

Study of Endotelon in Functional Manifestations of Peripheral Venous Insufficiency

Results of a study double blind for 92 patients

Non complicated venous insufficiency in the lower extremities, accompanied or not by valvular insufficiency, manifests itself essentially by a functional symptomatology.

Reading the bibliography relating the clinical studies in this pathology we see that the judging criteria used are multiple, at least in their terminology (heaviness, tiredness, pain...) to the point that they are poorly defined and sometimes redundant.

One of the difficulties of a therapy trial in venous insufficiency resides in the appreciation of the intensity of the troubles, those depending only on the interrogation.

The goal of this present work is to confirm the effectiveness of Endotelon using a valuation grid that is simple and precise in evaluating the functional manifestations and parallel to that studying the variations of the plethysmographic parameters during the course of the experiment.

Endotelon is a vasculo-protector that came onto the market in 1978. It's principal active ingredient are oligomers procyanidolic (OPC) which are vegetable extracts belonging to the chemical class flavan.

Materials and Method

Patients

In order to insure the necessary homogeneity of the patients participating in this study we included those who had complained of heaviness or sluggishness in the lower extremities. They had to be between the ages of 16 and 65 and been treated for any specific phlebologic (stripping or sclerosis) nor suffered any venous complications (deep or superficial thrombosis) during the six months preceding their acceptance into the study. The Doppler examination eliminated those patients with profound valvular insufficiency. Also eliminated were those patients suffering from post phlebitis disease, complicated varicose veins and lymphatic anomalies. Any treatment for the veins had to have stopped at least 4 weeks before the study and for reasons independent of the study.

Treatment

The method used was that of a controlled study with a double blind against placebo with attributed treatments drawn by lots.

Two groups were formed: Group "E" received 300 mg a day of Endotelon, 100 mg taken three times a day and Group "P" received the placebo taken in the same doses. The treatment lasted 28 days.

Judging Criteria

The valuation grid appreciating the venous functional troubles were comprised four distinct signs, each with a rating between 0 and 3 depending upon the intensity. These four signs were:

1. Heaviness or any other assimilative symptomatology clinically to pain (fatigue, swelling).
2. Paresthesia (tingling or creeping sensation) or any other sensitive manifestation felt by the patient.
3. Nocturnal cramps

4. Subjective oedema, that is to say any oedema felt by the patient such as a swelling of the foot that is not necessarily detectable by the examiner. The valuation for this sign was stronger than the one appearing right after the patient got up from bed in the morning.

The result was determined by the sum of the four valuations described above and could therefore vary between 0 and 12 points. The principal criterion was the difference Δ between the two results established by the same clinician for any given patient: $\Delta = \text{result DAY 28} - \text{DAY 0}$.

We defined a therapy success as a clinical amelioration more than 50% as compared to the importance of the initial symptomatology (fig. 1) or:
Success - - $\Delta > \text{Result DAY 0}/2$

From a paraclinical point of view a venous plethysmograph was given to each patient at time DAY 0 and DAY 28. The parameters analyzed were, in classic fashion, the filling indication (IDR), the variation of maximal volume (Dvmax), the waste indication (IDV), the time of semi waste (T_V) and the compliance calculated as the average of the IDR at three different pressures 30, 50 and 70 mmHg. All the apparatus used were the plethysmograph with mercury gauge.

Results

Unfolding of the study

The study was done from October 1983 to October 1984 in three vascular exploration laboratories in the Parisian region.

Ninety-two patients took part with twenty in one center and thirty-six in each of the other two centers.

Fourteen patients (15%) were kept out of sight, which corresponds to a habitual figure in that the conditions of the study (out patient treatment) and are statistically acceptable.

Seven observations were recognized as non-exploitable, three times for reasons independent of the study, four times for premature interruption because of undesirable effects. We will go into further detail of these four later on.

The statistical analysis of the study is therefore for 71 patients in which 67 were females with an average age of 40 who have suffered from venous problems on the average for seven years. In 9 of the patients (13%) we found phlebotic past histories and in 44 (62%) there were varicose diseases.

Comparability of the Groups

When the general characteristics (age, sex, and obesity) are considered or the characteristics dealing with venous diseases (age of the disease, venous past histories, presence of varicose veins), the two therapy groups E and P are comparable (Graph 1). Only one characteristic (the number of patients taking the treatment) is different between the two groups (it's higher in group P).

Effect on the Functional Manifestations

The result of the functional troubles starts at Day 0 from 3 to 11 for group E and 2 to 10 for group P (figure 2). Before the start of the treatment the average result is 6.9 points in group E and 5.8 points in group P.

The initial graveness of the functional troubles is slightly higher in group E. We admit nonetheless that in view of the distribution of the results that the two groups are stemming from the same

population of patients. After four weeks of treatment the average result is 2.3 points in group E and 3.2 points in group P, representing a drop of 4.6 points in group E and 2.6 points in group P.

The principal criterion (variation between the results Day 28 and Day 0) goes from -9 to 0 in group E and from -8 to +3 in group P (figure 3).

The therapy success as it was defined previously is observed in 24 of the 32 patients in group E (75% of the cases) and only 16 out of 39 patients in group P (41% of the cases). This difference is very significant ($p < 0.01$).

If we consider only the oedema symptom that is present in 43 out of the 71 patients, the oedema goes down in 13 of the 20 patients taking Endotelon (65% of the cases) and in 8 of the 23 patients taking the placebo (35%). The difference here is also significant ($p = 0.05$) (figure 4).

Effects on the Plethysmographic Parameters

The ensemble of the average values is shown in Table 2. From a statistical point of view there is no significant difference in evidence. Also, the analysis is going to limit itself to a description of the observed results. Three results bear emphasis:

- ❖ The reproducibility of the examination is verified: In effect the group taking the placebo the variation between Day 0 and Day 28 doesn't differentiate statistically from zero no matter which parameter is considered.
- ❖ For four parameters the variations observed between Day 0 and Day 28 are of the same type in both groups. On the other hand it is interesting to note that the compliance (that which reflects venous distension) goes up between Day 0 and Day 28 (correlation Day 28/Day 0 = 1.03 from right to left) in the group Placebo while at the same time it goes down (correlation Day 28/Day 0 = .95 on the right; = 0.90 on the left) in the group Endotelon.
- ❖ The reduction of the compliance corresponds, in the population of the patients studied, a clinical amelioration.

In effect, in the sub group "clinical success", the average variation of this parameter is from -0.12 (± 0.8) between Day 0 and Day 28 and in the sub group "failure" this variation is from + 0.13 (± 0.7) (members left and right pooled together).

Tolerance

Among the 71 patients who completed the treatment 7 said they felt undesirable side effects:

- ❖ Six patients from the Placebo group complained of diverse problems (constipation, epigastralgies, astenia, dry mouth and nausea)
- ❖ One patient from group Endotelon reported stomach pains.

In order to be complete we should remember that four patients out of the 78 had their treatment interrupted prematurely because of undesirable side effects.

- ❖ One patient from the Placebo group complained of stomach pains.
- ❖ Three patients from the Endotelon group (stomach pains, headaches and scalp itch).

All in all the undesirable side effects that were reported were neither specific nor widespread in the principle active group.

Discussion

The factors that are susceptible in modifying the functioning symptomatology of the venous insufficiency in the lower extremities are many. We note here the outside temperature, the degree of physical exercise, diet, the height of heels, etc.

To better appreciate the effect of the therapy it was researched to obtain the slightest variability possible between subjects:

- ❖ The same clinician for any given patient.
- ❖ The examination practiced during the same phase of the cycle (interval of four weeks between examinations).

Uncontrollable factors were spread out evenly between the two therapy groups due to the drawing of lots.

With all of these precautions were taken it appears that using a simple grid with four essential categories (heaviness, paresthesia, cramps and oedemas) from 0 to 3 permitted us to follow in a sensible fashion the medical effects of the therapy and to draw from it the essential usefulness.

Conclusion

Endotelon was studied during a comparative trial using a double blind against placebo on 92 patients with peripheral venous insufficiency. The effectiveness was studied on 71 of the 92.

The strict selection criteria gave us a homogenous group, predominantly female with an average age of 40 suffering from venous insufficiency for the last seven years. There was no valvular insufficiency or a past history of thrombosis or sclerosis.

The therapy lasted four weeks and the dosage was 300mg a day.

The results of the functional signs decreased on the average 4.6 points in the Endotelon group against 2.6 in the placebo group between Day 0 and Day 28.

A successful therapy described as a decrease in the results plus half of the initial result was observed in 75% of the patients using Endotelon and 41% of the patients using a placebo.

The effectiveness of Endotelon demonstrated by comparing it to a placebo throughout the therapy permits us to prescribe just such a treatment for patients suffering from venous functional problems.

Note: Endotelon is a French drug made from OPC extracted from Grape Seeds