Efficacy of CelluControl Cream in the Cellulite Treatment
Double blind, placebo controlled, randomized study

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ABSTRACT
Cellulite is probably the most frequent beauty problem affecting women and it appears to be the result of a number of biochemical and metabolic alterations that start on an interstitial matrix and connective structure level and continue to include microcirculatory functional changes. This study evaluates the effect of the 6 weeks administration of
CelluControl cream containing the active complex of bio-enhanced extracts (B.E.E.®) – a new phytotherapeutic product – using a number of parameters commonly acknowledged as being correlated with cellulite and evaluated possible differences in clinical results in relation to the given treatment.

INTRODUCTION

Cellulite is one of the most frequent beauty problems and its treatment is often the result of empirical therapeutic attempts not based on a precise rationale nor included in acknowledged protocols. Despite the varying opinions on the clinical classification and physiopathological evolution of cellulite, the idea of early diagnosis and treatment of initial stages is fundamental.

Today, cellulite appears to be increasingly the result of a number of biochemical and metabolic alterations, which start on an interstitial matrix and connective structures' level, rather than merely a degenerative hypodermal alteration either due to or associated with lymphatic venous stasis.

The human organism is characterized by basic vital functions occurring in cells and in the interstitial matrix of all tissues. Alterations in these basic functions (such as pH alterations, free radicals increase, temperature alterations, oxide-reduction alterations, and lymphatic stasis) are the beginning of chronic, degenerative diseases that are the cellular and tissue aging processes.

Cellulite has been defined as a "skin irregularity which visually appears in the form of orange peel or dimpled skin and can be associated with various types of dermal-hypodermal tissue alterations, i.e. alterations of adipose tissue, connective tissue, venous-lymphatic system and the interstitial matrix".

Cellulite manifests in five main changes:

1.
Increase in subcutaneous adipose tissue and free water inside the interstitial tissue (lipedema)
2.
Increase in subcutaneous adipose tissue and lymphatic fluid (lipolymphedema)

3.
Connective fiber sclerosis (fibrous cellulite)
4.
Interstitial alteration and adipose dystrophy (lipodystrophy)
5.
Localized adipose tissue increase (localized adiposity) The standard definition of cellulite as edematous fibrosclerotic panniculopathy (i.e., hypoderma alteration starting with venous lymphatic stasis and resulting in sclerosis) is generally outdated in reference to any type of
cellulite. It appears that many alterations occur in the interstitial matrix (to which the periangium belongs) and in the connective tissue, which are considered structures that play a role in regulating and purifying our organism instead of being passive structures.

The interstitial matrix and the connective tissue, as well as the microcirculatory system, thus function as a junction where the various fundamental trophic substances, which are essential for cell life, flow and should functionally balance. The lack of these substances, or the presence of an excessive amount of elements with toxic characteristics (e.g., heavy metals, oxidizing substances, excessive sugar, etc.), lead, in time, to imbalance and local alterations of the dermal-hypodermal tissue. Thus also affects the adipose and supporting connective tissues, causing the beauty problem known as cellulite.

GENERAL OBJECTIVE OF THE TRIAL

The trial was designed to evaluate the effect of the topical administration of CelluControl cream using a number of parameters commonly acknowledged as being correlated with cellulite, and to evaluate possible differences in clinical results in relation to the different formulae.

MATERIALS AND METHODS

Group of 77 patients were recruited, ages 18–45 (average, 31.6), with presence of cellulite for at least 2 years and who spontaneously requested anticellulite treatment.

Inclusion criteria

Criteria for inclusion included edematous cellulite, adipoedematous cellulite, fibrous cellulite (according to physiopathological evaluation of cellulite) and compact cellulite (according to cutaneous tone type; individuals presenting with sagging skin were not included). These
cellulitic conditions have the common characteristic of pain on palpation, skin irregularity, localized lipolymphedema, intestinal swelling and water retention with the absence of systemic venous lymphatic insufficiency.

Exclusion criteria

Exclusion criteria included body mass index exceeding 30, saphenous and collateral varicosis, phlebolymphedema, systemic lymphedema, venous insufficiency, adipose cellulite, postliposculpture, other anticellulite treatments in progress, menopause and premenopause, sagging skin, or other evident pathologic conditions.

All evaluations were conducted on each patient over a 24 h period. Patients were asked not to drink coffee or smoke for at least 2 hrs. prior to evaluations. The first test was carried out from 1 to 2 weeks after the end of the patient's menstrual cycle.

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After obtaining their informed written consent, the patients
underwent the tests described below. The patients who met the enrollment criteria were recruited in the order in which they appeared. The 77 patients have been randomized into two groups and received placebo or CelluControl treatments according to the double-blind method. The placebo group consisted of 26 subjects; CelluControl group consisted of 51 persons.

Product formulations

The investigated product – CelluControl cream – was delivered by Hamida Pharma Inc. The product is in a form of a light cream that is easy to apply, spread out and absorbed by the skin. CelluControl contains a specially prepared complex of bio-enhanced herbal extracts that have positive effects on cellulite. The unique and innovative extraction technology ensures fast action and effectiveness.

Placebo consisted of a cream base only – the same a used for the active product, and has been administered to 26 subjects referred hereinafter as a placebo group.

The active product could not be differentiated from the placebo based on their appearance.

Both placebo and CelluControl have been applied topically onto affected by cellulite areas (thighs, abdomen, legs, and buttocks) twice a day.

Parameters evaluated

The following parameters were evaluated on all 77 patients: height; body mass; arterial pressure; stress, fat mass index (FMI); abdominal, thigh, and ankle circumference; clinical cellulite evaluation; and self-assessment. Clinical and subjective evaluations were conducted by answering a questionnaire and assigning a score from 2 to 8, with 5 designated as the limit between adequacy and inadequacy.

The physician was asked the following questions:

1. Was the product tolerated by the patient?
2. Were the patient's legs less swollen?
3. Did cellulite improve?
4. Did weight decrease?
5. Was the product globally deemed effective?

The patients were asked following questions:

1. Do you see yourself as having improved?
2. Are your legs less swollen?
3. Has cellulite improved?
4. Have you lost weight?

5. Are you satisfied with the treatment?

According to the main investigator's indications, aimed at maintaining the ratio between active product and placebo constant, the following additional parameters were evaluated:

- Blood chemistry tests: cholesterol, triglycerides, non ester fat acids, glycemia, urea, creatinine, ions levels (sodium, potassium, chlorine, calcium, and iron), TSH and T3, T4 hormones.
- Echography
- Ultrasonic pain test

Most of the tests to which the patients were subjected are included in the European anticellulite treatment diagnosis and evaluation protocol. After the first visit, during which the evaluations listed above were carried out, the patients were dismissed with the following instructions:

- Do not change your lifestyle.
- Do not start other anticellulite treatments.
- Report any side effects or undesired effects.
- Apply CelluControl cream onto specific cellulite areas twice a day.
- Fill in the self-assessment forms you were given. The self-assessment form also asked for an opinion regarding edema, defined as a feeling of heaviness in the lower limbs and cellulite, at 2, 4, and 6 weeks. Patients were asked to return after each 2 weeks for a check-up and to ascertain that the product was being taken regularly.

RESULTS

After 6 weeks of treatment, 77 patients were examined, with confirmation that they had applied cream regularly. The patients were included in the following groups:

- CelluControl group comprised of 51 subjects.
- Placebo group comprised of 26 subjects.

The statistical analysis was made using the t-tests for paired data. Body mass slightly decreased in CelluControl group, although patients claimed that they did not modify their normal habits (**Table 1**). FMI decreased statistically in CelluControl group, while the result is not statistically significant in the placebo group (**Table 2**). This result, correlated with loss of body weight, leads one to believe that the loss mainly concerned fatty mass. This could be extremely significant, not so much for absolute values but rather in relation to the trend that we deem consequent to the improvement of microvascular

function and of the interstitial matrix regulating and purifying activity that causes greater cell membrane fluidity, with consequent increase of cell metabolism. Abdominal circumference was reduced in CelluControl group. The decrease in the placebo group was not statistically significant (**Table 3**). The hip circumference was significantly reduced in CelluControl group. The decrease in placebo group was not statistically significant (**Table 4**). The bitrochanteric circumference was significantly reduced in CelluControl group. The decrease in the placebo group was not statistically significant (**Table 5**). Thigh circumference was also significantly reduced in CelluControl group and not statistically significant changed in the placebo group (**Table 6**). The analysis of circumference variations shows that CelluControl caused higher quantitative variations with respect to placebo (**Table 7**).

Observation of these values indicates that the active substances used are effective on local lymphatic adipose metabolism and that the results were more evident in the patients in CelluControl group, whose product contained a component with a greater action on local adipose metabolism. The reduction of abdominal circumference, which justifies the feeling of well-being reported by all patients treated with the active products, is particularly interesting. The apparent lesser reduction of ankle circumference is justified by the fact that none of the patients suffered from venous lymphatic insufficiency (see section on Exclusion Criteria above).

The balanced reduction of all circumferences could most likely be correlated with the reduction of local lymphatic stasis due to improvement of the entire mesenchymal structure rather than only the direct effect on vessel walls (phlebolymphotrophic tonic action).

2 [Brian – see pdf for table(s)]

Table 1. Body mass Placebo CelluControl Baseline 61.88 64.64 Final 61.69 62.45
Final - baseline 20.19 (20.3%) 22.19 (3.4%)
Baseline vs. final p > 0.001 p < 0.001
Table 2. Fat mass index (FMI)
Placebo CelluControl
Baseline 26.36 28.29
Final 26.37 26.29
Final - baseline 0.01 –2.00 (–7.1%)
Baseline vs. final p > 0.001 p < 0.001
Table 3. Abdominal circumference (cm)
Placebo CelluControl
Baseline 73.61 77.54
Final 73.00 74.29
Final - baseline –0.61 (–0.8%) –3.2 (–4.1%)
Baseline vs. final p > 0.001 p < 0.001
Table 4. Hip circumference (cm)
Placebo CelluControl
Baseline 93.20 93.38
Final 93.08 92.92
Final - baseline –0.12 (–0.1%) –0.46 (–0.5%)
Baseline vs. final p . 0.001 p < 0.001
Table 5. Bitrochanteric circumference (cm)

Placebo CelluControl
Baseline 91 92.40
Final 90.92 90.88
Final - baseline –0.08 (0.1%) –1.52 (–1.6%)
Baseline vs. final p > 0.001 p < 0.001
Table 6. Thigh circumference (cm)
Placebo CelluControl
Baseline 59.5 60.66
Final 58.92 58.50
Final - baseline 0.58 (–1%) 2.15 (–3.6%)
Baseline vs. final p < 0.001 p < 0.001
Table 7. Ankle circumference (cm)
Placebo CelluControl
Baseline 22.73 23.55
Final 22.65 22.90
Final - baseline –0.08 (–0.4%) –0.65 (–2.7%)
Baseline vs. final p > 0.001 p < 0.001

Echography

Soft-tissue echography is an important test for the diagnosis of the various forms of cellulite syndrome despite being more qualitative than quantitative. The test was carried out with a high-resolution device (Sigma 330 High Performance [Kontron Medical], 7.5–12 MHz probe). The reference point for the test was the front area of the thigh on the vertical line at 15 cm from the saphenofemoral junction. The echography test was carried out after the microcirculatory and termographic tests so as not to distort the data obtained. Ultrasonography of cellulite syndromes typically shows small, thin hyperechogenic connective septa that are morphologically altered and disharmonic. The trend shows the recovery of normal hypoechogenicity associated with improved balance and the tendency for parallel, horizontal arrangement following treatment with the trial products, indicating recovered metabolic and microvasomotion activity (Table 8). The results also demonstrate a significant reduction of subcutaneous thickness with the tendency to balance connective septa, thus demonstrating localized lipoedema reduction.

Ultrasonic pain test

This test is used to attempt to make a more precise physiopathological diagnosis and to quantify responses to specific treatment of the different types of cellulite syndrome. It correlates echography indications with the pain response to compression of the probe on the tissues. The level of pain, due to dermal-hypodermal nocireceptor activation, reveals typical tissue cellulitic alterations and lymphatic stasis (Table 9). Lipedema and lipolymphedema, as well as lipodistrophy, normally present spontaneous pain following compression with the ultrasound probe. Pain corresponds to the quantity and quality of extracellular

edema and to the degenerative or inflammatory process that is typically related to cellulite and not to the amount of fatty tissue present. Normal subcutaneous tissue can be compressed with the probe well beyond 30% of its thickness while lipedema is painful at 15–20% of its thickness, with the possibility of compressing the subcutaneous layer on the muscular fascia. Considerable pain is reported in the event of lipolymphedema and lipodystrophy, on the other hand, at about 10% with a typical reduction of the possibility of compressing the subcutaneous tissue on the muscular fascia.

The tested area usually corresponds to Hunter's venous perforating region on the medial thigh, where the tissue is particularly sensitive due to the presence of important venolymphatic and neural stations. In medical practice several measurements, expressed in mean values, are recorded, in relation to the quantity of compressed tissue, measured in millimeters from the skin to the muscular

Table 8. Echography

fascia, until the moment that compression causes pain. Variations in the quantity of compressed tissue give an idea of the local metabolic variation related to the treatment carried out. The results show a considerable, predictable and statistically significant improvement in the possibility of tissue compression, with a negative effect in the placebo-treated cases. These results demonstrate functional and nutritional improvement of the interstitial and connective tissue previously observed in clinical practice and other trials. Pain reduction obtained after treatment with the active products, associated with a feeling of well-being, leads us to consider about the role of the improved metabolic and vascularfunctionality of the interstitial matrix, consequent tissue lymphatic depuration (means to eliminate interstitial toxic substances and improve lymphatic drainage), and the direct or indirect phlebolymphotrophic and phlebolymphotonic action.

Placebo CelluControl
Baseline 1.72 1.69
Final 1.70 1.06
Final - baseline –0.2 (–1.3%) –0.63 (–37%)
Baseline vs. final p > 0.001 p < 0.001
Table 9. Ultrasonic pain test
Placebo CelluControl
Baseline 19.66 19.91
Final 20.85 11.39
Final-baseline 1.19 (6%) –8.52 (–42.7%)
Baseline vs. final p > 0.001 p < 0.001
Table 10. Clinical evaluations

Tolerance Cellulite Edema Fat Efficiency
Placebo 7.92 4.21 4.14 4.30 4.00
CelluControl 8.31 6.09 5.57 6.35 6.35
CelluControl vs. placebo P > 0.001 p < 0.001 p < 0.001 p < 0.001 p < 0.001

Table 11. Self-assessment questionnaires

Subjective
improvement Cellulite Edema Fat Satisfaction

Placebo 4.81 5.12 4.75 4.27 4.82
CelluControl 6.60 6.59 6.11 5.99 6.90
CelluControl vs. placebo $p < 0.001$ $p < 0.001$ $p < 0.001$ $p < 0.001$ $p < 0.001$
Numerical values (scale 0 - 10) from subjective evaluations.

Table 12. Symptomatic improvements

After After After
N Group Symptoms 2 weeks 4 weeks 6 weeks
51 CelluControl Edema 8 19 42

Heaviness 24 39 51

Cellulite 0 5 48
26 Placebo Edema 0 0 2

Heaviness 0 1 2

Cellulite 0 0 1

One believes that there are three reasons for this improvement: less connective fibrosis, better interstitial exchange, and higher vascularization. We cannot determine whether the products used act directly with a vascularizing effect or as metabolic activators. Nevertheless, the final result shows improvement of the basic clinical parameters – vascular, metabolic, and structural – which fully justify the simultaneous improvement aesthetically related to the cellulite, as also seen in the patients' self assessment tests.

Blood tests

No significant changes have been found.

Clinical evaluations

Analysis of the questionnaires filled out by physicians showed definite satisfaction with the products used concerning both clinical and cosmetic appearance (Table 10).

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Data were analyzed on a specially prepared scale. The evaluation criteria were based on five parameters to which scores from 2 to 8 were assigned (5 being the borderline between adequacy and inadequacy). The evaluated parameters were cellulite, edema, fat, tolerance, and global efficiency.

Table 10 indicates substantial clinical and cosmetic satisfaction expressed for all parameters, which, in the case of active treatments, are all adequate. The difference between active products and placebo evaluations is statistically significant.

Subjective evaluations

Patient questionnaires mainly focused on the feeling of well-being and how the product used matched the patients' cosmetic expectations. All values were positive and statistically significant with respect to the placebo group. The self-assessment questionnaire (**Table 11**) was extremely important for physicians because the results indicate the motivation and the objectives for which the patients involved had spontaneously asked for an anticellulite treatment. The data show that the administration of an active product was satisfying for patients. The placebo group, on the other hand, provided inadequate scores for four of five parameters.

Statistical analysis of the results confirmed the speculative analysis and showed subjective improvement in 50/51 patients in CelluControl group (98%) and in 4/26 patients in the placebo group (15.4%).

Table 12 documenting symptomatic improvements over the 6 weeks of the trial, is very interesting. The well-being feeling has been reported after 2 weeks by the patients in the groups treated with CelluControl. No significant improvements were reported by the group of patients treated with the placebo.

DISCUSSION

The aggregated results obtained in this double-blind vs. placebo trial shows the efficacy of the phytotherapeutic product examined for treatment so-called cellulite. Despite the controversy concerning the etiopathogenesis of cellulite, the improvement in a number of clinical and instrumental parameters is generally associated with improvement of the cellulite condition.

To comprehend better the global efficacy of the product under examination, it has been decided to associate clinical evaluations and self-assessment questionnaires with other tests, which, although being carried out according to rigorous analytic methods, inevitably do not include the subjective assessment of experimenters.

The improvements in the cellulitic condition must include the patient's assessment of appearance. Patients would deem useless a treatment that improves the various instrumental parameters without being effective in terms of their own perception of appearance. In commenting on the results of the trial, we must emphasize that an essential improvement in cellulite-related problems was found in self assessment and clinical contexts: a decreased feeling of heaviness in the legs and a substantial improvement of the orange peel appearance of the skin, commonly known as cellulite.

One has to focus on the data related to the cosmetic evaluation of cellulite. Physicians base their opinions in this field on clinical data, always referring to dysfunctional issues and lacking genuine cosmetic data on which to work on. Photographs, for example, do not indicate response: they are artifacts that change three-dimensional and dynamic shapes into flat, static images. Photographs likewise lack fundamental individual subjectivity.

Cosmetic evaluation cannot be set apart from the patient's final assessment. Clinical data must be correlated with the patient's degree of satisfaction in order to assume true meaning. This concept also applies to the feeling of wellbeing; being individual, subjective, and not quantifiable it must be gauged using generic, subjective scales.

The positive results found in clinical and subjective evaluations were backed up by the experimental test results. Echography showed reorganization tending toward normality of the connective septa and a significant reduction in subcutaneous thickness. This was confirmed by the circumferences measured in the various reference points: these decreased in a statistically significant way. A balanced reduction of the circumferences measured in the various parts of the body is mainly related to reduction in the lymphoadipose component. This, in turn, related to a more correct and functional microperfusion and metabolic activity recovery.

The ultrasonic pain test also confirmed the positive reorganization of subcutaneous tissue showing decreased compression pain. This also confirms that cosmetic improvement, such as the reduction of circumference and improvement in orange peel skin corresponds to a physiological parameter, such as pain in body districts affected by edema and tissue alteration.

These results are even more relevant if we consider that the anticellulite treatment lasted only 6 weeks. The complexity of the zones involved and the combined results of this trial confirm facts that are clinically demonstrated everyday: cellulite at an initial stage can be considered a simple beauty problem but if not suitably treated it can evolve into physiopathological processes that leads to tissue alterations. These alterations are often difficult to resolve and are irreversible in some cases, such as fibrosclerotic and lipodystrophic degeneration. We believe that improvement depends on improved vascularization, better interstitial metabolic activity, and decreased connective fibrosis. We cannot determine whether the products usedact directly with a vacularizing effect or as metabolic activators.

CelluControl has shown the best results, especially in relation to decrease in volumes and circumferences, due to the better metabolic action induced locally on adipocyte membranes.

CONCLUSIONS

1. The 6 weeks of the CelluControl cream treatment has shown statistically significant improvement both objectives and subjective cellulite measures as compared with placebo

2. CelluControl is easy to apply and well tolerated treatment.

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