

A RANDOMISED PLACEBO CONTROLLED DOUBLE-BLIND PARALLEL GROUP STUDY IN THE TREATMENT OF AGING SYMPTOMS OF THE SKIN.

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Received: June 18, 1998

Key words: Marine proteins, aging skin, placebo, skin elasticity, skin thickness.

Synopsis

The present placebo controlled double blind study was carried out in 59 non smoking females with aging symptoms of the skin. Skingain[®], a new preparation, containing marine proteins, vitamins and minerals, was given twice daily to 29 persons, and an identical placebo capsule was given twice daily to 30 persons in a randomised way. The study had a duration of four months. The two treatment groups were comparable at the outstart of the study with respect to the main parameters such as age and grade of aging symptoms of the skin.

Objective measurements, skin thickness and elasticity, as well as subjective observations in form of clinical parameters were used for evaluation of the effect of the treatments. In addition the participants made their own self evaluation of the effect. Photos were taken of all participants initially and after 2 and 4 months treatment.

The results show a significant improvement in skin quality both with regard to objective parameters as well as in subjective parameters after treatment with Skingain[®]. No significant treatment effects were detected after treatment with placebo. The participants self evaluation showed also a highly statistical difference in favour of the active treatment. The majority of the participants taking Skingain[®] would like to continue with the treatment after the study was concluded.

The tolerability of the treatments were excellent. Two patients in the active treatment group stopped the treatment due to rash like symptoms during the first two months of the study.

Riassunto

Il presente studio a doppio ceco e controllato con placebo è stato condotto su 59 donne non fumatrici che presentavano sintomi di invecchiamento della pelle. È stata somministrata una nuova preparazione denominata Skingain[®] e contenente proteine marine, vitamine e minerali. Skingain[®] è stato somministrato due volte al giorno a 29 persone, e contemporaneamente un'identica capsula placebo è stata data due volte al giorno a 30 persone in modo randomizzato. Lo studio ha avuto una durata di quattro mesi. All'inizio dello studio i due gruppi erano paragonabili per quanto riguarda i parametri principali quali età e livello del sintomo di invecchiamento della pelle.

Misurazioni obiettive dello spessore e elasticità della pelle e osservazioni soggettive sotto forma di parametri clinici sono state usate per valutare gli effetti del trattamento. Inoltre i partecipanti facevano delle autovalutazione degli effetti. Sono state scattate delle foto di tutti i partecipanti all'inizio e dopo 2 e 4 mesi di trattamento. I risultati hanno mostrato un miglioramento significativo nella qualità della pelle sia con riferimento ai parametri oggettivi che a quelli soggettivi dopo il trattamento con Skingain®. Nessun effetto significativo è stato invece riscontrato dopo il trattamento con placebo. Anche l'autovalutazione dei partecipanti ha indicato una differenza altamente significativa a favore del trattamento attivo. La maggioranza dei partecipanti che ha assunto Skingain® vorrebbe continuare il trattamento anche dopo la fine dello studio.

La tollerabilità del trattamento si è dimostrata eccellente. Due pazienti nel gruppo di trattamento attivo hanno dovuto interrompere il trattamento a causa di prurito durante i primi due mesi dello studio.

INTRODUCTION

Several treatment opportunities are available for the antiaging treatment of the skin. Prescription drugs, cosmeceutic and cosmetic agents as well as food supplements are claimed to have antiaging effects on the skin. However, for most of these agents, at least for the last two groups, acceptable scientific efficacy and safety documentation is lacking. Launching highly priced preparations without effect are unethical to the consumers, and have therefore also been heavily criticised and even stopped by consumer authorities in some countries. One exception, however, is retinoic acid, which has been convincingly documented to have effect on aging skin symptoms in a number of well performed clinical studies (1-4). Retinoic acid is in most countries a prescription drug and thus not possible to advertise directly to the consumers or sell without a prescription from a physician.

The investigational preparation is a food supplement mainly based on marine proteins from a deep water fish living along the Norwegian coastline¹. In addition the product is containing minerals and vitamins. In open studies the preparation has been shown to have a favourable effect on the aging skin. No controlled studies have so far been carried out. The tolerability of the preparation has been reported to be excellent, while it is well known that treatment with retinoic acid can give side-effect in some patients (4-10%) in form of soreness and redness of the skin (2). We decided, based on the above mentioned to carry out a controlled study to investigate the efficacy and tolerability of the preparation in females with aging symptoms of the skin.

MATERIAL AND METHODS

The study was carried out as a randomised placebo controlled double blind study in 63 non smoking females aged 35-70 years. Thirty four of the participants received the active preparation, while 29 were randomised to placebo. Blinding of the treatments was achieved by using identical appearing active and placebo capsules. The total treatment

period was 4 months and the participants came to follow-up controls after 2 and 4 months.

The participants were asked to take two capsules per day (one in the morning and one in the evening) together with food and to swallow them with water. Each capsule contains 250 mg of the marine protein. All patients received verbal and written information about the aim of the study before they gave their informed consent to participate.

The aging symptoms of the skin were evaluated clinically by use of a five point scale. 0 = Absent, 1 = Very modest, 2 = Modest, 3 = Moderate, 4 = Pronounced.

The following symptoms were scored: fine wrinkles, coarse wrinkles, tactile roughness and teleangiectasia. On the two follow-up visits, after 2 and 4 months, the effect of the treatment was evaluated by using VAS (Visual Analogue Scales) of 10 cm with defined endpoints "no change" and "pronounced change" for the four symptoms listed above. An overall rating of the extrinsic aging was also performed using a 3 point scale; 0 = Modest, 1 = Moderate, and 2 = Pronounced. In addition, a global evaluation of the effect of the treatment was made also by using VAS with the same defined endpoints.

In addition, the patient themselves performed self evaluation by using VAS with defined endpoints "no change" and "very pronounced change" when returning to the follow-up visits.

Objective measurements of the skin thickness and skin elasticity were performed initially and at each of the follow-up visits using two measuring sites, right, and left sides of the face (lateral angle of the eyes). Each measurement was done in duplicate and the mean value was registered. In the following the mean values of the measurements on the right and left of the face are listed. Measurements were carried out with Dermascan A and Dermaflex (Cortex; Århus, Denmark).

In order to avoid interobserver variability all objective skin measurements were carried out by the same person.

Close-up pictures of the face of the participants were taken initially and at each of the follow-up visits under standardised conditions.

1. Marketed under the name Skingain®

Statistical methods

Mean was used for estimation of continuous and near - continuous variables and Student procedure was used for construction of confidence interval of mean. The one-sample t-test was used for analysing change over time within groups. Analysis of covariance and two-sample tests were used to compare between groups with regard to continuous variables. Categorical variables were reported using contingency tables. Fisher's exact test was applied when testing 2 x 2 tables. A Network Algorithm for Performing Fisher's Exact Test in r x c contingency tables was used when testing tables greater than 2 x 2.

A significance level of 5% was used in tests, and two-tailed tests were applied.

RESULTS

Subject population

A total of 59 subjects concluded the study according to the protocol, 29 in the active and 30 in the placebo group. Five persons, three on active preparation and two on placebo withdrew or dropped out of study at the first follow up visit. Two persons in the active group got skin rash, while one could not tolerate the taste of the capsules and stopped the treatment. The 2 persons on placebo did not show up at the control visit. These persons are not included in the statistical evaluation.

In table 1 the demographic as well as the global rating

of the aging symptoms initially in the two treatment groups are shown.

As can be seen from the table the two treatment groups are comparable initially with respect to age and the severity of the aging symptoms. No statistical differences either in age or distribution of aging symptoms are detected between the groups.

The results of the global clinical evaluation are shown in table 2. Following a four months treatment period no significant differences in the global evaluation could be detected in the persons receiving placebo, while a significant effect could be seen in the group receiving the active preparation. It worthwhile to stress that this effect was more pronounced after four months than after two months as can be seen from the table.

Objective skin measurements

In table 3 the measurements of the skin thickness and elasticity are presented respectively. When comparing the two treatment groups with regard to change in skin thickness, a significant increase between the initial value and the value seen after 4 months was found in the group treated with the active preparation, but not in the group treated with placebo. The difference in the increase in skin thickness between the groups is significant. The increase in skin elasticity in the active group was significant when comparing the initial value and the value after four months treatment. The change in skin elasticity in the same period was not significant in the placebo group. The dif-

Group	Age (yrs)	The grade of the aging symptoms (No of patients)		
		Modest	Moderate	Pronounced
<i>Active</i>	49,6 (9,2)	10	15	4
<i>Placebo</i>	47,0 (9,5)	11	14	5

Table I. Demographic data for the participants in the two treatment groups (SD in parentheses).

Group	After 2 months (cm)	After 4 months (cm)
<i>Active</i>	5,0 (1,9)	7,8 (3,2)
<i>Placebo</i>	0,6 (0,7)	0,9 (0,8)

Table II. Global assessment of the skin aging symptoms as function of the treatment duration using VAS (SD in parentheses).

	Active		Placebo	
	Skin thickness (mm)	Elasticity %	Skin thickness (mm)	Elasticity %
<i>Initially</i>	0,85 (0,12)	47 (8,1)	0,90 (0,15)	48 (7,6)
<i>8 Weeks</i>	0,97 (0,15)	50 (8,5)	0,89 (0,13)	47 (8,2)
<i>16 Weeks</i>	1,20 (0,17)	62 (8,4)	0,87 (0,12)	44 (8,5)

Table III. Mean skin thickness and elasticity index of 59 females treated with active capsules or placebo for a period of 4 months (SD in parentheses).

ference in the increase in skin elasticity was significant between the two groups.

Participant's assessment of effect

The self-evaluation of the effect of the treatment by the participants revealed a significant difference in favour of the active group after a treatment period of four months, as shown in table 4. Of the 29 persons in the active group, 20 persons felt that they saw an improvement in their skin quality on self inspection, while one of the 30 placebo treated persons felt that she had a small effect.

The 20 persons in the active group that had a positive effect of the treatment would like to continue the treatment while none of the placebo treated persons would like to continue.

Tolerability

The overall tolerability was good. Two participants in active group stopped the treatment due to rash and one because she did not like the taste and smell of the capsules. None of the persons on placebo reported any side-effects.

Table IV		
Group	After 2 months (cm)	After 4 months (cm)
<i>Active</i>	4,5 (1,7)	7,4 (2,7)
<i>Placebo</i>	0,2 (0,7)	0,3 (0,8)
<i>p-value</i>	< 0,001	< 0,0001

Table IV. The results of the participants self evaluation of the effect of the active treatment and placebo as function of treatment duration on VAS (SD in parentheses).

DISCUSSION

The results from this study indicate that the active capsules have a significant positive effect on the skin quality in middle-aged females with skin aging symptoms as compared to a placebo treated group. The effect of the treatment seems to develop over time being less pronounced after two months than after four months. By comparing the objective measurements of skin thickness and skin elasticity with the clinical observations and the participants own evaluations show that the efficacy of the treatment as revealed by the changes in these parameters is highly correlated. No pronounced effect of the active treatment can be expected before the treatment has been applied for two months or more, even if it was significant also after a treatment period of two months. Even after 4 months a number of the participants in the active group (approx. 30%) could not detect any change in skin quality by self evaluation. However, by looking at this subgroup we found a smaller, but still a significant positive change in the skin thickness and elasticity, as compared to the group reporting a positive self evaluation. By comparing the age and the grade of aging symptoms we could not detect any significant differences between this group of none responders and the 20 persons responding to the treatment. We have no reasons to believe, after asking them about compliance to the intake of the preparation, that the none responders had not taken the preparation as recommended. It might be that

they have to use the preparation for a longer time than the responders to obtain a similar effect.

Although the mode of action of Skingain® is unclear, the results of the present study indicate that the preparation seems to have a favourable effect on degenerated elastic and collagen tissue of the dermis. Skingain® can therefore, based on its efficacy and excellent tolerability, be an attractive alternative in the treatment of aging symptoms of the skin.

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