WIRKSAMKEIT EINER CRÈME MIT CENTELLA ASIATICA UND PINUS SYLVESTRIS ZUR BEHANDLUNG HYPERTROPHER NARBEN UND KELOIDE – RESUMEE EINER KLINISCHEN ANWENDUNGSBEOBACHTUNG

The efficacy of a cream with Centella Asiatica and Pinus Sylvestris to treat hypertrophic scars and keloids – resume of a clinical observation

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KEY WORDS:
Centella asiatica, hypertrophic scars, keloids, therapy, Pinus sylvestris

SUMMARY:
Hypertrophic scars and keloids are especially problematic for patients because they can hinder movement, cause itching and pain and are a constant reminder of the trauma suffered. Although there are numerous types of treatment, none of them are completely effective. Traditional natural medicine has increased the therapeutic arsenal available against different conditions and Laboratorios Catalysis, S.A. from Spain has now developed a new cream whose main components are Centella asiatica and Pinus sylvestris (Cicatrix®), which can be used to treat hypertrophic scars and keloids. In order to assess the effectiveness of the cream, a Phase III double-blind, placebo-controlled and randomized clinical trial was carried out on patients suffering from the aforementioned conditions who had gone to the dermatological service at the Hospital Clínico Quirúrgico Manuel Fajardo (Havana) between October 2009 and October 2010.

90 people who had satisfied the inclusion criteria were selected and women who were pregnant, breast feeding and children were excluded. The clinical response evaluation was based on a reduction in the height of the scars and the occurrence of adverse events. The initial variable composition of the groups was homogenous, except for age. The cream was to be applied three times a day, according to the prescribed regimen for the treatment group, and their adherence to this was much better than that of the control group with placebo in the first eight weeks. The adverse events seen were hypochromia, itching and folliculitis.

SCHLÜSSELWÖRTER:
Centella asiatica, Hypertrophe Narben, Keloide, Therapie, Pinus sylvestris

ZUSAMMENFASSUNG:
Hypertrophe Narben und Keloide sind sehr problematisch für Patienten, da sie die Bewegungsfreiheit beeinträchtigen, sowie Juckreiz und Schmerzen auslösen können, und sie erinnern ständig an das erlebte Trauma. Obwohl es zahlreiche Behandlungsmöglichkeiten gibt, sind keine sehr gut wirksam. Die Traditionelle Naturmedizin hat das therapeutische Arsenal vergrößert und die Laboratorios Catalysis, S.A. aus Spanien, haben eine neue Creme für die Behandlung hypertropher Narben und Keloide entwickelt, deren Hauptwirkstoffe Centella asiatica und Pinus sylvestris (Cicatrix®) sind. Um die Wirksamkeit zu beurteilen, wurde eine doppelblinde, placebo-kontrollierte klinische Studie der Phase III durchgeführt, an der Patienten teilnahmen, die zwischen Oktober 2009 und Oktober 2010 die dermatologische Abteilung der Clinico Quirúrgico Manuel Fajardo (Havana) besuchten.

90 Patienten die die Studienkriterien erfüllten wurden ausgewählt. Schwangere, junge Mütter und Kinder wurden ausgeschlossen. Die klinische Auswertung der Ergebnisse orientierte sich an der Reduktion der Narbenhöhe und dem Auftreten von Nebenwirkungen. Die Zusammensetzung der Patientengruppen war bis auf das Alter homogen. Die Creme sollte, laut ärztlicher Anweisung, 3-mal täglich aufgetragen werden. In der Verumgruppe wurde das auch in den ersten 8 Wochen besser befolgt, als in der Kontrollgruppe mit Placebo. Die Nebenwirkungen, die beobachtet wurden, waren Hypochromie, Juckreiz und Folliculitis.

INTRODUCTION

The word keloid comes from the Greek word kele, which means tumour, and eidos, appearance. It probably comes from the word chele that is also Greek, which means crab pincers. This is used to describe how it tends to invade the neighbouring tissues sideways. The lesion had already been described in the Edwin Smith Papyrus (3000 BC.). These lesions were also depicted in ancient statues of the Yoruba tribe from Nigeria (Africa) that date back to the 13th century. Alibert was the first person to use the term keloid in 1816. The fact that it does not exist in animals makes the research work difficult.

They are abnormal scars that develop from scarring in certain individuals. A keloid (K) is distinguished as being excess growth in the scar tissue that starts around the borders of the original skin injury, whilst the Hypertrophic Scar (HC) is a large quantity of scar tissue that stays within the boundaries of the original wound [1–3].

Although the aetiology of both is unknown, they only occur in humans and they are more common among dark skinned people, under 30, with atopic symptoms [1, 4, 5].

Hormone levels are also associated with these conditions; keloids occur during puberty and improve after menopause. Even though they are part of body art or aesthetics in some

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cultures, many patients want to minimize the appearance of the scars and by doing so improve their quality of life [6–8].

There are numerous kinds of treatment and prevention methods such as surgical excision, radiation, laser treatment, pressure therapy, intralesional corticosteroid, cryotherapy, using silicone products or various local and oral medicines [1, 4, 7–9].

Alternative therapy continues to be based on a source of natural active ingredients. Laboratorios Catalysis (Spain) has developed crème Cicatrix®, a new product that contains Centella asiatica (asiaticoside and madecasosside) and Pinus sylvestris, which is prescribed to treat HC and K [10, 11].

The objective of this study was to assess the efficacy of cream with Centella Asiatica and Pinus Sylvestris on treating HC and Q, according to the clinical response whose evaluation was based on a reduction in the height of the scars and the occurrence of adverse events.

METHOD

A Phase III, randomized, double-blind, monocentric clinical trial was carried out in which one group was treated with cream containing Centella asiatica and Pinus sylvestris and the other with placebo. Both groups had the same organoleptic characteristics.

The universe of the study was made up of patients who had been clinically diagnosed as having HC and K at the outpatient's unit of the Hospital Comandante Manuel Fajardo, Havana. The sample was made up of 90 patients who satisfied the following inclusion criteria:

- Aged between 18 and 55, male and female
- Signed the informed consent
- Completed any type of treatment for scars at least a month before being included in the clinical trial
- Not being treated with any type of steroid or have a malignant process anywhere
- Be physically and mentally fit enough to follow the treatment instructions.

Anyone who did not want to take part in the clinical trial was excluded, as were pregnant or breast feeding women, children and those who were being treated with another research programme product or who had an intercurrent illness or decompensation.

The patients were randomly assigned to the two treatment groups by means of the EPIDAT 3.1 statistics programme (Spanish version from 2006).

TREATMENT

Both groups were told to wash and dry the affected area, apply the cream and gently rub it on all over until the product had been completely absorbed, three times a day for at least two minutes and for twelve weeks. They were careful not put the cream anywhere near their eyes.

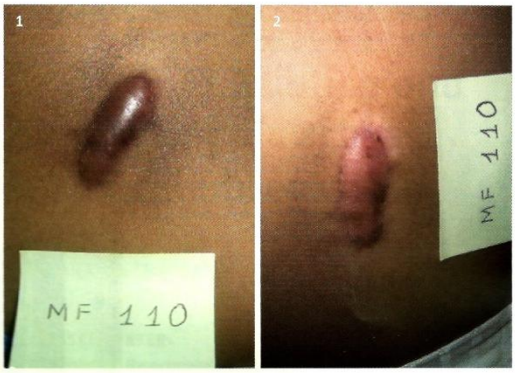

Fig. 1: Patient No. 1 before therapy with Cicatrix®.
Fig. 2: Patient No. 1 after 12 weeks therapy with Cicatrix®.

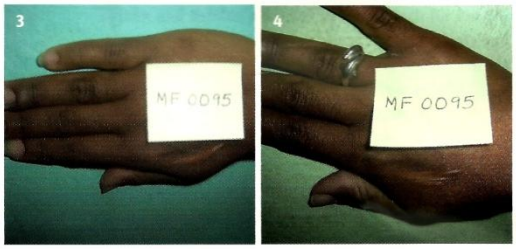

Fig. 3: Patient No. 2 before therapy with Cicatrix®.
Fig. 4: Patient No. 2 after 12 weeks therapy with Cicatrix®.

General research ethics

The clinical trial (CT) was carried out in accordance with the principles established in the Declaration of Helsinki (2008) and the corresponding state regulations in force in the Republic of Cuba. All the patients or a relation of the patient were asked to sign the informed consent form agreeing to take part in the clinical trial after having been informed orally and in writing about the research programme.

Patient follow-up: Each patient was physically examined at the start of the study, then after 2 and then 3 months, the height of the scars was measured using a millimetre ruler and classified according to the Vancouver Scar Scale. Photos were taken at the start and at the end of the study to be documented.

Efficacy evaluation

The response to the procedure was assessed according to the reduction in the height of the scars and the occurrence of any adverse events.

Statistical analysis

The intention to treat principle (ITT) was used taking into account all the patients who had been randomly selected to take part in the clinical trial.

TABLE 1: GENERAL CHARACTERISTICS OF THE PATIENTS WITH HYPERTROPHIC SCARS AND KELOIDS. HOSPITAL MANUEL FAJARDO. CUBA 2009–2010

Variable	cream with Centella Asiatica and Pinus Sylvestris (n=43)		Placebo (n = 47)	
	X2	DE	X2	DE
Age (years)	38.6	± 12,2	33.0	± 11.4
Gender	n =	%	n =	%
Male	17	(39.5)	10	(21.3)
Female	26	(60.5)	37	(78.7)
Phototype				
III	13	(30.2)	24	(51.1)
IV	15	(34.9)	12	(25.5)
V	10	(23.3)	7	(14.9)
VI	5	(11.6)	4	(8.5)
Lesion location				
Face	4	(9.3)	2	(4.3)
Skull	2	(4.7)	2	(4.3)
Lower limb	3	(7.0)	7	(14.9)
Upper limb	7	(16.3)	7	(14.9)
Chest	17	(39.5)	16	(34.0)
Abdomen	10	(23.3)	13	(27.7)
Height of the lesion				
Normal	6	(14.0)	14	(29.8)
< 2 mm	10	(23.3)	10	(21.3)
2–5 mm	23	(53.5)	22	(46.8)
> 5 mm	4	(9.3)	1	(2.1)

The differences between the groups for the quantitative variable were analysed by means of the Wilcoxon T test and the Mann-Whitney U test. For the qualitative variables, the Chi-square test was used; P < 0.05. In the analysis, P > 0.05 was obtained for all the variables except age (P = 0.02).

The in-depth data analysis was achieved using absolute and relative frequencies for the qualitative variables and the mean, median maximum and minimum values and the confidence interval at 95% for the average were used to summarise the quantitative variables.

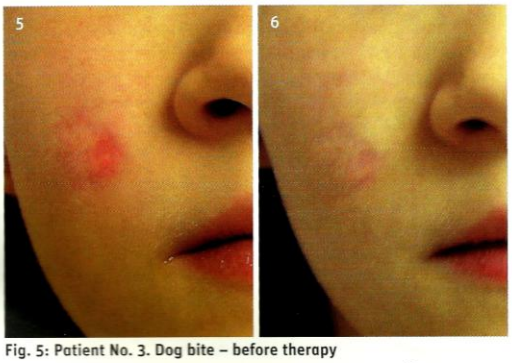

Fig. 5: Patient No. 3. Dog bite – before therapy
Fig. 6: Patient No. 3 after 12 weeks therapy with Cicatrix®
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The Chi-square test was used to determine the homogeneity in the behaviour of a qualitative variable in the treatment groups and the Mann-Whitney U test was used to determine that of the quantitative variables.

Efficacy evaluation

The Wilcoxon T test for paired samples was used to identify the changes in the behaviour of the quantitative variables on two different occasions during the study and then the Freidman test was used for comparison on three different occasions. The average values of the quantitative variables in the treatment groups were compared by means of the Mann-Whitney U test.

A significance level of $\alpha = 0.05$ was obtained in all cases. The analysis of the adverse events and drop-outs from the programme (type and intensity) were described. The results are shown in tables and graphs.

RESULTS AND DISCUSSION

90 patients were included in the clinical trial. 10 patients (11.1%), 4 of them were being treated with cream with Centella asiatica and Pinus sylvestris and 6 with the placebo, were considered to have left the programme either because they did not

TABLE 2: PROGRESS OF THE HEIGHT OF THE SCAR DURING THE TREATMENT. CUBA 2009–2010

Height of the scar	Start				Week 8				Week 12			
	cream with Centella Asiatica and Pinus Sylvestris (n=43)		Placebo (n=47)		cream with Centella Asiatica and Pinus Sylvestris (n=39)		Placebo (n=41)		cream with Centella Asiatica and Pinus Sylvestris (n=39)		Placebo (n=41)	
	n=	%	n=	%	n=	%	n=	%	n=	%	n=	%
Normal	6	14.0	14	29.8	7	17.9	13	31.7	12	30.8	17	41.5
< 2 mm	10	23.3	10	21.3	11	28.2	10	24.4	12	30.8	16	39.0
2–5 mm	23	53.5	22	46.8	20	51.3	18	43.9	14	35.9	8	19.5
> 5 mm	4	9.3	1	2.1	1	2.6	0	0.0	1	2.6	0	0.0

The differences between the groups were analysed by means of the Wilcoxon T test and the Mann-Whitney U test. The differences among the three evaluations in each of the groups were analysed by means of the Friedman test. To determine the differences between the two evaluations, the Wilcoxon T test for paired samples was used; $P < 0.05$.
In the treatment group cream with Centella asiatica and Pinus sylvestris, $P = 0.005$ for the start / 8 week difference, $P < 0.001$ for the start / 12 weeks and $P = 0.001$ for 8 weeks / 12 weeks. In the placebo group, $P < 0.001$ for the start / 12 week difference and 8 weeks / 12 weeks difference. In the other comparisons $P > 0.05$.

TABLE 3: RESPONSE TO THE TREATMENT IN THE LAST FOUR WEEKS

Response	Week 8				Week 12			
	cream with Centella Asiatica and Pinus Sylvestris (n=39)		Placebo (n=41)		cream with Centella Asiatica and Pinus Sylvestris (n=39)		Placebo (n=41)	
Excellent	2	5.1	3	7.3	8	20.5	12	29.3
Favourable	5	12.8	12	29.3	9	23.1	13	31.7
Acceptable	7	17.9	10	24.4	14	35.9	5	12.2
Unfavourable	25	64.1	16	39.0	8	20.5	11	26.8

The differences between the groups were analysed by means of the Wilcoxon T test and the Mann-Whitney U test. The differences among the evaluations of each of the groups were analysed by means of the Wilcoxon T test for paired samples; $P < 0.05$. In both groups, $P < 0.01$ for the 8 week / 12 week difference.

come to their appointments for 2 weeks in a row, or for other reasons beyond their control. Finally, the sample was left with 43 patients in the Treatment group (cream with Centella asiatica and Pinus sylvestris) and 47 in the Control group (placebo).

Table 1 shows that both samples were homogenous with regard to the gender, phototype, lesion location and lesion height variables. However these were longer-lived in the treatment group compared to the control group. Even though our findings on the height of the lesion were insignificant, it should be pointed out that there were more patients in the treatment group with grade 3 lesions according to the Vancouver Scar Scale.

Hypertrophic scars (HC) and keloids (K) are said to appear more in dark skinned individuals that are younger than 30 years of age [1]. In this research programme the results are in line with the aforementioned, as most patients in both groups were from the adult population (between 20 and 60 years old according to the WHO) [12] and the skin phototype III [13], which is the most common in the existing half-caste Cuban population of mainly African and European origin. Therefore, the appearance of keloids in this skin phototype can be justified.

Other authors state that anyone of whatever race can suffer from this type of scarring, although Asians and black people (up to 15 % of people) are more prone to it. No albino patients have been reported to have this type of scarring, which suggests that the melanocytes probably play an important role in the development of the cutaneous condition [14].

Just like in the pilot study carried out by Zelenkova in Slovakia, there were more females than males in our clinical trial. This might be explained by the fact that women are more concerned about their appearance than men.

The clinical response to the treatment that was assessed on three occasions, shows that there was a significant decrease in

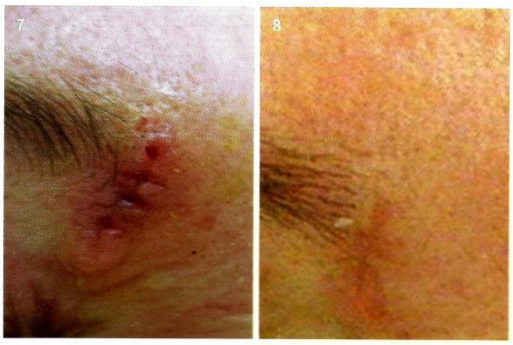

Fig. 7: Patient No 4. Surgical scar before therapy with Cicatrix®
Fig. 8: Patient No. 4. Surgical scar after 3 weeks therapy with Cicatrix®
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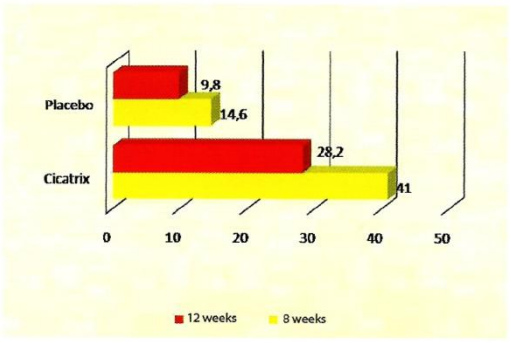
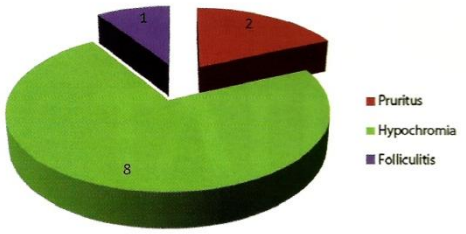


Graph 1: Adherence to the HC and K treatment. Hospital Manuel Fajardo. 2009–2010.



Graph 2: Adverse events.

the height of the scar at the 8–12 and start–12 week stages; there were no differences between the groups. Nevertheless, results were better in the treatment group than in the control group with placebo in the first eight weeks.

The research team believes that this effect could be explained by the fact that the patients from this group adhered better to the treatment (Graph 1).

As we can see in the first 8 weeks, 41% patients adhered to the treatment (frequency of cream applications, 3 times a day), a figure that almost triples the percentage of that of the control group.

Both groups responded significantly well to the treatment in the last four weeks, in which there was a 43.6% drop in the unfavourable response in the treatment group with cream with Centella asiatica and Pinus sylvestris compared to the 12.2% drop of the control group with placebo. Therefore, the acceptable response increased (double), favourable (nearly double) and excellent (quadrupled) for the treatment group and only the excellent response for the control group with placebo improved (quadrupled).

In turn, the research team believes that this result is due to the patients adhering better to the cream with Centella Asiatica and Pinus Sylvestris treatment, as shown in graph 1.

In the pilot study carried out by Dr. Zelenkova, 3 patients out of 30 (10%) did not respond to the treatment, while in our study 11 or 21% did not respond.

Out of all the patients from the treatment group, 11 of them (28%) had adverse events, mainly hypochromia in 8 of them, which stands for 20.5%. This adverse event was not mentioned by Dr. Zelenkova in her study, although she did find erythema (17%) itching (10%) a burning feeling (3.3%), skin xerosis (3.3%) and bacterial infections (6.6%). Out of all these, only itching and bacterial infections (namely folliculitis) coincided with our findings.

This is thought to be due to one of the cream's components, aggravated by the warm weather and dryness in our country, although us mentioning this possible relationship is not one of the objectives of this research programme.

CONCLUSIONS

1. The samples were homogenous in terms of the gender, skin phototype, lesion location and scar height variables; they were not the same for the age variable.
2. Cream with Centella asiatica and Pinus sylvestris was better than the placebo in terms of altering the height of the hypertrophic scar/keloid in the first eight weeks of the treatment.
3. There was an increase in the acceptable, favourable and excellent responses for the treatment group using cream with Centella asiatica and Pinus sylvestris although statistically it was not higher than that of the placebo group.
4. There were a few minor adverse events. Hypochromia was the most common.

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