

DOUBLE BLIND TEST OF ENDOTELON IN TREATING CHRONIC VENOUS INSUFFICIENCY

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(Summary appears in English on last page)

The work done in clinical pharmacology have shown that the OPC (Endotelon) have the effects of capillary resistance (Professor Hugonot, on capillary permeability [Professor Lagrue, Professor Agache}) as well as the properties on the tonicity of vascular walls (Professor Paitel).

The clinical tests done on the functional manifestations of venous insufficiency in the lower limbs allowed us to put into evidence the favorable effects of this of the product in this indication.

In light of what will precede we undertook to study the efficiency of OPC in chronic venous insufficiency using a controlled double blind in comparison with another product of reference.

Experimental Protocol

Definition of the conditions of the study

We decided to do this study on two parallel groups of 25 patients each with one group getting Endotelon (150mg/day) and the other getting 450mg a day of semi-synthetic Diosmine. The capsules containing Diosmine looked and tasted just like Endotelon.

The jars containing each of the two products were numbered in a randomly ordered sequence and given to each patient based upon his chronology at the beginning of the test.

Choosing the subjects.

The goal of the study was to measure the activity of Endotelon on the functional manifestations linked to chronic venous insufficiency. These manifestations were observed in an OB-GYN clinic where we defined a certain number of criteria had to be met by the subjects taking the treatment.

Each subject in this test was placed in one of the three following categories:

- ✓ Varicose veins from pregnancy
- ✓ Varicose veins from oral contraception
- ✓ Functional manifestations of chronic venous insufficiency

Excluding Criteria

Patients fitting one or more of the following criteria were excluded from the test:

General Criteria

- ✓ Younger than 20 or older than 80 years old
- ✓ In the first two months of pregnancy
- ✓ Unstable, undisciplined or neurotic

Criteria linked to another vascular pathology of the lower limbs

- ✓ Arteriopathy
- ✓ Lymphoedema
- ✓ “Painless” varicose veins

Criteria inherent to the associated therapies

- ✓ Salt-free diets
- ✓ Diuretics
- ✓ Anti-inflammatory
- ✓ Any other major therapies, medical or surgical that could disturb the test

Therapeutic Modules

Two successive phases were foreseen after the patients entered into the test.

Preliminary Phase – A

In order for the patients to not know the exact start time for taking the active product an initial *simple blind* placebo phase was put into place. The placebo resembled the active product in every aspect and was prescribed in the same frequency of 3 times a day. This placebo sampling constituted Condition A and lasted one month (Day 0 to Day 30).

Real Phase – B

Succeeded the previous phase and lasted 30 days (Day 0 to Day 30) with a dosage of 3 capsules a day.

Criteria for Evaluating Results

Judging the therapeutic effects was done before and after one month of treatment was based on several criteria.

Functional Criteria

Typical “pain” from venous insufficiency:

Takes into account disagreeable sensations in the lower limbs causing complaints a few variations of which are listed below:

- ✓ “Heaviness” (sensation of “heavy legs”)

- ✓ “Sluggishness” (sensation very close to the above but with the added significance of feeling a lack of agility, a feeling of being “nailed to the floor”)

These symptoms are of a venous character, that is to say they are linked to an orthostatism with maximum sensation during the evening, less so when resting, at an incline and conversely walking on flat ground.

- ✓ Atypical pains: pruritus, nocturnal crampes, from working, diverse feelings of tiredness.
- ✓ A feeling of “swelling”: tension sensation, infiltration, and painful oedemas.

All of these criteria were duly noted during an office visit as a function of their intensity using the following barometer:

- 0 = absent
- 1 = light
- 2 = average
- 3 = severe or intense

Objective Criteria

- ✓ Oedemas:

Done by measuring the leg at two levels (15cm above the interline intercondylian) more or less as a function of the measurements.

- ✓ The thick layers of hypodermis
- ✓ The eventual coetaneous signs: vericose veins, capillaritis, skin blotches, and eventually ulcers.

Analytical Procedure

This study was submitted to a statistical study:

On one hand to recognize the homogeneous of the two groups which were necessary to compare the therapeutic effects of the two products by analyzing:

- ✓ The initial criteria we needed to know:

Age, sex, weight, previous pregnancies, the actual state of pregnancy, use of oral contraceptives, previous cases of phlebitis.

- ✓ The functional criteria and objectives at Day 30, that is to say the shared placebo period for all the patients.

If the two lots are found to be homogenous from following the evolution of the criteria at Day 30 and Day 60 then the criteria will be compared on Day 60.

In following the cases the comparison of the two groups was effectuated by one of these three procedures:

- ✓ Either by comparing the average value of the two groups.
- ✓ Either by comparing data from zero to the average and seeing the paired differences.
- ✓ Either by comparing one observed distribution to another.

Results

Homogeneity of the two groups.

This homogeneity analyzes by comparing the criteria of the two groups at Day 30.

A - Descriptive Criteria Table

	Endotelon	Diosmine	Conclusion
Number of Patients	25	25	
Age	35.4 ± 6.86	33.4 ± 4.9	N.S.
Sex	F	F	
Weight	63.67 kilos	64.4 kilos	N.S.
Prior Pregnancies	23	23	
Nr of Prior Preg.	2.52	2.24	
Pregnancy State	10	10	
Oral Contraceptive	38%	44%	N.S.
Prior Phlebitis	16%	12%	N.S.

B – Subjective Criteria Table

Symptoms	Products	Intensity at Day 30			
		0	1	2	3
Heaviness	Endotelon	0	5	20	25
	Diosmine	0	7	25	18
Sluggishness	Endotelon	0	7	21	22
	Diosmine	0	9	22	19
Cramps	Endotelon	30	10	7	3
	Diosmine	34	10	5	1
Listlessness	Endotelon	41	4	3	2
	Diosmine	42	6	0	2
Swelling	Endotelon	2	11	34	3
	Diosmine	1	11	33	5

The two groups were homogenous after Day 30 following the placebo phase for five criteria (heaviness, sluggishness, cramps, listlessness and swelling). Pruritus was abandoned due to the lack of number of cases.

Symptoms	Endotelon	Diosmine	Statistical Significance
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	Number	Number	
	25	25	
Heaviness	4.81 ± 0.83	4.44 ± 1.04	N.S.
Sluggishness	4.64 ± 0.90	4.40 ± 1.04	N.S.
Cramps	1.32 ± 1.18	0.92 ± 1.15	N.S.
Listlessness	0.64 ± 0.99	0.48 ± 1.04	N.S.
Swelling	3.52 ± 0.71	3.68 ± 0.90	N.S.

C – Objective Criteria Table – Varicosity Objectives

Intensity	Endotelon	Diosmine	Results
0	17	20	N.S.
1	26	23	N.S.
2	7	7	N.S.
3	0	0	N.S.

The comparison of the other objective criteria was abandoned because they were too constraining (hypodermititis, capillaritis).

The conclusion is that the two groups were homogenous at Day 30 according to the three criteria (descriptive, functional and objective). These conditions were necessary in order to compare the therapeutic effect of the two drugs and to compare the two groups after one month of treatment.

Clinical Results

A – The evolution of the Endotelon group at Day 30

Intensity	Heaviness	Sluggish	Cramps	Listless	Swelling	Varicose
0	0	0	30	41	2	17
1	5	7	10	4	11	26
2	20	21	7	3	34	7
3	25	22	3	2	3	0

The Evolution of the Endotelon Group at Day 60

Intensity	Heaviness	Sluggish	Cramps	Listless	Swelling	Varicose
0	34	35	50	48	37	16

1	16	14	0	2	13	32
2	0	0	0	0	0	2
3	0	0	0	0	0	0

All of the functional systems had improved after one month of treatment of Endotelon using a daily dose of 150mg divided into 3 capsules. The comparison between Day 30 and Day 60 is statistically significant.

All the symptoms had improved using Endotelon. After one month of treatment 65% of the patients no longer showed any sign of vascular insufficiency.

Evolution of the Criteria of the Diosmine group at Day 30

Intensity	Heaviness	Sluggish	Cramps	Listless	Swelling	Varicose
0	0	0	34	42	1	20
1	7	9	10	6	11	23
2	25	22	5	0	33	7
3	18	19	1	2	5	0

Intensity	Heaviness	Sluggish	Cramps	Listless	Swelling	Varicose
0	22	22	44	48	25	20
1	26	25	6	2	25	23
2	2	3	0	0	0	7
3	0	0	0	0	0	0

Evolution of the Criteria of the Diosmine group at Day 60

In this group the evolution of the studied parameters starts of in the direction of improvement except for the varicose criteria, which is not modified.

The comparison of the two different results of the two groups at Day 60 will point out to us which product is more efficient.

Evolution of the Criteria at Day 60 of the Two Groups

	Endotelon				Diosmine			
	Intensity				Intensity			
Symptoms	0	1	2	3	0	1	2	3
Heaviness	34	16	0	0	22	26	2	0
Sluggish	36	14	0	0	22	25	3	0
Cramps	50	0	0	0	44	6	0	0
Listless	48	2	0	0	48	2	0	0
Swelling	37	13	0	0	25	25	0	0

Varicose	16	32	2	0	20	23	7	0
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Endotelon appears to be more effective in four categories: Heaviness, sluggishness, cramps and swelling.

Of all the functional criteria Endotelon relieved more than 65% of the patients compared to 45% for other group.

This work therefore shows that Endotelon has a greater activity when compared to semi-synthetic diosmine on the functional problems attained from venous insufficiency in the lower limbs.

Delay and Duration of the Activity

In addition to the measure of efficiency of these drugs in the treatment of peripheral vascular insufficiency the author also studied the delay of improvement of the functional signs as well as the residual therapeutic effects after the treatment had ended.

Improvement Delay

For those patients treated with Endotelon the improvements of the different criteria appeared on the average 9 days after beginning the treatment compared to 14 days for the other treatment. This is statistically significant.

Prolongation of the Favorable Effects

For those patients treated with Endotelon the therapeutic effect continued 15 days after stopping the treatment. Those treated with Diosmine had the therapeutic effects for only 10 days. This is statistically significant.

Those patients treated with Endotelon felt relief much more rapidly and much more efficiently than those in the other group.

Tolerance

Side effects from taking both products were minimal with nothing recurring after stopping the treatment.

There were a few fleeting gastrological problems with both products and a few felt slightly dizzy and there was one small case of nausea in the Endotelon group.

Pregnant women should have no qualms about taking Endotelon.

Conclusions

It would appear that the 50 female patients who took 150mg of Endotelon daily to counter attack chronic venous insufficiency in the lower limbs for thirty days greatly benefited from this treatment.

The comparison with the other product (Diosmine) and the statistical analysis done of the different criteria shows that therapeutic qualities of Endotelon are more intense, more constant and show that it can be usefully employed in the treatment of venous insufficiency.