DOUBLE BLIND CLINICAL TRIAL COMPARING THE THERAPEUTICAL EFFICICACY OF THE PREPARATION F-117 (HIDROSMIN) VERSUS DIOSMIN IN THE TREATMENT OF PATIENTS SUFFERING FROM PERIPHERAL VENOUS DISORDERS

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Summary

A controlled double blind clinical trial was performed comparing therapeutic efficacy of hidrosmin versus diosmin in patients suffering from chronic venous insufficiency with varicose sympthomatology in the inferior limbs.

Ten patients were treated with hidrosmin and other 10 with diosmin randomly.

The controls carried out during the trial were as follows: basal control before the beginning of the trial and therapeutic controls on days 15, 30, 60 and 90 of the study. With that aim, clinical examinations and different explorations were performed: phisical exam, phlebography, electrocardiogram, ophtalmological examination and biochemical analyses (hemogram, globular sedimentation rate, platelet counts, etc.).

The clinical therapeutic efficay of hidrosmin in the treatment of chronic venous insufficiency of inferior limbs was superior to the diosmin in most of the studied parameters even though a lower posology was employed.

From a clinical point of view, the clinical improvement in the subjective sympthomatology (heaviness, local tenderness, cramps, parenthesias, etc.) was very superior to the one obtained with the objective signs (phlebography, skin trophism, evolution of the edema, etc.) No significative adverse reactions appeared.

Introduction

The product F-117 or hidrosmin is a soluble derivative of 7-Ramnoglucoside of 5, 7, 3-trihydroxy, 4 metoxyflavone (diosmin), and is pharmacologically characterized by performing a selective activity on venomotricity**.**

Through experimentation, hidrosmin has been proven to perform two fundamental actions: restoration of an adequate venous tone, and the increase of resistance index in microvessels.

By means of these effects, it reduces the caliber of dilated varicose veins and restores valvular functioning.

At the same time as it increases the resistance rate of microvases, hidrosmin controls the excess of permeability, responsible for the appearance of local edemas.

Finally, it has been proven that hidrosmin also has a favourable effect on microcirculation in the sense that it increases erythrocytic deformability and decreases blood viscosity, which helps even more to correct venous stasis**,** starting with the microcirculation unit.

Our objective in this this study was to compare the therapeutical efficacy and clinical tolerance of hidrosmin preparations versus diosmin, in patients suffering from chronic venous processes and venous insufficiency.

Material and method

A total of ten patients were treated with hidrosmin and another 10 with diosmin.

Both the clinical staff who followed the patient's evolution and the patient himself ignored which of the two preparations was being used for treatment.

The employed inclusion criteria were accepting patients of both sexes, aged 25 to 70, who had suffered from venous diseases which could be included in the following clinical patterns: chronic venous insufficiency, varicose syndrome, trophic skin disorders due to venous alterations, postphlebitic syndrome and alteration of oedemas due to difficulties in venous return.

The average age in both groups was 46 ± 9 years for the hidrosmin group and 47 ± 8 for the diosmin group. Their weight was 78 ± 9 kilos in the hidrosmin group and 74,5 ± 4 for the diosmine one. Sex distribution was proportional in both of them.

As a whole, there were no basal differences between the two groups which could justify a different clinical evolution, so both groups were considered homogeneous.

Patiens with severe cardiac, renal or haepatic diseases, pregnant -or possibly pregnant- or lactating women, patients who from the beginning were not able to finish the study or patients with proved hipersensibility to similar medicines were not included in the study.

Medication

Each patient received two kinds of pharmaceutical formulae:

A. A liquid formula to be taken orally in drops

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B. A solid formula in the form of capsules.

Every patient took 30 drops three times a day and a capsule three times a day.

The patients in the hidrosmin group took drops with active substance hidrosmin and placebo capsules, so that they received 600 mg. of hidrosmin a day.

The patients of the diosmin group took capsules with active substance and placebo drops, so they received 900 mg. of diosmin a day.

Guideline for the trial

Once the patient was accepted into the trial, a blank period of at least two weeks was spent, during which the patient did not receive any phlebotropic medication.

Afterwards, an evaluation of the basal state of the patient was performed, including: clinical exploration, phlebography, electrocardiogram, examination of the oculi fundus and analitical determinations such as haemogram, globular sedimentation rate, platelet counts, prothrombine time**,** bilirubin**,** transaminase**,** alkaline phosphatase**,** creatinine**,** abnormal urea and urine and sedimentation.

Clinical and analytical examinations were repeated on the days 15, 30, 60 and 90 of the study. On the 90th day, the specialized explorations were repeated.

The following were especially evaluated in the clinical examinations:

– A.T. the patient's general state, pain, leg heaviness, peripheral pulse in the lower limbs, sensations of local tension, pruritus, cramps, paraesthesias, state of the skin, trophism, skin colour and existence of edemas or ulcers.

The evaluation of clinical parameters has been performed on a scale from 0 to 4, according to the following guidelines:

Absence of sign or symptom: 0
Slight sign or symptom: 1
Medium sign or symptom: 2
Intense sign or symptom: 3
Very intense sign or symptom: 4

The evaluation of the objective parameters was also performed according to this scale.

Discussion of the results

The evolution of the studied parameters is explained in the following.

No changes were observed in the patients' A.T., taken at the time of consultation and, except for a few oscillations which do not have any statistical value, the figures of A.T.s. at the end of the study were similar to those found at the start.

Basal figures of 141/88 were taken at the start in the hidrosmin group, whereas a basal mean of 148/90 was taken for the diosmin group.

The patients' general state was defined as good in all the cases, and was kept likewise until the end of the trial, with no objective variations.

The patients' pain in those limbs involved developed as follows according to the groups:

Control	Basal	15	30	60	90 days
Group					
H	1,4	0,8	0,4	0,2	0,2
D	1,2	0,4	0,4	0,6	0,6

That is, in the hidrosmin group the starting point is a light to medium pain, which develops until reaching a minimum one.

In the diosmin group the start is a less painful, only light, basal situation, and after a temporary recovery, pain increases on the days 60 and 90 of the treatment to reach a worse final situation than in the hidrosmin group.

The sensation of heaviness in the lower limbs developed according to the following chart:

Control	Basal	15	30	60	90
Group					
Hidrosmin	1,8	1	0,6	0,6	0,2 (p<0,05)
Diosmin	1,4	1,2	1,2	1,2	1,2

Starting from a worse basal situation for the hidrosmin group, the achieved improvement is more important than in the diosmin group, where after an improvement during the two first weeks of treatment, the situation is stabilised and finally was worse than in the hidrosmin group (p<0,05, according to Fisher's exact probability calcuation).

As peripheral pulses are concerned, there was no important variation during the treatment, because except for one patient in the diosmin group whose peripheral pulse was weak and did not change during the treatment, the peripheral pulse was easily felt in the rest of the patients.

The sensation of local tension developed as follows:

Control	Basal	15	30	60	90
Group					
Hidrosmin	1,4	1	0,6	0,4	0,4 (p<0,05)
Diosmin	1,2	1	0,6	0,4	0,4

So starting from a worse situation in the hidrosmin group, a similar situation was reached at the end of the treatment.

We cannot evaluate what happened with the pruritus because only two patients in the diosmin group had this feeling, and it had already disappeared by the first control. It did not appear again during the rest of the treatment.

No patient in the hidrosmin group had pruritus; thus there is no comparative value.

The existence of a sensation of cramps developed acording to the following chart:

Control	Basal	15	30	60	90
Group					
Hidrosmin	-	1	0,4	0	0 (p<0,05)
Diosmin	-	0,6	0,4	0,4	0,4

Summarising, it is again something similar to what happens with the rest of the symptomatology, i. e., starting from a slightly worse situation in the hidrosmin group, the patients' state is asymptomatic by the end of the treatment, whereas in the diosmin group, although a certain recovery is achieved, the final situation is not completely asymptomatic.

Paraesthesias develop as follows from the following chart:

Control	Basal	15	30	60	90
Group					

Hidrsmin	0,8	0,6	0,4	0,2	0,2 ($p<0,05$)
Diosmin	0,8	0,4	0,8	0,8	0,8

As the state of the skin and its colour are concerned, there are no important changes during the treatment, although it must be observed that the first level of alteration was never passed in the basal visit or, in other words, alterations found in this respect at the beginning of the treatment were of little importance. Therefore, the fact that there was no noticeable recovery would be logical to a certain extent.

The evolution of oedema is satisfactory in both groups. However, while the perimeter reduction of the limb was achieved in 80% of the patients included in the hidrosmin group, in the diosmin group it only happened in half of the cases. The limb perimeter was normal in 20% of the cases in the hidrosmin group, while it only happened in one case in the diosmin group.

As for the existence of ulcers, there were two patients -one for each group- who showed this damage. The patient in the hidrosmin group recovered favourably but did not achieve complete recovery, passing from a level 2 ulcer to a level 1 ulcer at the end of the treatment. However, in the diosmin group patient, the first level ulcer did not modify, keeping the same level at the end of the treatment.

No important modifications which could justify haemodynamic changes in the lower limbs were observed in the patients' weight,

The performed phlebographic tests did not show relevant differences in any of the two treatments.

There were no electrographic alterations, and the outlines obtained at the end of the study did not change with regard to the basal plot.

The performed analitical controls were within the normal limits, except for some statistically irrelevant modifications.

The patients' cooperation in their treatment was good and using drops as dosage did not represent a problem.

No adverse reactions appeared except in one diosmin group patient who had a sensation of nausea between the third and the sixth day of treatment, which did not oblige to its suspension. It disappeared spontaneously.

Nor were there any alterations in the performed ophthalmological examinations.

Conclusions

The efficacy of hidrosmin in treating venous insufficiency was superior in most of the studied parameters to that of diosmin, even though a lower posology was employed.

It should be observed that the subjective recovery in hidrosmin group patients (heaviness, pain, local tenderness, cramps, etc.) is much higher than it could be expected from the objective data (phlebography, trophism, skin colour, evolution of the oedema, etc.).

No significant adverse reactions appeared.

No analytical, electrocardiographic or ophtalmologic alterations appeared during the treatment.

The pharmacological formula was well accepted by most of the patients and the posology was followed well adjusted to the treatment.

As a whole, patients did not show any kind of intoerance to the employed medication.

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