Dermatologic Therapy, Vol. 22, 2009, 74–84
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DERMATOLOGIC THERAPY
ISSN 1396-0296

HOT TOPICS

A multicenter study of cellulite treatment with a variable emission radio frequency system

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ABSTRACT: Radio frequency (RF) systems have been reported as producing electrothermally mediated and subcutaneous effects. The present study evaluates a new approach to treat cellulite with a bipolar RF device. The buttocks of 50 patients were treated, 10 from each of five multinational centers with a novel bipolar RF technology set at 6 J/cm^3, which changes its frequency between 0.6 and 2.4 MHz according to impedance of tissue. Twelve weekly sessions were given for 12 minutes on each buttock, with a treatment end point of 42°C external skin temperature. Cellulite changes and tissue condition were assessed before and immediately after the first session, before the final 12th session, and 2 months thereafter. The patient Satisfaction Index was recorded. Objective evaluation involved clinical photography, three-dimensional optical skin surface measurement, and histological findings. Almost all patients noted improvement of cellulite and body silhouette at the final session, which slightly decreased at the 2-month assessment. Improved skin appearance was objectively detected. Histological findings following the first session showed reactive edema and lysis of adipocyte membranes, possibly implicated in the final effects achieved. The RF technology used in the present multicenter study improved the general aspect of skin and cellulite, with high patient Satisfaction Index. Maintenance sessions might lead to even better and longer-lasting results.

KEYWORDS: cellulite, effects of multifrequency radiofrequency, RF technology

Introduction

Cellulite is a disorder of the subcutaneous layer that adversely changes the appearance of the overlying superficial skin. Changes in the fibrotic septae between fat cells and tissue reduce the metabolic rate, thus congesting the tissue repercuting on the skin's external aspect. Skin roughness alteration translates to bumpy, uneven skin (1). Cellulite occurs from puberty onwards in almost all women and when it becomes excessive, it is difficult to control and treat. Several treatment modalities exist, with varying degrees of success (2).

Conflict of interest: None.
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Table 1. Patient characteristics

Number	Age	Skin type	Weight	Number	Age	Skin type	Weight
1	43	II	Stable	26	35	IV	Stable
2	27	III	Stable	27	39	II	Stable
3	33	III	Stable	28	28	II	Stable
4	38	IV	Stable	29	35	III	Stable
5	25	II	Stable	30	27	IV	Stable
6	44	II	Stable	31	27	III	Stable
7	46	II	Stable	32	26	IV	Stable
8	35	III	Stable	33	38	IV	Stable
9	32	IV	Stable	34	42	III	Stable
10	40	II	Stable	35	35	II	Stable
11	44	IV	Stable	36	32	III	Stable
12	34	III	Stable	37	41	IV	Stable
13	28	III	Stable	38	29	IV	Stable
14	44	IV	Stable	39	38	II	Stable
15	31	II	Stable	40	54	IV	Stable
16	57	IV	Stable	41	36	III	Stable
17	28	II	Stable	42	28	II	Stable
18	26	IV	Stable	43	56	III	Stable
19	52	III	Stable	44	36	IV	Stable
20	31	II	Stable	45	42	III	Stable
21	51	II	Stable	46	24	II	Stable
22	29	II	Stable	47	38	IV	Stable
23	27	III	Stable	48	35	II	Stable
24	58	II	Stable	49	37	II	Stable
25	32	IV	Stable	50	37	III	Stable

1–10, Meijel, Holland; 11–20, Cambrils, Spain; 21–30, Milan, Italy; 31–40, Dubai, UAE; 41–50, Alicante, Spain.

Reports have suggested that radio frequency (RF) is effective against cellulite (3–5); however, objective and detailed assessments of its beneficial effects on the skin's external aspect are lacking, and a good understanding of RF effects on the subcutaneous tissue have not yet been clarified.

RF current can be low or high frequency, depending on the emission settings of the RF generator. RF is usually applied in mono or bipolar manner. Both methods employ two electrodes: a delivery and a return electrode. In the case of most "monopolar" RF systems, the delivery electrode is located over the target tissue, and the return electrode is attached at some distance away. In the case of "bipolar" RF, the two electrodes are incorporated in a single handpiece, with the current passing into and through the local tissue between electrodes. The depth of penetration of RF into the tissue is recognized as approximately one-half of the distance between the electrodes.

The therapeutic effects of RF are electrothermal, created by the impedance or resistance of the tissue to the electricity flow through it. The electrothermal damage induces the wound healing process, leading to therapeutic effects. To facilitate good electrical contact between the skin and the electrodes, a transparent coupling gel is applied.

The majority of RF devices operate at a fixed frequency. A novel technology, called automatic multifrequency and low impedance (AMFLI) RF delivers variable frequencies, continuously governed by changes in tissue resistance. The present study, of five multinational centres, was designed to assess the efficacy of this new technology for cellulite in the buttocks.

Subjects and methods

Patients and treatments

Fifty females aged 24–58 (average 36 years), skin phototypes II–V, participated in the study. All patients had maintained a stable weight for the 8 months prior to the trial (Table 1). Patients presented with similar cellulite depositions located in various body areas, especially in the lower limbs, but the buttocks were selected for treatment. No patient had undergone any previous treatments for cellulite. The degree of cellulite was established following Rossi classification (6). All patients had

similar cellulite characteristics, fatty tissue volume, and history of cellulite formation, which was classified as Grade 3, which corresponded to an "orange peel" roughness to the skin, visible at rest. Thin granulations in the deep levels of the skin could be detected by palpation.

All patients were informed of the study purpose and signed a consent form agreeing to clinical photography, biopsies, and to respond to questionnaires. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committees of the respective institutions conducting the trials.

The ThermaLipo™ RF bipolar device (Thermamedic Ltd., Alicante, Spain) is a novel system that incorporates the proprietary AMFLI technology already mentioned. A sensor constantly monitors the return current as an indicator of impedance and adjusts the frequency to achieve total tissue volume penetration while maintaining deeper tissue temperatures to achieve electrothermal damage deposition. The AMFLI technology pulsed-mode RF has the ability to rapidly deposit a high energy load, which increasingly raises the temperature of the subcutis and skin. Pain is experienced when sufficient heat flow is transmitted to the skin's nociceptive receptors of the papillary dermis, stimulating them into action (7). AMFLI RF operates without the need for epidermal cooling, using a coupling gel for electrical contact between the electrodes and the skin.

One treatment per week for 12 sessions was given at a constant fluence of 6 J/cm^3. A minimum of six passes over each area were carried out with the handpiece, maintaining the skin temperature between 40 and 42°C for a minimum of 12 minutes. Burning sensation or pain and/or erythema were used as end points of treatment. The increase in skin temperature to 42°C, monitored by an infrared (IR) thermometer, was taken as the signal to move onto a neighboring area, continuing the treatment. Once the handpiece was moved to another area of the buttock, and one or more of the end points were again achieved, the handpiece was moved back to a previously treated area, and so on. The achievement of end points usually required several handpiece passes. The aim was to maintain stable temperature for 12 minutes. Therefore, movement was constantly going to and from one area to another. End points were supervised at all times and served for maneuvering the handpiece over the buttock.

Noticeable pressure was put on the handpiece at the time of treatment while tracing a figure of eight on the skin surface, and also following the orientation of the Langerhans lines, always moving the tissue upward toward bony prominences in a maneuver to hold and "hook" tissue. Treatment sessions were 45 minutes long. Aloe vera gel was gently applied at the end of each session, and subjects were recommended to avoid exposing treated areas to the sun for 24 hours.

For the histological assessment, 15 of the 50 patients agreed to undergo biopsies for tissue examination before and after the first session and 2 months after the 12th and last session. Samples were routinely processed and stained with hematoxylin-eosin. Digital photography was taken before the first session (baseline) before the final 12th session and at 2 months thereafter.

To subjectively determine the results, 2 months after the last session and, based on the clinical photography, two blinded, independent expert aesthetic surgeons were asked to score the outcome as follows: Very good, if the results were very noticeable; Good, if the results were readily apparent; Fair, if there were few positive changes; and Bad, if there were no changes or cellulite condition was visually worse than before treatment. Any major differences in assessment between the assessors were resolved by discussion until consensus was reached.

Patients were asked to grade their Satisfaction Index (SI) regarding the results by means of questionnaires administrated before the 12th (final) session and 2 months thereafter. At both assessment points, the results were scored as: Very good (65–80% improvement); Good (40–60% improvement); Fair (0–39% improvement); or Bad (0 improvement or worse). No 100% results were expected to be obtained.

In order to assess changes in skin texture, examination of surface roughness was carried out on 10 patients, as a cross-sample with a CLINIPRO Anti-aging SD camera, (Barcelona, Spain), which examined the surface with a 3-D optical image. The area of cellulite chosen for testing was constant and mapped out in order to repeat accurate measurements. Examination of skin surface texture was done at baseline and at the final 2-month assessment point.

The optical surface analysis examined the surface anisotropy surface as well as micro-relieves via the measurement of the depth of depressions and roughness in the skin. The area of cellulite was examined by a computer profilometry software incorporated in the three-dimensional (3-D) system. Skin profilometry was performed with patients in the erect position, and the camera device was placed vertically on the selected area. An in vivo microtopographic scanner recorded images using optical triangulation, with a video light projection

technique and digital image processor. Images were digitized and transferred to the computer for assisted quantitative measurement. Mathematical algorithms embedded in the analytical software reconstructed the data into a highly precise 3-D profile of the skin surface. Evaluations of the software enabled image measurements of 5 × 5 mm (25 mm^2) and calculation of the cellulite texture to be compared with data obtained from an image taken from an area of normal skin of the same patient outside the cellulite area. Images of the 3-D profiles were arranged in a parallel array for comparative checking. The roughness index was determined by the computer, represented by *R* corresponding to the difference between the maximum and minimum mean values, i.e., peaks and valleys of the skin surface of the area examined. Five and 40 were the minimum and maximum values, respectively; the former being baby skin texture and the latter the severely aged skin.

Results

The 10 patients from each of the five centers completed the study. Upon visual examination, most of them scored as "Good" regarding the aspect of the cellulite areas treated at the assessment before the final 12th session. Scores showed a slight tendency to decrease at the 2-month assessment. All 50 patients noticed an improvement in skin characteristics. Less surface depressions were reported and all said that the skin appeared smoother to the touch. Scores, subjectively, at the final 2-month assessment were: 12, Very good; 26, Good; and 12, Fair. No Bad results were scored. Results varied a little from the evaluation requested before Session 12 (Table 2). The SI as calculated by the sum of the Very good and Good scores, expressed as a percentage, was 76%. Based on the photography at baseline and at the 2-month assessment, the clinicians' objective assessment of the cellulite appearance was: 12, Very good; 21, Good; and 17, Fair. No Bad results were scored. The overall clinical efficacy

Table 2. Results at final assessment

Scores	Patient	Doctor
Very good	12	12
Good	26	21
Fair	12	17
Bad	0	0

Satisfaction Index deduced from adding Very good and Good results was 76%.

Table 3. Results per center

	Holland			Spain			Italy			UAE			Spain		
	Patient before Session 12	Patient, 2 months after	Doctor, 2 months after	Patient before Session 12	Patient, 2 months after	Doctor, 2 months after	Patient before Session 12	Patient, 2 months after	Doctor, 2 months after	Patient before Session 12	Patient, 2 months after	Doctor, 2 months after	Patient before Session 12	Patient, 2 months after	Doctor, 2 months after
Scores	Subjective evaluation		Objective evaluation	Subjective evaluation		Objective evaluation	Subjective evaluation		Objective evaluation	Subjective evaluation		Objective evaluation	Subjective evaluation		Objective evaluation
Very good	4	3	3	2	1	1	4	3	3	3	2	3	4	3	2
Good	4	5	4	6	5	3	5	6	5	6	5	4	6	5	5
Fair	2	2	3	2	4	6	1	1	2	1	3	3	0	2	3
Bad	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Patient's results correspond to the subjective evaluation before session number 12 and 2 months after the last session. Doctor's evaluation (objective) was carried out by examining photographs of before and 2 months after the last session.

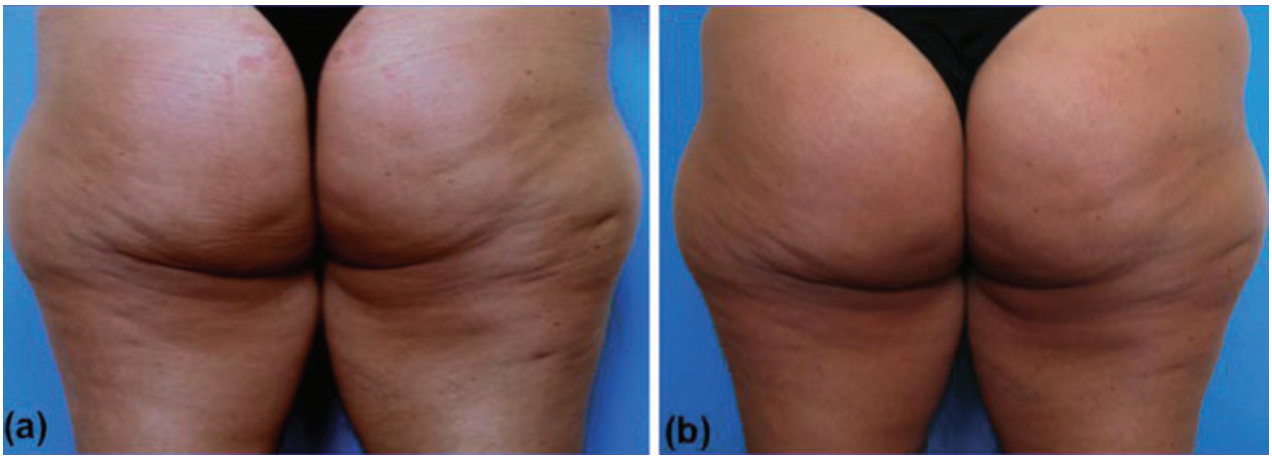

FIG. 1. **(a) Before treatment. (b) Before the 12th treatment session. Note the clear changes achieved on the cellulite conformation.**

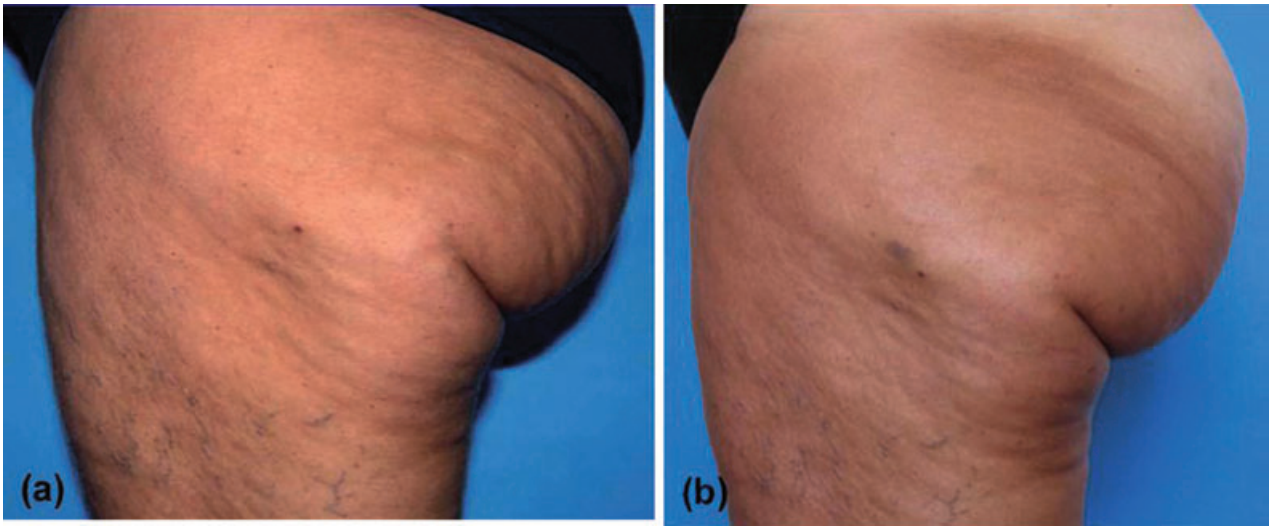

FIG. 2. **Same patient as FIG. 1. (a) Before treatment. (b) Before the 12th treatment session. Favorable changes are more evident in the lateral photography of the area of the buttock treated.**

calculated as the sum of the Very good and Good, expressed as a percentage, was 66%. (Table 2). As for the sensation of pain during treatment, a fairly constant correlation was noted between pain and a temperature of around 42–44°C as seen on the IR thermometer. No patient asked for the treatment to be stopped because of pain, and no complications were observed at any center.

During treatment all patients showed erythema, which was usually reported to disappear 4 and 24 hours after treatment; FIGS. 1–4 represent an example of the clinical photography at baseline, before the 12th session, and at the 2-month final assessment. Table 3 and FIGS. 5 and 6 show results at baseline, before Session 12, and at the 2-month assessment as reported by patients and doctors at the various centers.

The histological findings immediately after the first session showed separation of fibers in the dermis which was presumed to be a consequence of oedema. The epidermis appeared without alterations and the dermis showed some lymphocytic inflammatory infiltrate. Dilated, ectatic vessels were in between the adipocytes, which also presented membrane lysis. This was noticed as a constant sign in all samples examined. No lipid related material was identified outside the adipocytes (FIGS. 7–9).

In specimens of the 2-month assessment, the epidermis appeared multicellular with good rete peg formation. The dermal collagen appeared more plentiful, tighter, and better organized, particularly visible as a band of linearly organized fibers under the epidermal basal membrane

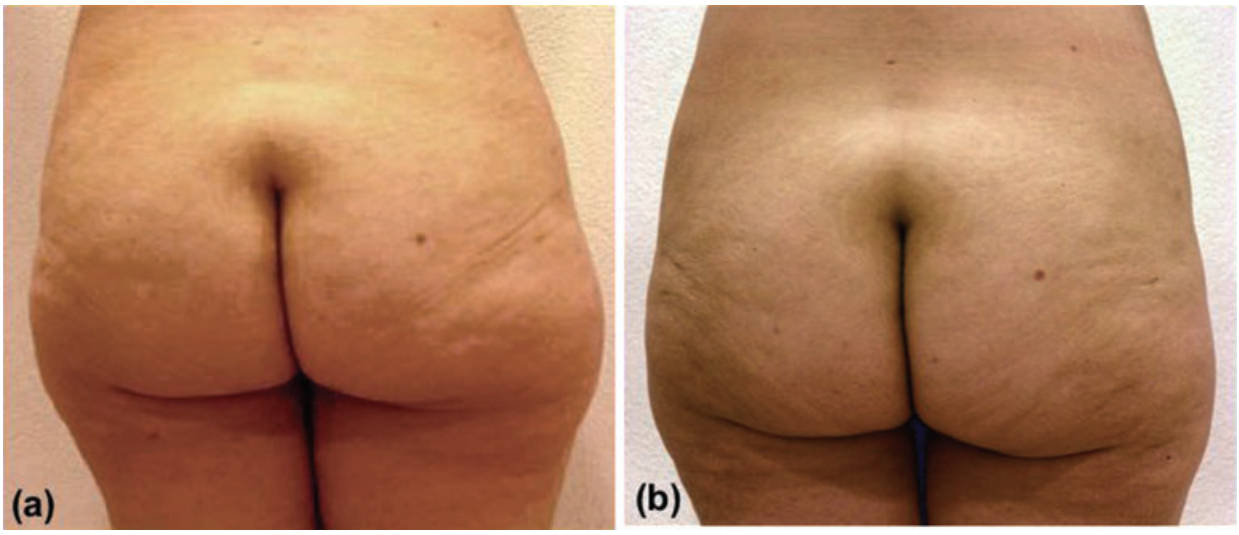

FIG. 3. **(a) Before treatment. (b) Before the 12th treatment session. Notice the appreciable changes in volume as well as improved skin appearance with smoother surface.**

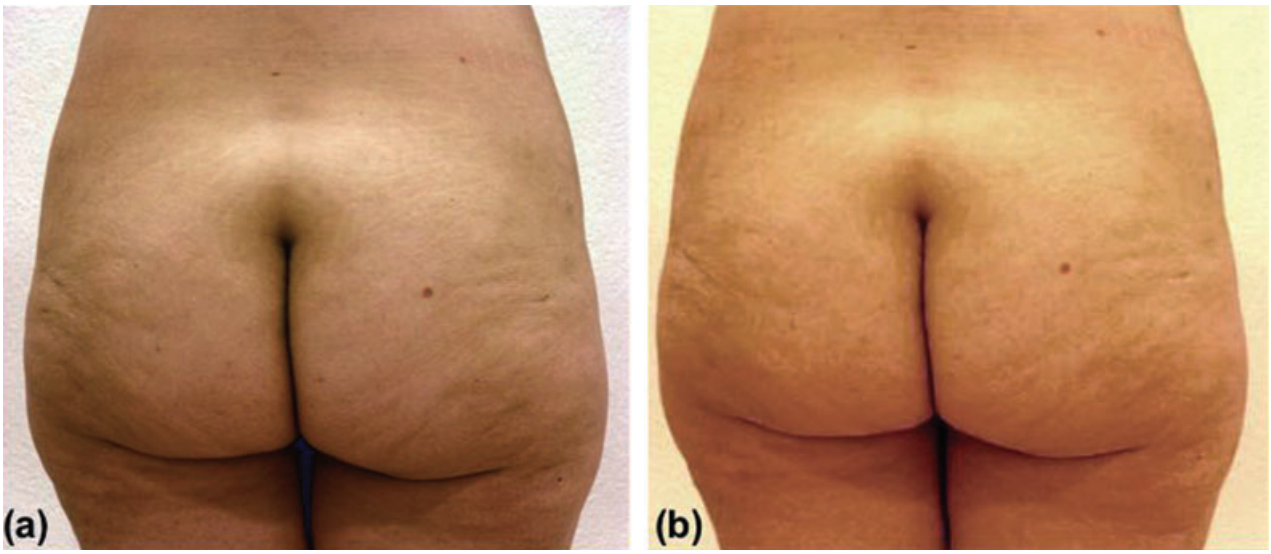

FIG. 4. **Same patient as in FIG. 3. (a) Before the 12th treatment session. (b) Two months after the 12th treatment session. Maintenance of benefits achieved by the radio frequency treatment sessions continue. Moreover, favorable changes can be seen 2 months after the last treatment, which may a result of the further effects of skin tightening by collagen action**.

(FIG. 10). Skin texture using 3-D optical skin imaging showed improvement at the final 2-month assessment compared with baseline, of less depth component in the *R* value of skin roughness, that is to say, a smoother-looking skin. On the 3-D scale, the skin surface micro-relieves were between 16 and 22 points better at the final assessment than at baseline, which corresponded to an improvement of about 42–55% in texture (FIG. 11). The logarithmic tables delivered by the computer calculation presented a significant improvement in the skin texture with a more even skin surface.

Discussion

The results obtained on the treated areas of cellulite were clearly apparent upon examination of the before and after photographs demonstrating an overall improvement of the shape of the buttocks, and less evidence of the usual cellulite-associated dimpled appearance. Patients were also satisfied with the treatment, and there was high compliance with the program of sessions. In an unusual result, the patient SI of 76% was higher than the overall efficacy of 66% as evaluated by the clinicians,

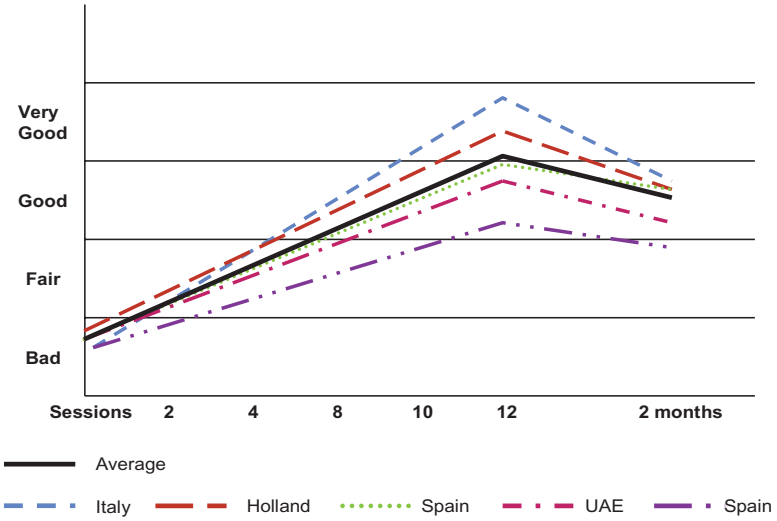

FIG. 5. Results given by patients of the various centers.

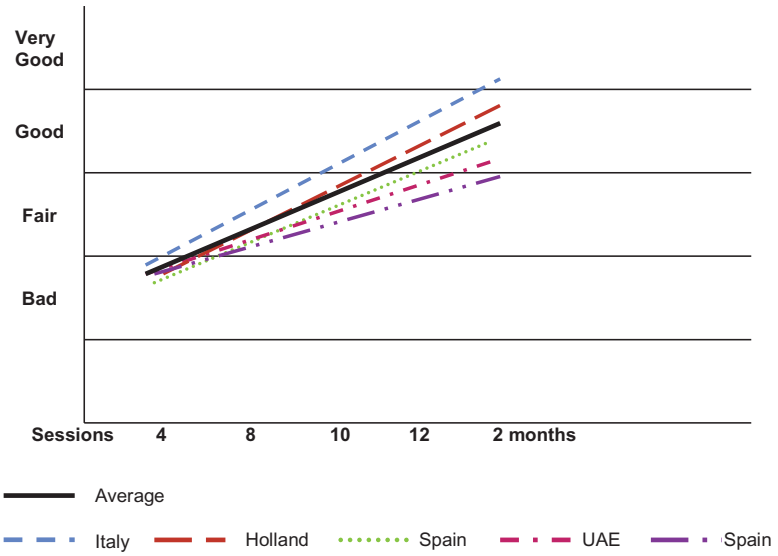

FIG. 6. Results given by doctors at the various centers, 2 months after the last treatment session.

which accounts for the excellent compliance across all subjects at all five centers.

The variable-frequency RF system used does not deliver the energy in stacked pulses, which usually build up a bulk block of energy, resulting in overheating and excessive pain. In the system of the present study, the continuous emission of different frequencies, acting on different tissue depth, produces a progressive increase in the heat deposit. The regimen of repeated handpiece passes over the skin, then moving to the next area once a minimum temperature of 42°C, pain, unpleasant heat sensation, or significant erythema were present, before moving back to the previous treated area to deliver more passes, maintains a reasonably steady profile of thermal increase. This would be crucial necessary to induce the cascade of inflammation needed for adipocyte lysis and to stimulate neocollagenesis. The good control of the treatment based on the consistent guidance of end points allowed for safe and well-tolerated treatments. According to the authors' observations, efficacy is based on the change of frequencies that treat different levels, depending on the tissue impedance. Safety is safeguarded by the peripheral nociceptive receptors. A pain signal will appear when thermal profile increases (8).

The improvement in skin roughness detected by the 3-D skin surface analysis system agreed with the objective results, and in addition, all

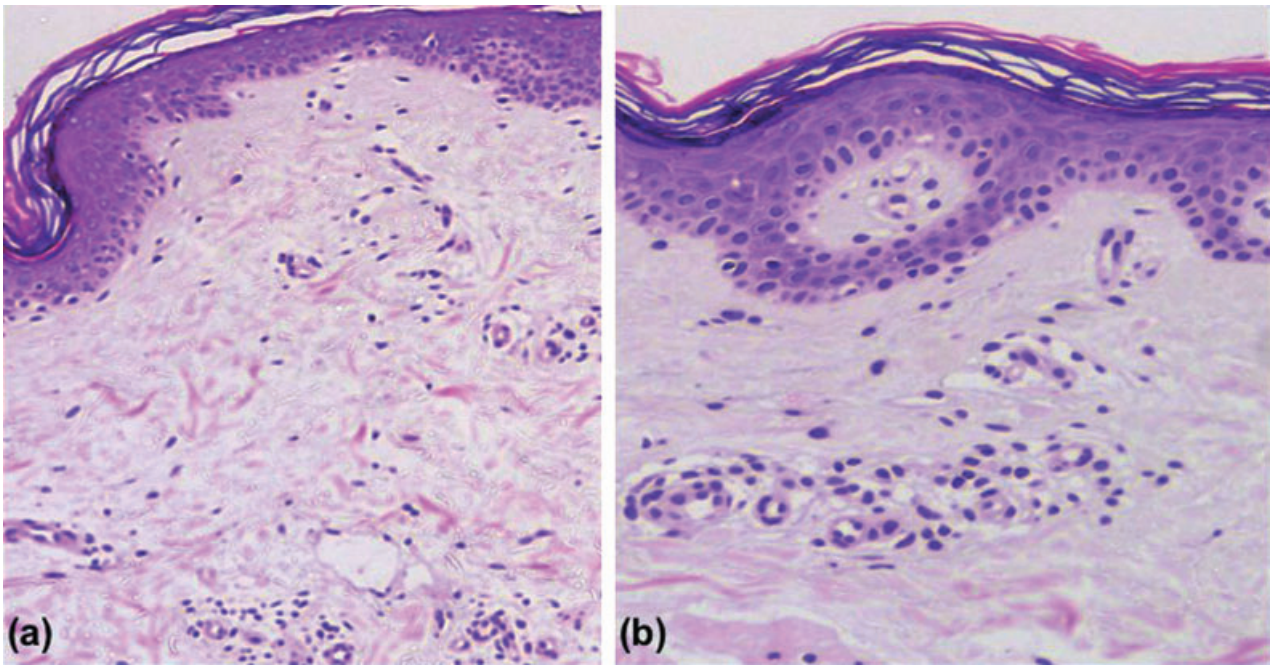

FIG. 7. Histology (a) before treatment and (b) immediately after the first treatment session. Keratin layer appears flatter and epidermis presents slight dilation, apparently with cells somewhat separated, which could be attributed to edema. Fibers in dermis are more aligned.

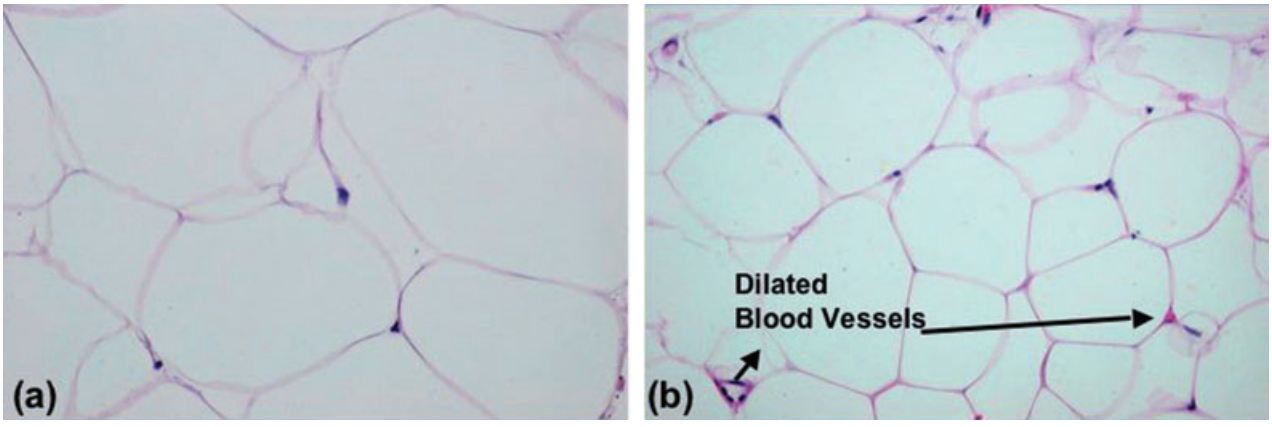

FIG. 8. Histology (a) before treatment and (b) immediately after the first treatment session. Vessels are dilated in contrast to before treatment, where their lumen cannot be noticed.

patients reported better skin condition upon visual examination and tactile checking of the treated area.

The histological findings showed that absorption of RF energy, transformed into a thermally mediated inflammatory reaction in the dermis, led to the wound healing process and an improvement in the overall tissue characteristics with new collagen formation. Effects on the subcutaneous fat layer seemed to be consequent to heat propagation occurring during the consistent minimum of 12 minutes treatments per area with various handpiece passes. Heat conducted to the subcutaneous layer is absorbed by adiposities because of lower water content than other tissue, which may also present a higher resistance to any RF current, the combination of which produced the membrane lysis.

During treatment, pain was only reported when the IR thermometer-measured skin temperature increased to 42–44°C, detected by the papillary dermis nociceptive receptors; however, no patient asked for the treatment to be halted. Prior to the skin reaching this temperature, the system under

AMFLI monitoring delivers low-frequency RF, which produces deeper and stronger thermal effects in the dermis and subdermis. The electrodes in this "bipolar" system are comparatively far apart, 4 cm, so the maximum theoretical penetration into the target tissue will be in the order of 20 mm, with the current being delivered at a low frequency. The higher the temperature within the path of the current, the lower the impedance, and thus the greater the resulting wave of heat will be.

Once the impedance is detected by the built-in microprocessor, the system automatically switches to a higher frequency while maintaining the fluence, thus producing more superficial effects but still maintaining deeper tissue temperature increase under external controlled skin temperature within the 42–44°C range to prevent the occurrence of pain. Raising the frequency thus allows the deeper tissues to cool slightly to avoid overheating and epidermis damage through the propagation of heat. This automatic switching of the incident current frequency is further believed to deliver a homogeneous level of electrothermal and conducted heat damage down through tissue layers while sparing the epidermis, which is both safe and well tolerated by the subject. This novel technology is promising because it allows maintenance of the heat developed in tissue to bearable levels of pain and provides burn-free thermal accumulation, which is nicely implemented for the treatment of cellulite.

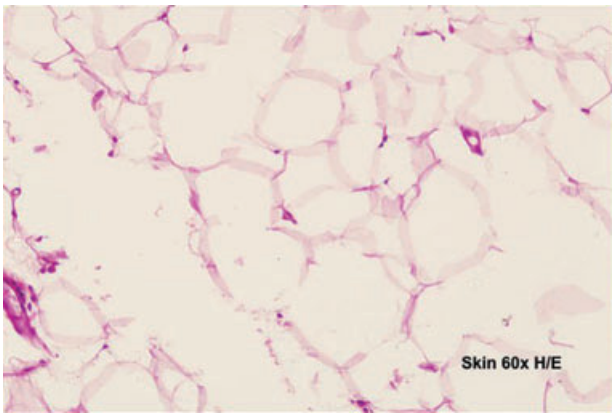

FIG. 9. Histology immediately after the first treatment session. Notice adipocyte membrane lysis. Also, membrane appears thicker and with changes in its conformation.

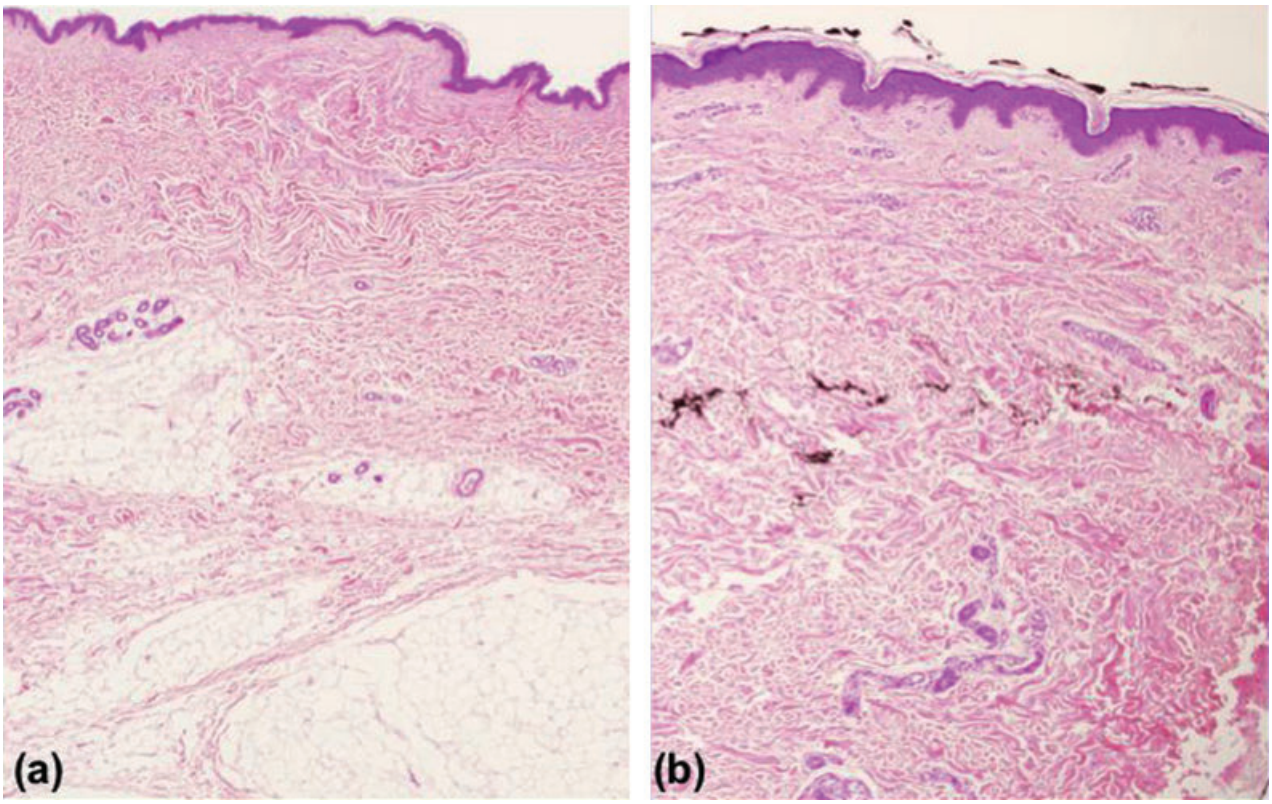

FIG. 10. Histology (a) before treatment and (b) 2 months after the 12th treatment session. Epidermis appears thicker, with more cell layers, dermis is somewhat more compacted, and fibers appear aligned and parallel. Notice that there is a difference in the subcutaneous layers: before fat tissue was entering in dermis, and after treatment it is being "pushed" down.

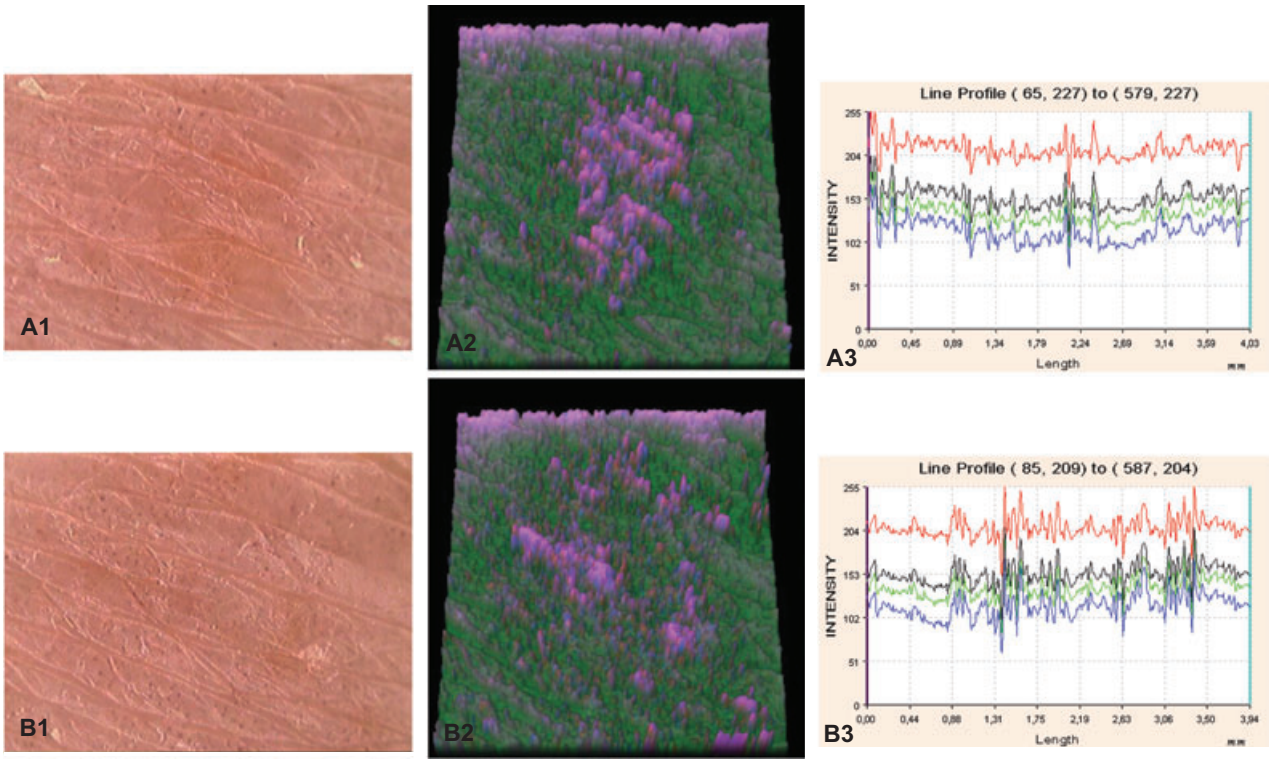

FIG. 11. Three-dimensional visual images as shown by the computer analysis. A1 represents cellulite skin of the selected area for comparative tests. B1 is 2 months after the last treatment session. Notice the differences in the skin condition, with changes in surface appearance and depth. A2 and B2 are computer-generated graphic representations of the cellulite skin area selected for treatment in relief to express the depth of skin surface. The graph is achieved by making a three-dimensional cut after breaking down the skin surface image, which permits the exact recreation of the surface relief in micrometers. These data are also displayed in logarithmic tables (see A3 and B3) so that percentages can be calculated as how the depth in tissue surface variation is presented according to the moment of treatment. Lines on the graphic representation of after treatment are flatter, which corresponds to a smoother, more even skin surface.

When using high monopolar or bipolar RF energies in a pulsed mode, the effect in the skin is limited only to a certain volume, directly in relation to the programmed pulse width and energy. Usually, when energy is delivered in pulses, deposits of energy occur rapidly, producing significant pain resulting from the "stacking" of the individual pulses. However, the system used delivers RF in a pulsed wave, so that temperatures are kept high. When combined with the variable-frequency technology, the subject's own nociceptors will act as an early warning system and prevent any tissue burning. This is reinforced by the continuous figure-of-eight motion of the handpiece over the target, ensuring even propagation of electrothermal energy conducting heat to surrounding and deeper tissues.

At the start of treatment, the temperature detected by the IR thermometer, measured on skin surface, is low; approximately 32°C. During treatment, the skin temperature increases to the 42–44°C range, which corresponds to an estimated temperature around 45–48°C at a maximum depth of 20 mm. This range of temperature has been detected in a pilot study conducted by one of the coauthors of the present study (CVDL, data not published). At this temperature range, protein degradation will occur together with protein denaturation, thus providing the impetus for the wound healing process.

The tissue temperature increase resulting from the resistance to the electric current depends on the state of hydration of the tissue and its electrolytic concentration (9). Hypothetically, applying the handpiece in eight hand movements might encourage random inhomogeneous tightening of collagen. Then, when tissue temperature reaches the skin surface and the handpiece applied with more pressure following traction lines and Langerhans lines, the heat-labile intermolecular collagen hydrogen bonds will denature (i.e., protein denaturation), enabling collagen fibers to be stretched and

reshaped in an upward direction. This physical effect has been reported to occur under a certain pressure, and it has been proven in endothelial vessel cell cultures and in fibroblasts, which were induced to produce more collagen synthesis under rhythmic unidirectional traction (10,11). In the meantime, the nonheat-sensitive bonds and collagen monofilaments (peptides) shrink. When the tissue temperature returns close to its base temperature, the denatured bonds will reform, but in a different position to before denaturation (12,13). This will eventually lead to skin tightening in addition to the neocollagenesis induced by the inflammatory process associated with the repair of the microwounds, caused by the RF electrothermal effect.

This hypothesis is supported by the results that have been obtained consistently in the population of 50 patients treated in the five multinational centers. The application of the handpiece in a specific pattern and pressure, in addition to sufficient time in every area of treatment of the skin, maintaining heat increase, optimize the outcome. It is also important to put emphasis on bony protuberances, which act as "coat hooks" or landmarks for pulling the tissue in the desired direction. These areas may be subject to pain upon treatment because of the proximity of the bone to skin surface, but a firming reaction will be more clearly obtained in the treated area, as the authors have observed clinically. The fact that progressive tissue heating with bearable pain and/or burning sensation actually does lead to tangible results and to excellent treatment compliance would also be a reason for patients to accept maintenance sessions, which should be carried out every 2 months. Without further treatment a slight decrease in the objective and subjective positive effects occurred, as shown by the assessments. Further investigations are warranted to determine the effects of treatment conducted for longer periods and with prolonged follow-up.

Acknowledgement

The authors acknowledge receipt of a grant for the present study from Thermamedic. The ThermaLipo device was on loan during the period of trials for the present study.

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