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ORIGINAL CONTRIBUTION

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# A two-center, assessor-blinded, prospective trial evaluating the efficacy of a novel hypertonic draining cream for cellulite reduction: A Clinical and instrumental (Antera 3D CS) assessment

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## Summary

**Introduction:** Gynoid lipodystrophy, also known as cellulite, is a very common skin alteration representing mainly a cosmetic problem rather than a real disease. An effective treatment of cellulite has not been well established. The initial phase of cellulite is characterized by subdermal tissue edema with interstitial fluids retention. A new hypertonic topical product with draining action (HTC) containing NaCl 13%, escine, caffeine, and beta-sitosterol has been recently developed. A 28-day double-blind placebo-controlled study has shown that this cream is able to reduce thigh circumference and the thickness of adipose tissue. No data so far are available regarding an objective evaluation of skin appearance for a longer application period.

**Study aim:** To evaluate the clinical efficacy of 2-month HCT treatment with clinical and instrumental assessments.

**Subjects and methods:** In a prospective, 2-center, assessor-blinded trial 20 women (mean age 34 years) with cellulite of Grade I-III in severity were enrolled after their informed consent. HTC was applied once daily for 60 days. Primary outcomes of the trial were the evolution of thigh circumference measurements (assessed at baseline, after 1 and 2 months) and the computer-analysis of skin profilometry (ie, skin volumes) of a prespecified target area evaluated by means of Antera 3D CS digitalized images (assessed at baseline and at the end of the trial). Secondary outcome was the orange peel severity score (from 0 to 5) before and after pitch test.

**Results:** All subjects concluded the study period. Thigh circumference was reduced by −0.88 (right)/−1.2 cm (left) and by −1.8(right)/−2.1 (left) cm, after 30 and 60 days of treatment, respectively ($P$ = .001, Wilcoxon test vs baseline). Antera 3D profilometry of the target zone showed a significant reduction in skin depression expressed in $mm^3$ of −56% (from 59.7 to 26.73 $mm^3$) after HTC application. Orange peel (no pitch test) mean (SD) score was 2.3 (1) at baseline, 2.0 (1) and 1.8 (0.8) after 1 and 2 months ($P$ = .0031), respectively. After-pitch orange peel score was significantly reduced after treatment (from 3.3 to 2.2).

**Conclusion:** Once daily application of HTC for 2 months has confirmed its efficacy in the improvement of objective and subjective assessments of cellulite parameters.(*Trial Number registration*: ISRCTN15111614).

  

KEYWORDS
Antera 3D CS, controlled trial, gynoid lipodystrophy, hypertonic draining cream

## 1 | INTRODUCTION

Gynoid lipodystrophy, also known as cellulite, is a common skin alteration representing mainly a cosmetic concern rather than a pathological condition.[1] Cellulite affects 85%-98% of postpubertal women.[2] In cellulite, the skin appears mottled, dimpled and it often described as resembling "cottage cheese" or "orange peel."[3] The thighs, hips, and buttocks are the most common involved body area.[4] The initial phase of cellulite is characterized by subdermal tissue edema with fluids retention[5]; for this reason, cellulite is also known as edematous fibrosclerotic panniculopathy.[6] Furthermore, in the early phases of cellulite formation, retention of water at the adipocytes level has been documented.[7] A role in the pathogenesis of cellulite could be also played by a vasomotor alteration of dermal and subcutaneous microcirculation.[8] An exclusive and effective cellulite treatment has not been so far established[9] probably because the pathogenesis of cellulite is multifactorial and many processes are simultaneously involved.[10] Therefore, an effective treatment should have multiple and possibly synergistic levels of action. A new hypertonic topical product with draining action (HTC) containing NaCl 13%, escine 0.5%, caffeine 0.1%, and beta-sytosterol has been recently developed (Dermolipid Aqua®; Difa Cooper, IFC Group, Caronno Pertusella, Italy). Escine and caffeine are 2 active compounds commonly used in topical products for the treatment of cellulite.[11] Escine is a natural mixture of triterpene saponins able to decrease capillary permeability with an anti-edema action.[12] Caffeine is a xanthine derivative which has shown to be effective in the topical treatment of cellulite.[13] The anticellulite effect of topical caffeine seems to be due to lipolytic effects via induction of cAMP and inhibition of phosphodiesterase enzyme in adipocytes.[14] Topical application of hypertonic solution could exert a "draining" effect at dermal and subdermal tissue level.[15] In a human skin model experimental study, HTC has demonstrated to be able to drain from the skin a water amount of 5% of its weight applied.[16] This draining effect could be useful in the treatment of early stage of cellulite. A short-term (ie, 28 days) double-blind placebo-controlled study has shown that this cream is able to reduce thigh circumference and the thickness of adipose tissue.[17] No data so far are available regarding an objective evaluation of skin appearance before and after the application of this cream and for a longer application period.

## 2 | STUDY AIM

To evaluate the clinical efficacy and the local tolerability of 2-month treatment HCT in the clinical improvement of cellulite with clinical and instrumental objective assessments.

## 3 | SUBJECTS, MATERIAL, AND METHODS

### 3.1 | Subjects

This was a prospective, 2-center, assessor-blinded trial conducted in 2 Italian dermatological clinics. A total of 20 women (mean age 34 years) with cellulite of Grade I-III (according to Rossi et al[18]) were enrolled after their informed consent and after clinical assessment by the physician investigators. HTC was applied once daily for 60 consecutive days. Eligible participants were adult (>18 years of age) women with a BMI <30 kg/m$^2$, with regular menstrual cycle and presence of cellulite at gluteal and thigh level, bilaterally. Exclusion criteria were as follows: a previous treatment (within 2 months of the study period) for cellulite (topical or oral); positive history for lower limbs venous or lymphatic insufficiency; pregnancy or breastfeeding and a positive history of allergic contact dermatitis to any of the component of the cream. The trial protocol was approved by the local IRB. (Trial Number registration: ISRCTN15111614). The study was conducted in accordance with ethical principles of the Declaration of Helsinki and consistent with the GCP regulatory requirements.

### 3.2 | Outcomes

Primary outcomes of the trial with respect to efficacy were the evolution of thigh circumferential measurements (assessed at baseline and after 1 and 2 months) and the computer-analysis of skin profilometry of a prespecified target area (in general in the zone above the trochanteric eminence or gluteal zone) evaluated by means of *Antera 3D CS* (Miravex, Dublin, Ireland). Antera 3D pictures were performed at baseline and after 2 months. Thigh circumference measurements were taken using a flexible measuring ruler. Measurements were taken with the subject in standing position and performing the measurement up to 25 cm from the superior pole of the patella. This procedure was carried out by an evaluator (office clinic nurses) blinded to the type of treatment. The Antera 3D CS images system could measure in an objective and operator-independent manner the volume of skin protrusions and depressions[19] of a prespecified area. Volume of depressions in the target zone was expressed in mm$^3$. Secondary outcome was the orange peel severity score (from 0 to 5) before and after pitch test, and also this procedure was performed by an evaluator blinded to the type of treatment. High-quality color digital photographs of posterior and lateral thighs were also taken at baseline and at the end of trial.

## 4 | STATISTICAL METHODS AND SAMPLE SIZE CALCULATION

Statistical analysis was performed using GraphPad statistical software (GraphPad Software, Inc. La Jolla, CA, USA). Continuous

variables were expressed as mean ± standard deviation (SD). The primary endpoint of the trial was the evolution of thigh circumference from baseline and after 60 days of treatment. The paired *t* test and the Wilcoxon test were used for the evaluation of the variables during the study (baseline, day 30 and day 60). For the primary outcome variables, we calculated also the 95% confidence intervals. Analysis was performed on the basis of intention-to-treat principle. Sample size calculation was performed according to the following assumptions: A previous trial has showed that 1-month treatment with HCT reduced in comparison with baseline values thigh circumference by −1 cm with an effect size of 0.6. We wanted to evaluate whether 2-month treatment with HCT could induce a reduction of ≥2 cm with an effect size of 0.8. With an alpha error of 0.05 and a power of 90% a total of 20 subjects should be enrolled in the trial.

## 5 | RESULTS

All the enrolled subjects concluded the trial phases. At baseline, the mean (SD) body mass index was 22.8 (2.4) and the mean body weight 62.4 (9.6) kg. No difference in BMI and mean body weight was observed at the end of the trial. Mean BMI was 22.7 (2.3) and body weight was 62.1(9.6) kg at month 2. At baseline, thigh circumference values were 60.5 cm (right site) and 60.2 cm (left site). Thigh circumference values were reduced by −0.88(right)/−1.2 cm (left) and by −1.8(right)/−2.1 cm (left), after 30 and 60 days of treatment, respectively ($P = .001$, Wilcoxon test vs baseline). Evolution of thigh circumferences is presented in the Table 1. Antera 3D CS profilometry of the target zone showed a significant reduction in skin depressions expressed in $mm^3$. A reduction of −56% (from 59.7 to 26.73 $mm^3$) ($P = .0001$) was observed after HTC application in comparison with baseline. Orange peel score, (no pitch test) mean (SD) was 2.4 (1) (range 1-5) at baseline and 2.0 (1) and 1.8 (0.8) after 1 and 2 months ($P = .0031$) (Figure 1). Improvement of no-pitch orange peel score was observed in 12 (60%) of 20 subjects. Pitch orange peel score mean (SD) was 3.4 (1) at baseline, 2.3 (1.1) after 1 month and 2.2 (1.1) at the end of the study ($P = .0002$; Wilcoxon test) (Figure 2). Improvement of pitch orange peel score was observed in 18 of 20 subjects (90%). Figure 3 reports 2 Antera 3D profilometry assessments at baseline and after 2 months of HCT application. Figure 4 reports 2 pictures of subjects at baseline and after 2 months of treatment with HCT. The cream was very well tolerated. No side effects were reported during the study duration.

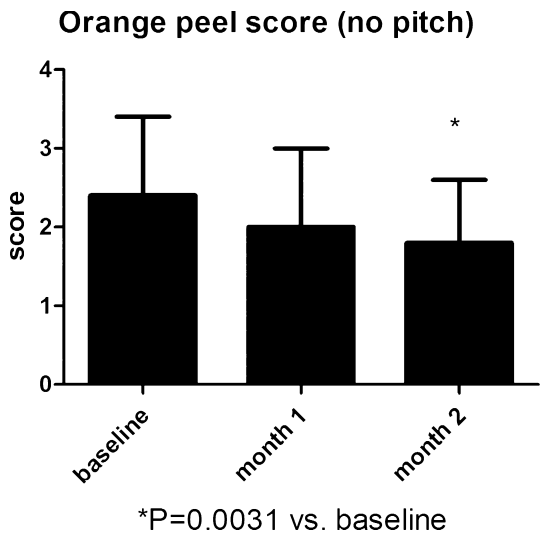


**FIGURE 1** Evolution of orange peel score (no pitch); at baseline, after month 1 and month 2

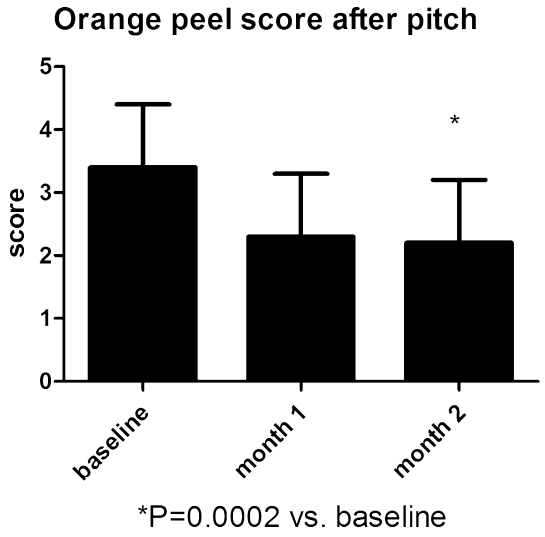


**FIGURE 2** Evolution of orange peel score after pitch; at baseline, after month 1 and month 2

## 6 | DISCUSSION

The present trial confirms that this hypertonic draining cream applied for 2 months is effective and well tolerated in the treatment of cellulite with both clinical and objective improvements. Cellulite is

**TABLE 1** Evolution of upper thigh circumference values (expressed in cm)

| Mean (SD) | Right thigh | Delta cm (95% CI) | *P* values (vs baseline) | Left thigh | Delta cm (95% CI) | *P* values (vs baseline) |
|---|---|---|---|---|---|---|
| Baseline | 60.5 (5.8) | | | 60.2 (6.5) | | |
| Month 1 | 59.6 (5.6) | −0.9 (−0.5/−1.2) | .007 | 58.9 (6.3) | −1.3 (−0.9/−1.5) | .005 |
| Month 2 | 58.7 (5.9) | −1.8 (−1.5/−2.1) | .001 | 58.1 (6.2) | −2.1 (−1.7/−2.4) | .001 |

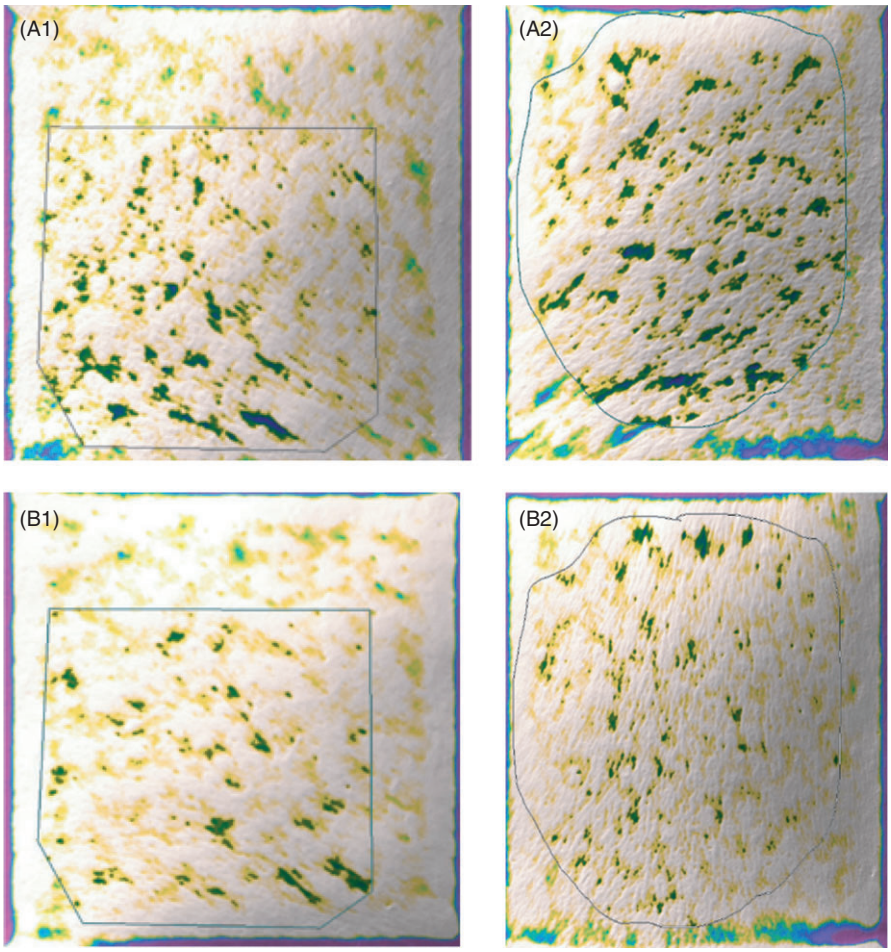


**FIGURE 3** Antera 3D pictures of 2 subjects (1 and 2) of a target zone at baseline and after 2 mo of HCT application (Subject 1: A1: Baseline. Volume of skin depressions: 5.98 $mm^3$; B1: After 2 mo of HCT treatment. Volume of skin depression: 2.76 $mm^3$) (Subject 2: A2: baseline. Volume of skin depressions: 11.8 $mm^3$; B2: After 2 mo of HCT treatment. Volume of skin depression: 3.4 $mm^3$)

considered a nonpathological skin disorder with structural changes at the level of dermis and hypodermis.[20] The term cellulite commonly refers to dimpling of the skin of the thighs and buttocks.[21] This condition, mainly in the early phases, can cause the retention of water at the adipocytes level.[22] This process induces a dramatic increase in adipocyte volume. The increased volume of adipocytes eventually induces the characteristic modifications of hypodermis structure with the classical formation of orange peel appearance.[23] The HTC evaluated in this study has previously demonstrate in an in vitro human skin model to be able to drain from the skin a water amount of 5% of its weight when applied over the skin specimen.[16] This draining effect could be useful in the treatment of early stage of cellulite. The tested cream contains also escine, beta-sitosterol, and caffeine. These components could exert both lipolytic and positive vascular effects.[24] When applied on the skin, this emulsion could therefore induce an osmotic process which releases the liquids accumulated between cells, thus allowing subsequent elimination through the skin. However, a hypertonic solution could also play a beneficial effect at microvascular level improving the vasomotion of microvessels.[25] The clinical results we have observed in this trial could be considered quite relevant in comparison with data available in the literature. In comparison with baseline values, in our study thigh circumference was reduced by −1.8/−2.1 cm. This reduction is greater than the reduction described in a quite recent systematic review[26] evaluating the clinical efficacy of cosmetic products for cellulite treatment where the pooled mean difference of thigh circumference reduction observed was −0.46 cm. In a study conducted in 15 women, a cream containing caffeine 3% reduced thigh circumference by 0.7 cm.[27] In a trial conducted by Sparavigna et al, a cream containing escine 1% and Ginkgo Biloba induced a −0.9 cm reduction in thigh circumference.[28] Circumference measurement is one of the most often used parameters for efficacy evaluation in cellulite treatments trials.[29] It is commonly stated that reduction in thigh circumference is mainly due to reduction in edema and subcutaneous fatty layer. Some authors[17] however consider thigh circumference measurements not accurate for cellulite as there may be weight loss during the study period. In our study, no significant changes in BMI and body weight were observed between baseline values and the values recorded at the end of the trial. The reduction in profilometry parameters we observed in this trial (−56%) supports a relevant "smoothing" effect of the cream. Some limitations should be taken in account in evaluating our results. First, we have performed an open noncontrolled trial. To increase the internal validity of the trial results, we therefore adopted an assessor-blinded approach in evaluating the primary outcome of the study (thigh circumference) and in addition, we use an objective, operator-independent evaluation of efficacy of the tested product (skin profilometry with Antera 3D CS). Future comparative explanatory studies are warranted to evaluate

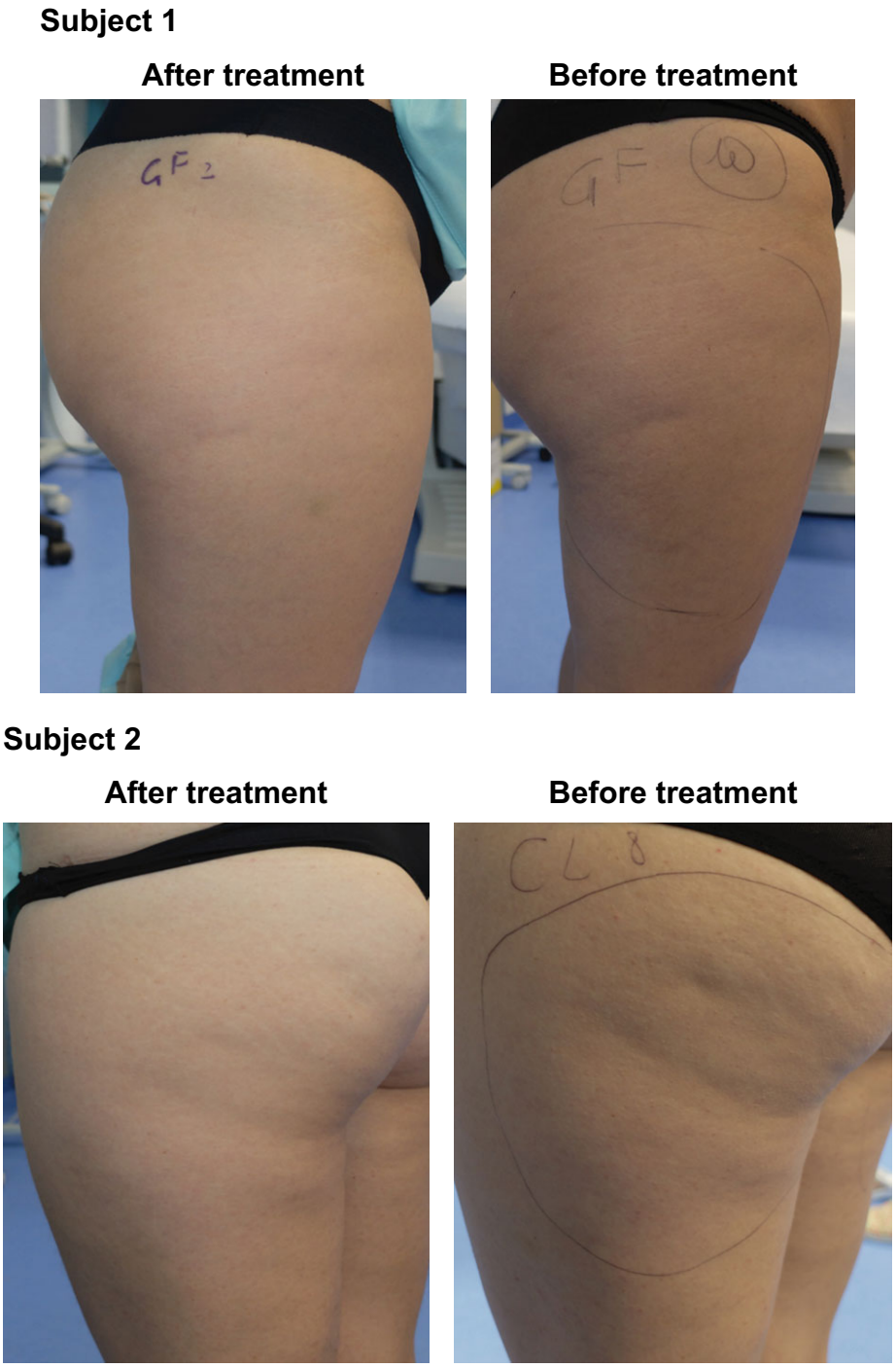


**FIGURE 4** Pictures at baseline and after HCT treatment of 2 subjects (subject 1 and subject 2)

the efficacy of this draining cream in comparison with other anticellulite standard topical products.

## 7 | CONCLUSION

This new HTC has confirmed its efficacy in the improvement of objective and subjective assessments of cellulite parameters.

### ACKNOWLEDGMENTS

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### CONFLICT OF INTEREST

The authors (MP and FT) report no conflict of interests in this work. MM is an employee of Difa Cooper, IFC group.

## AUTHOR CONTRIBUTIONS

MP and FT conducted the trial performing visits and instrumental evaluations. MM involved in study protocol design. All the authors involved in database collection and statistical analysis.

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