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PHOTODYNAMIC THERAPY IN THE TREATMENT OF VARICOSE VEINS

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INTRODUCTION

Sclerotherapy has proven to be an effective, and safe method for many years in the treatment of varicose veins of the lower limbs. This method resolves vessel lesions of any calliper. However, the presence of clots, persistent haemosiderin spots, and the high number of sessions required, represent the "less satisfactory" effects, which, have, in part, been ameliorated, by the increasing use of sclerosing solutions in the form of foams. Nevertheless, despite the excellent advantages and scarce drawbacks of sclerotherapy, there has always been an active search for other alternatives that could improve this technique.

On the other hand, the contribution of the ND:YAG laser and other type of lasers, to the treatment of vascular lesions of the lower limbs, has felt short to meet the expectations prompted by a vanguard high-cost technology. The limitation in vessel calliper imposed by this therapeutic modality, the recurrence rate, and the pain associated to the treatment, prevent this modern technique from becoming a consolidated addition to the therapeutic arsenal, which is yet to happen.

The aim of our study is to present a new procedure for the treatment of leg veins based on the combination of the two aforementioned techniques. This new procedure combines the well established action mechanism of chemical sclerotherapy with that of

photosclerotherapy. As we will now explain, the method here depicted, is based on three fundamental effects:

- The biochemical transformation of haemoglobin into metahaemoglobin in the presence of intravenously injected polydocanol. Metahaemoglobin presents a much higher absorption coefficient against the elemental emission of 1064 nm Nd:YAG (a biochemical change, which in turn, induces a change in its physical behaviour).

- The presence of the actual polydocanol, whose absorption coefficient against an elemental emission of 1064 nm Nd:YAG, is higher than that of pure haemoglobin (a physical change).

- The presence of intravascular polydocanol foam changes the surface tension of the intravascular fluid, making it behave as a light superconductor (a physical change).

This new treatment, which we have called "PHOTODYNAMIC VEIN THERAPY", optimises the therapeutic performance in vein pathology of the lower limbs by inducing biochemical and physical changes that modify the composition and response of the target chromophore in the presence of an elemental emission of Nd:YAG (1064Nm). Its clinical basis and utility of this brand new technique are the subject of this paper.

FUNDAMENTALS

The Nd:YAG laser has been shown to be effective in the treatment of venous dilations of up to 4 mm of the lower limbs, inducing the release of cytokines (hps70 and GTF2) with dermal repair and vessel reabsorption (Saddick) (Figures 1 and 2).

Nevertheless, the low absorption coefficient of Hg for 1064 nm make it necessary for clinicians to use high fluencies with a higher risk of unwanted thermal damage, hypo or hyperpigmentary sequelae and significant discomfort during the treatment. The low absorption coefficient of Hb prevents access to vessels greater than 4 mm in diameter.

Our recently adopted working guidelines, based on the "*Extended Theories of Selective Photothermolysis*" (Altshuler), have lead us to gain further understanding on "heater" characteristics (target of the laser emission). On the one hand, we should avoid a sudden and excessive heating that would cause coagulation, which, would stop the transmission of heat to the target (therapeutic objective), given

that venous thrombosis is followed, on most cases, by recanalisation and re-permeabilisation of the vessel.

Studies carried out by Mordon show that the heating of Hb causes it to change into metahaemoglobin (with an absorption coefficient 3 to 4 times higher than that of haemoglobin), contributing to the first optimisation factor in the treatment of varicose veins using the Nd-YAG laser.

Previous studies have described that the use of a detergent sclerosant (Aethoxysklerol or polydocanol) induces the formation of fast-elimination uroporphyrins (Van Dam). In the same line, our initial studies and the studies conducted by Miyake, appear to suggest that polydocanol also causes an increase in metahaemoglobin. In any case, be it due to the increase in uroporphyrins or to the increase of metahaemoglobin, the absorption coefficient of our heater increases 3 to 4 times above the baseline absorption coefficient of haemoglobin.

Additionally, polydocanol -in microfoam form- causes, depending on the existing surface tension, an increase in thermal transmission through the submolecular microwholes (Ebbensen).

As discussed previously, the choice to use a laser system in sclerosis for the treatment of varicose veins, is based on faster and longer-lasting therapeutic results, especially, as the performance of the Nd:YAG laser improved.

OBJECTIVES

The purpose of our study is to improve the capture of energy by blood and to improve the transmission of heat to the vessel.

The term "Photodynamic Therapy in Varicose Veins", as applied to the treatment of vein dilatations, is defined as a process that optimises the photothermal effect of the Nd:YAG laser emission. This optimisation is achieved by injecting polydocanol foam into the vessels to be treated prior to the actual procedure.

The aim of this study is to show the biochemical changes resulting from the administration of polydocanol that are responsible for the greater absorption of the energy transmitted by the Nd:YAG laser. The entire process achieves better results in the treatment of varicose veins, with fewer failures and a lower incidence of secondary effects.

MATERIAL AND METHODS

150 patients were studied over a period of 2 years. Patients were distributed into three groups, of 50 patients each (mean age 43.7 years, with peaks at 17 and 74 years). According to gender, there were 46 men and 104 females. Our patients were assigned to three different groups:

Group 1: patients with truncular varicose veins

Group 2: patients with reticular varicose veins

Group 3: patients with micro varicose veins or telangiectasias

Protoporphyrin IX and intraerythrocytary metahaemoglobin values were determined before and after injecting polydocanol microfoam.

The absorption for a 1064nm Nd:YAG laser emission in total blood was determined and compared against that of total blood with polydocanol in liquid state and total blood with polydocanol in a microfoam form.

All our patients were assessed and treated using colour Echo-Doppler (Siemens) (Fig. 3 and 4) in a treatment room especially designed for that purpose.

The treatment technique was carried out by means of an intravenous injection of polydocanol microfoam at 0.5% for truncular veins and at 0.3% for the remaining cases. Foam polydocanol was obtained by passing the polydocanol repeatedly between two syringes that were connected by way of a 3-way stopcock (Figure 5), following the conventional sclerosis procedure.

We used a Nd: YAG laser from Laserscope, models Geminia and Lyra "I" (Figures 6 and 7), and the Cryosmart cooling system.

Dosimetry of laser Nd: YAG:

Group 1: truncular veins

Spot: 5 mm

Fluence: 100 J

Pulse: 100 ms

Group 2: reticular veins

Spot: 3 mm

Fluence: 200 J

Pulse: 80 ms

Group 3: telangiectasias veins

Spot: 2 mm

Fluence: 300 J

Pulse: 60 ms

In truncular veins, the leg was wrapped in 4 layers for one week, following the usual procedure. For the rest of conditions, compression with 140 DIN elastic stockings was applied and maintained for 4 weeks.

Subsequent sessions were administered at 60 days intervals until complete remission of the clinical symptoms. Follow up visits were carried out every 4 months for a period of 2 years after the initiation of the research.

The criteria for complete results were based on Echo-Doppler examination for truncular veins and on a clearance greater than 90% of dilated veins in the remaining cases.

RESULTS

1) Number of sessions:

Truncular veins: 1 session, excepting 2 patients who received 2 sessions.

Reticular veins: 2, 3 +/- 0.8 sessions.

Telangiectasias: 3, 4 +/- 1.2 sessions.

2) Blood assessments:

Metahaemoglobin: Mean basal values were 0.87 mcg% and after the administration of polydocanol, the mean value raised to 4.17 mcg% (Figures 8 and 9).

Protoporphyrin: Mean basal figures were 37.6 mcg% and after the administration of polydocanol, the mean value raised to 46.8 mcg% (Figures 10 and 11).

Laboratory results were statistically analysed using the Wilcoxon test. Mean values of both metaheamoglobin and protoporphyrin increased significantly ($p > 0.003$).

3) Assessment of Nd:YAG laser absorption:

The absorption coefficient of polydocanol at 0.5% in total blood was 4 times greater than that of baseline blood.

The absorption coefficient of total blood in the presence of polydocanol microfoam was 29 greater than that of baseline blood (Figures 12 and 13).

The significant increase in absorption in the presence of polydocanol microfoam can be owed to the superconducting phenomena caused by the superficial tension of the foam (Ebbensen and Hillebrandt).

4) Clinical results:

During the application of the treatment, Echo-Doppler examination demonstrated the absence of flow with closure of the vessel (Figures 14 and 15).

In most cases, effective thermal damage was achieved without intravascular thrombosis (Figures 16 and 17). Marked intravascular thrombosis, accompanied by haemosiderin pigmentation, was observed in some isolated cases (Figures 18 and 19).

The disappearance of inflammatory signs and the vessel's reabsorption occurred between the 4th and 8th week.

Figures 20 to 31 show the excellent clinical results obtained in truncular veins, reticular veins and telangiectasias.

5) Secondary effects:

- a) Pain: Tolerance to the laser system and to the injection of foam was similarly good and/or acceptable in all our patients, at the described dosimetry.
- b) Burns: 3 cases of first degree burns in patients with telangiectasias, which resolved satisfactorily within 4 weeks. If we take into account that the average number of shots per patient was 1,200, the presence of burns accounts for only 3 incidences in about 180,000 shots.
- c) Hypopigmentations: One 2 mm shot in telangiectasias in a patient with phototype IV. As stated before, the incidence is 1/180,000.
- d) Hyperpigmentations:

Truncular veins:	6 patients (12%)
Reticular veins:	5 patients (10%)
Telangiectasias:	1 patient (2%)

Hyperpigmentations resolved in 9 +/- 3 months, excepting one case in which the Alexandrite Q-switched laser was used (Alex Lazr Candela®). Hyperpigmentations affected 8% of the patients in our series.

e) Intravascular thrombi

Truncular veins:	12 patients (24%)
Reticular veins:	2 patients (4%)
Telangiectasias :	1 patient (2%)

The presence of intravascular thrombosis affected 9.33% of patients in the series.

All patients suffering from truncular and reticular veins underwent a puncture thrombectomy 4 weeks after the treatment.

f) Matting:

Truncular veins:	1 patient (2%)
Reticular veins:	2 patients (4%)
Telangiectasias :	2 patients (4%)

3.33% of the patients presented matting.

g) Failure rate: (0%), we achieved elimination of all truncular and reticular veins and telangiectasias.

h) Recurrence rate: there have been no recurrences of the vascular lesions in any of our patients throughout the 2 year follow up period.

DISCUSSION AND CONCLUSIONS

The measurements performed haven proven that the absorption coefficient of our "target" (varicose vein) in the presence of an emission of Neodimium YAG laser (1064 nm) increases 29 times if we administer an endovenous injection of foam polydocanol into the vessel prior to the treatment.

This increase in the absorption coefficient is brought about by:

- An increase in the intraerythrocytary concentration of metahaemoglobin and protoporphyrin IX that is four times above the normal concentration.
- The superconducting effect of the light provided by the polydocanol microfoam that causes changes in the superficial tension of the intravascular fluid.

The thermal damage caused by the laser is more permanent than the thrombosis caused by standard sclerosant solutions, particularly in small-sized vessels. Intravascular thrombosis can be recanalised over the course of time in a high percentage of cases.

Objections to the treatment of varicose veins with laser systems have been eliminated, namely:

- Limitation of the vessel calibre
 - Intense pain
 - Skin lesions
 - High cost
1. The presence of polydocanol foam in total blood significantly improves the performance of the emitted light energy. It also increases the thermal damage in the vein wall, effectively reaching larger vessels.
 2. The high performance of the light absorption allows the clinician to work with lower fluencies, significantly decreasing pain and increasing the integrity of the skin surface. This results in less pain and fewer skin lesions.
 3. The high performance of the light absorption allows the clinician to work with smaller spots, resulting in less discomfort. We have been able to show that the pain experienced by the patient is directly proportional to the spot size. To date, the isolated treatment of varicose veins with the Neodimium YAG laser has required the employment of larger spot sizes. This is due to the fact that larger spot sizes enhance the performance of the emitted light energy in deeper lesions.
 4. This decrease in pain may be associated with the anaesthetic effect of the polydocanol. We should not forget that originally polydocanol was used as a local anaesthetic.
 5. A significant enhancement is achieved in the treatment of varicose veins by using Nd:YAG laser photodynamic therapy, which involves the joint application of laser and an intravascular injection of polydocanol foam. This combined therapy results in fewer sessions with optimal results. The permanence of the results has been maintained over the 2-year study period.

Photodynamic therapy of leg veins has proven to be an effective method for the treatment of varicose veins of the lower limbs. The procedure is performed on an outpatient basis and it does not restrain the patient who can resume his or her normal routines. This technique does not require any type of anaesthesia and is well

tolerated by the patients. None of the 150 patients treated have presented a recurrence over the 2-year follow up period. Lastly, secondary effects are similar or less severe than those associated with any of the other currently employed methods.