 1 Clearing ratings are specified by groups for each treatment and type of varicose vein, throughout the follow-up period (mean, SD, median, and range). The average rating of all three evaluators was used for statistical analysis

Varicose veins	The average rating of all three evaluators					
	Clearing rating, 3 years (%)	Clearing rating, 5 years (%)	Mean	SD	Median	Range
Class I	89	85	4.01	1.01	4.52	1.7–5.0
Class II	94	89	4.52	0.69	4.1	0.9–5.0
Class III	95	92	4.61	0.97	4.12	1.1–5.0

Efficacy results

The clearance percentage 5 years after treatment with POL and laser is shown in Table 1. Average rating by each of the three evaluators is specified for each group. Values of Kappa test between the second and third evaluators, in comparison with the first, were $k = 0.85$ and $k = 0.83$, respectively. The combined POL and laser treatment reached average clearance rates of 90% in the follow-up visit after 3 years, while in the follow-up visit after 5 years, the observed rates were 85% for class I varicose veins, 89% for class II varicose veins, and 92% for class III varicose veins. At 5 years, the clearance rates were very high: patients were included in class CEAP C1 showing vessels of 0.5 to 3 mm diameter. Recanalization can be due to neovascularization but in this case, the aspect of the new vessels is very different to normal appearance of the vessels due to recanalization. We want to exclude the presence of reflux as a possible evolution of venous disease without relationship with the treatment. The diagnosis of neovessels is easy only with the clinical exam.

The results of the satisfaction level at 5 years had slightly decreased and were related with the decrease of clearance rates (Table 2).

The photographs show examples before and at 3 and/or 5 years after treatment (Figs. 1 and 2).

Table 2 Degree of patients satisfaction 5 years after two-session combined treatment (POL + Nd:YAG laser) compared with results 3 years after (first study). Only the self-assessed patients that keep the appointment check were taken into account

Satisfaction POL + laser / GAIS score	3 years ($N = 517$)	5 years ($N = 404$)
Very dissatisfied / − 1	9 (1.7%)	4 (1.0%)
Dissatisfied / 0	21 (4.0%)	11 (2.7%)
Somewhat satisfied / 1	42 (8.1%)	37 (9.1%)
Satisfied / 2	205 (39.7%)	195 (48.3%)
Very satisfied / 3	240 (46.4%)	157 (38.9%)

In the photographs, one may see that, practically, complete clearance persists in classes I, II, and III treated varicose veins.

Adverse effects

According to our observations, 5 years after the combined treatment (POL + 1064-nm Nd:YAG laser), results show that it is effective and safe. Patients reported good tolerance to treatment, and the most frequent symptom was pain, especially during laser application. The experienced pain was evaluated at 5 years as to how it had been: light (8.6%), moderate (26.5%), severe (50.4%), and very severe (14.5%), matching the assessments carried out at 3 years.

The interviews identified that the adverse effects occurred after about 3 months in 40 treatments, which meant 7.73% of the treated legs. The most common were hyperpigmentation, hypopigmentation, blisters, and matting (Table 3).

All mentioned cases had been resolved over time, except in four cases of permanent hypopigmentation (0.8%) confirmed 5 years after treatment. There is no doubt that this type of sequela has special relevance given that it is generally unresolved, and patients always display some anxiety regarding it. On the other hand, no secondary effect or complication was observed either in the third or the fifth year.

Discussion

According to the results reported in this study, combined POL and 1064-nm Nd:YAG long-pulse laser treatment is effective and achieves a high level of clearance for class I to III varicose veins. In the results observed at 5 years, we have confirmed that clearance persists in 89% of the treated vessels.

According to our reported follow-up [7], clearance rates obtained 3 years after treatment through combined POL + laser method remained between 4 and 5 points, matching the control results 5 years after treatment.

The limitations of this work and the statistics are:

a) Clearance rates do not offer precise discrimination of the values comprised between 4 points (80% clearance) and 5 points (100% clearance). A value of 5 only indicates that

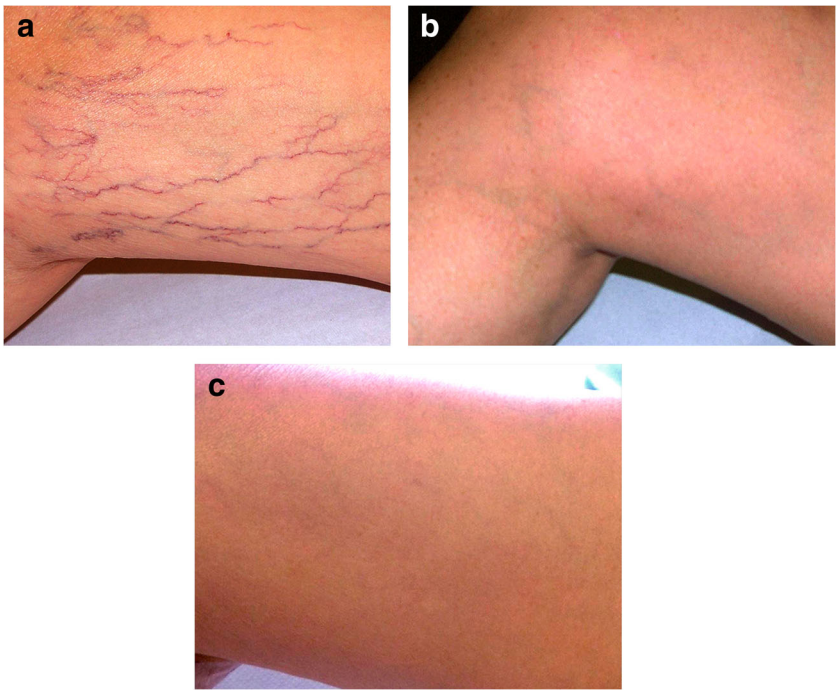

Fig. 1 Leg image shot for one of the patients (case number 1) chosen as an example: **a** Before treatment, the whole leg presents multiple varices of various degrees. **b** Aspect or the same area, 3 years after treatment. **c** Results maintained 5 years after treatment

the evaluated results are closer to 100% than to 80%. The results close to 5 points were classified as such because the three evaluators assigned 5 points to all the areas treated with POL + laser, based on examined photographs.

b) The statistics 5 years after treatment may not match with the photographs and the expectations classified as 100% results.

Various authors have reported on the results reached with the application of Nd:YAG laser in the elimination of varicose veins from the legs. However, in all reports, these results refer to selected areas or partial treatments of the lower limbs, but no author has reported on the treatment of the entirety of both legs in a single session [5, 6, 9, 10, 16–18]. This detail gives clear advantages to the efficacy, speed, and safety of POL and Nd:YAG laser treatment reported here, with a control visit 5 years after the two treatments.

Laser treatment following POL injection is fast, but, obviously, the time needed depends on the number of varicose veins in each leg.

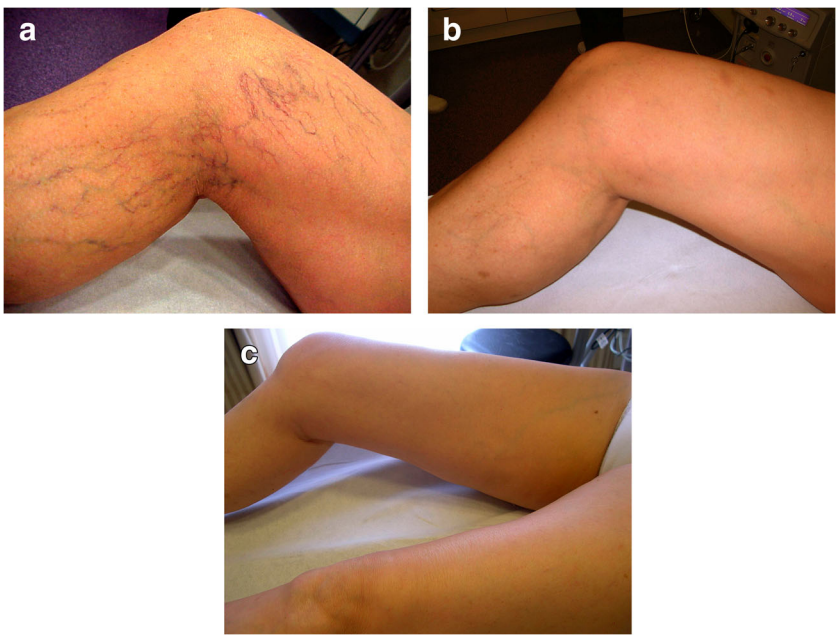

Fig. 2 Leg image shot for a second patient (case number 2) chosen as an example: **a** Before treatment, observe various varices having randomly distributed degrees and covering the whole area of treatment. **b** The same area shows results obtained 3 years after treatment. **c** Achieved outcome is maintained 5 years after treatment

Table 3 Adverse effects during the 5-year follow-up of POL + laser treatment ($N = 404$). All adverse effects were resolved over time, except for four cases of hypopigmentation observed in the 3-year follow-up

Adverse effects	Hyperpigmentation	Hypopigmentation	Blisters	Matting
3 months $N = 517$	26 (5.0%)	6 (1.2%)	6 (1.2%)	8 (1.5%)
2 years $N = 517$	0 (0%)	4 (0.8%)	0 (0%)	2 (0.4%)
3 years $N = 517$	0 (0%)	4 (0.8%)	0 (0%)	0 (0%)
5 years $N = 404$	0 (0%)	4 (1.0%)	0 (0%)	0 (0%)

The possibility of working with a 5-Hz Nd:YAG laser significantly decreases the duration of the treatment; however, the greater frequency of pulses applied over the course of the vein results in increased pain. This symptom is classified as a low level one, as the estimation tends to soften and patients do not remember the treatment as being as painful as in the previous evaluation. That is, patients tend to consider that pain was not so strong as time goes by.

The interaction mechanism between the wall of varicose veins, POL foam, and 1064-nm laser irradiation is not well clarified [19–22]. Altshuler reported in 2001 about the need to effectively heat the haemoglobin chromophore so that the vessel wall, which acts as a target, receives sufficient thermal effect to induce irreversible damage due to protein coagulation [23]. In order to achieve blood heating, Altshuler first and Bäumler [24] later, clinically indicated how to work with the laser appropriately and focus on the following points:

(i) The diameter of the spot must be greater than the diameter of the vessel. (ii) The fluence must be sufficient to heat the chromophore, but not excessive in order to prevent it from coagulating. If this occurs, the thermal transmission decreases abruptly and the vessel wall is not heated. (iii) Lastly, pulse must be sufficiently long in order to allow the heat to denature the proteins corresponding to the vessel's structure [19–22].

The control carried out 5 years after treatment and the efficacy observed with the persistence of effects and closure of the veins follow Altshuler's expectations. However, in order to reach irreversible thermal damage of the varicose vein wall, we have considered that it is more convenient to use relatively low fluences in each of the laser pulses. The series of pulses, when added together, complete an accumulative thermal effect capable of progressively, but consistently, achieving the thermal propagation which affects the protein structure, thereby denaturing it. Consequently, vessel coagulates and remains closed over time [25, 26].

On the other hand, upon injection in the vein, POL as nonionic surfactant forms a lipid bilayer that causes disruption of the cell surface membrane dependent of its concentration; it activates calcium signalling and nitric oxide pathways and produces endothelial cell death [27]. This achievement might be augmented by the effect of Nd:YAG pulsed laser radiation, whose mechanism of action to assist the drug administration in different therapies was lately explained also by the effect of lasers on the microfluidic properties of the cells. There are theories showing that pulsed laser radiation induces changes of the cell membrane and forces it to admit the medicine by convection. If sent directly on tissue, a laser beam is supposed to produce water nanolayers in the cells which favour drug convection through the cell membranes [28–31].

Hypothetically, POL would give rise to the development of a resonance effect between the fraction of ethanol from the commercially available Aethoxysklerol® and the emission of the 1064-nm Nd:YAG laser [9]. Ethyl alcohol has significant absorption peaks at 900, 1000, and 1200 nm. At 1064 nm, absorption could be carried out by ethanol and by the rest of the chromophores, such as haemoglobin and methaemoglobin although melanin would absorb the 1064-nm wavelength, but to a lesser degree. However, at around 250 nm, there is an absorption peak of POL itself. In this way, the effects would be the consequence of a nonlinear absorption which could also occur in the tissue, and which would translate into absorption of four photons at 1064 nm; this would correspond to the transition at 266 nm, responsible for the greatest effect in the tissue [7, 8].

The experimental measurements suggest that the use of foamed POL leads to the increase of laser radiation optical path in foam sample by light scattering. This fact causes an increase of total absorption, since this is proportional with the product between absorption coefficient, optical path length in the sample, and concentration of the absorbent (according to Lambert-Beer's law). Laser energy absorption in foam can be boosted by the multiplication of impacts of photons at collisions with gas bubbles. Moreover, under these circumstances, the number of changed POL molecules could also increase [32].

As a result of the foaming process, FTIR spectra have highlighted vibrational changes of POL molecules, respectively C–H out-of-plane bending and C–O–H bending. Furthermore, the FTIR spectrum of POL microfoam

prepared after 10 min of laser beam exposure exhibits the long chain bending and C–O stretching along with sp^3 C–H stretching vibrations [33].

By discharging laser pulses on the tissue, a progressive heating occurs, starting with absorption of haemoglobin chromophore. POL microfoam induces endotheliitis, which would make the vessel more sensitive to thermal propagation of laser irradiation effect derived from the high frequency of the used pulses [16]. This effect has been confirmed by our group through spectroscopy studies [9]. The fact that the clearance obtained in class II and class III varicose veins was greater at 3 years in comparison with the third month, as indicated in the previous report [7] and that effects are maintained later at 5 years, would indicate the existence of continued vascular sclerosis, with a progressive, effective, and stable formation in the long-term follow-up.

On the other hand, we did not precisely quantify the role that POL foam scattering may play. Likewise, we do not know the effect, on tissues, of the resonance of Nd:YAG laser with ethanol fraction existing in POL sample. Also, in a certain way, the greater distribution of thermal effect caused by laser pulses and the increase of scattering would contribute to pain being tolerated by patients, without the need to use any type of anaesthesia. In our opinion, the application of cold air in addition to the cooling effects produced by the chamber of laser nozzle prior to laser treatment, or the anaesthetic effect attributable to POL itself, contribute to prevent pain from being unbearable during treatment [21].

The discrepancies that we have observed in the analysis of the ratings from the three independent evaluators concerning the level of satisfaction expressed by patients are not significant in the second statistical study. This would explain the low level of withdrawals and the agreement to undergo control after 5 years.

We consider that one of the most interesting points of combined POL + laser method is that it allows the complete treatment of legs to be finished in practically one single session. The possible toxicity of POL is decreased due to its use at low concentration (0.3%). A second treatment session, 3 weeks after the first, is a touch-up session, as it allows residual venulectasias with a diameter lower than 4 mm to be eliminated. With these two treatment sessions, results are effective and are maintained in the control performed 5 years after treatment.

In conclusion, the POL + 1064-nm Nd:YAG laser treatment can be considered an effective alternative treatment, especially for those patients who present numerous varicose veins of various classes which are extended in both limbs.

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Compliance with ethical standards

The interview and study methodology were approved by the Ethics Committee of the Fundación Antoni de Gimbernat, and all patients who agreed to participate at control visit for evaluation of the results signed an informed consent form.

Conflict of interest The authors declare that they have no conflict of interest.

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