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CASE REPORT AND SHORT REPORT

Placebo controlled, prospectively randomized, double-blinded study for the investigation of the effectiveness and safety of the acoustic wave therapy (AWT®) for cellulite treatment

KATHARINA RUSSE-WILFLINGSEDER[1], ELISABETH RUSSE[1], JOHANNES C. VESTER[2], GERD HALLER[3], PAVEL NOVAK[3] & ALEXANDER KROTZ[3]

[1]*Praxis und Laserzentrum, Haydnplatz 4, Insbruck, Austria,* [2]*idv Datenanalyse und Versuchsplanung, Krailling, Germany, and* [3]*Storz Medical AG, Productmanagement, Lohstampfestrasse 8, Tägerwilen, Switzerland*

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Abstract

Placebo controlled double-blinded, prospectively randomized clinical trial with 17 patients (11 verum, 5 placebo) for evaluation of cellulite treatment with Acoustic Wave Therapy, (AWT®) was performed.

The patients were treated once a week for 7 weeks, a total of 8 treatments with the D-ACTOR® 200 by Storz Medical AG. Data were collected at baseline, before 8th treatment, at 1 month (follow-up 1) and at 3 months (follow-up 2) after the last treatment with a patients' questionnaire, weight control, measurement of circumference and standardized photography. Treatment progress was further documented using a specially designed 3D imaging system (SkinSCAN^{3D}, 3D-Shape GmbH) providing an objective measure of cellulite (primary efficacy criteria).

Patient's questionnaire in the verum group revealed an improvement in number and depth of dimples, skin firmness and texture, in shape and in reduction of circumference. The overall result (of skin waviness, Sq and Sz, surface and volume of depressions and elevations, Vvv and Vmp) at two follow-up visits indicates a more than medium sized superiority (MW = 0.6706) and is statistically significant ($p_{\text{Wei–Lachin}} = 0.0106$). The placebo group revealed no statistical significance. No side effects were seen. This indicates the efficacy and safety of AWT® for patients with cellulite.

Key Words: *acoustic wave therapy, adipose tissue, cellulite, extracorporeal pulse activation technology, extracorporeal shock wave treatment, 3D skin measurements*

Abbreviations: *AWT, acoustic wave treatment; EPAT, extracorporeal pulse activation technology; ESWT, extracorporeal shock wave treatment; BMI, body mass index; Sq, root mean square height of the surface; Sz, absolute height of the surface; Vvv, normalized volume of depressions; Vmp, normalized volume of elevations*

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Introduction

Although not considered a disease, but rather a purely aesthetic problem, cellulite describes the mattress phenomenon of the skin and affects 95% of women of all ethnics. It can lead to negative consequences, primarily from a psychological point of view like low self-esteem. The pathophysiology of cellulite is complex.

The cellulite-typical appearance of female skin is caused by the specific structure of the collagen fibre bundles: the fat cell chambers with the surrounding fibre bundles project straight upwards into the corium. The male subcutis, on the other hand, is held together by lattice-shaped tangential fibre bundles. The enlarging of fat cells between the septa not only causes the dimpling effect, but also reduces microcirculation of blood and lymph which may lead to intracellular oedema and reduced lymphatic drainage resulting in an increased storage of fat (1). The pathophysiology involves alterations of adipose tissue and microcirculation causing a fibrosis of the connective tissue. This is a non-inflammatory degenerative process which results in the well-known mattress aspect on the skin surface (2,3).

This study applies acoustic wave treatment (AWT®) for the dermatological/aesthetic application of temporarily reducing the appearance of cellulite. It is known that metabolism and circulation are

Correspondence: Dr Katharina Russe-Wilflingseder, Praxis und Laserzentrum, Haydnplatz 4, A – 6020 Innsbruck, Austria. Tel: + 43-(0)512-58 72 27-0. Fax: + 43-(0)512-58 72 27–30. E-mail: ordination@russe.at; Website: www.russe.at and www.laserinnsbruck.com

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stimulated through the use of acoustic waves (4). Neovascularization (the growth of new blood vessels) and increased cell proliferation are proven mechanisms of action of pressure waves (5). AWT® showed evidence of collagen remodelling within the dermis (6) and of stimulating microcirculation in fatty tissue (7). Extracorporeal shock wave treatment (ESWT) also is concluded to have a fibrosclerosis-preventing effect and is free of side effects (8). The side effects of acoustic pressure waves tailored to the subcutis are reduced to a minimum; at most, mild pain and a reddening of the skin can be expected during the treatment.

The objective of this study is the demonstration of the efficacy and safety of AWT in the treatment of cellulite. A clinical evaluation by comparing before and after pictures as well as an objective measurement using skin topography measurements from a 3D imaging system is used for demonstrating these features.

Materials and methods

Treatment was performed using the D-ACTOR® 200 by Storz Medical AG (Tägerwilen, Switzerland) (Figure 1).



Figure 1. D-Actor® 200 with handpiece.

The D-ACTOR® 200 is a vibrating massage system (extracorporeal pulse activation technology (EPAT®)) that operates via compressed air to perform AWT® on targeted tissue. The system consists of a control unit, a pneumatically driven handpiece with multiple types of transmitters, and a pressurized air source. The pulses are generated in a ballistic way by accelerating a projectile with pressurized air, which strikes a stationary surface, the vibration transmitter. The generated vibrations, the radial acoustic waves propagate directly into the treated tissue.

Two different transmitters were used in this study, the Deep Impact® transmitter DI15 and the D-Actor® transmitter D20-S.

Patients in the placebo group were treated with the same parameters, but with a specially designed placebo handpiece, where the energy transfer to the transmitter was blocked and thus an effective treatment prevented.

During screening, patients completed also a questionnaire covering: demographics, medical background and potential contraindications to this therapy. Each patient signed an informed consent covering the risks and benefits of the procedure.

In previous studies (9,10) patients were treated only on one side while the other side served as control. As also the control leg is being improved the authors explained this finding with a systemic effect of AWT®.

The patients are randomly assigned into a verum and a placebo group with a block size of six and a ratio of two verum to one placebo.

Each thigh was partitioned in three areas: front side, back side and buttocks.

The treatment was performed with the DI15 transmitter within an energy range of 2–3 bar and the D20-S transmitter at 3–5 bar pressure setting, depending on pain sensation that was tolerated by the patient. Each area was treated with a dose of 1000 pulses with the DI15 transmitter and 2500 pulses with the D-20S transmitter.

The patients were treated once a week for 7 weeks, a total of eight treatments. The handpiece emitting radial acoustic waves was moved with slight pressure in skin contact towards the lymph nodes and backwards without pressure, expecting a centripetal direction of treatment.

During and after the treatment period, the patients had to rank the number of dimples, depth of dimples, skin firmness, skin texture, shape and reduction of circumference with worse, equal or improved. This was done before the first treatment (baseline), before the 8th treatment (2), at follow-up 1 (3), 4 weeks after the last treatment and at follow-up 2 (4), 12 weeks after the last treatment.

Treatment progress was documented using a specially designed camera system (SkinSCAN^{3D}, 3D-Shape GmbH, Erlangen, Germany). 3D images of the skin structure were taken using fringe

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projection technology. Different patterns of fringes were projected onto the skin surface, and the deviations of the patterns were recorded with two cameras. From these deviations the height coordinates could be calculated. These 3D images were used as the primary criterion in the study.

One 3D image of the skin contains the X, Y and Z coordinates for each pixel of the surface. The surface analysis software Mountains Map (www.digitalsurf.com) was used to perform a number of different image operations. The goal was to obtain the surface of the same area at the four time intervals: baseline, before the 8th treatment, follow-up 1 and follow-up 2. At first, unrealistic deviations in the height coordinate of single pixels, resulting from occasional image sensor errors, were smoothed using a 9×9 pixel circular smooth filter. Afterwards it was necessary to find the common area where all four images were matching. This was an important step, because it was not possible to place the patients in exactly the same position, when the images were taken.

From this maximal matching area, which still had as example the curved form of the thigh, a polynomial of 5th order was fitted and subtracted to obtain a flat surface. As really small structures are not interested in, like pores or goose skin, a Gauss waviness/roughness filter of 2.5 mm was applied. The result was a false colour waviness image (Figure 2) where the height information is colour coded. At last, the largest common area size fitting for all patients was identified as a square of size 60×60 mm^2. The result was an equally sized area for all patients.

The standards dealing with areal surface textures are included in the ISO 25178 standard. For the description of our surfaces, we took the following parameters:

Sq: root mean square (rms) height of the surface [mm]

Sz: absolute height of the surface [mm]

Vvv: normalized volume of depressions [mm^3/mm^2]

Vmp: normalized volume of elevations [mm^3/mm^2]

In addition, 2D picture of the same area were taken with an additional camera. The field of view was approximately 10×12 cm^2. Therefore a series of photographs had to be taken to cover the whole treatment area. Photographs were taken at baseline, before the 8th treatment, at follow-up 1 and follow-up 2.

Figure 3 also shows patient 04LS at baseline, before the 8th treatment, at follow-up 1 and at follow-up 2. The circle shows the improvement of the dimples.

Four blinded observers were asked to rate the therapy by evaluation of the 2D photographs. For each patient two areas at the following time intervals, baseline, follow-up 1 and follow-up 2 were selected and the blinded observer had to judge the photographs according to a "Modified Hexsel Scale" (11). The modification was necessary, as point E of the Hexsel scale can only be assessed by palpation in direct contact with the patient.

The statistical analysis of the "Modified Hexsel scale" was performed with the software SigmaStat 3.5 (www.systat.com). All other statistical analyses were performed using the statistical software package TESTIMATE (idv/Krailling), version 6.5, figures have been created using ScienceGraph, version 4.9. The according statistical test details are given in the particular graph.

Results

Demographic data and baseline comparability

There were 17 female patients included into this study. One patient dropped out due to pregnancy,

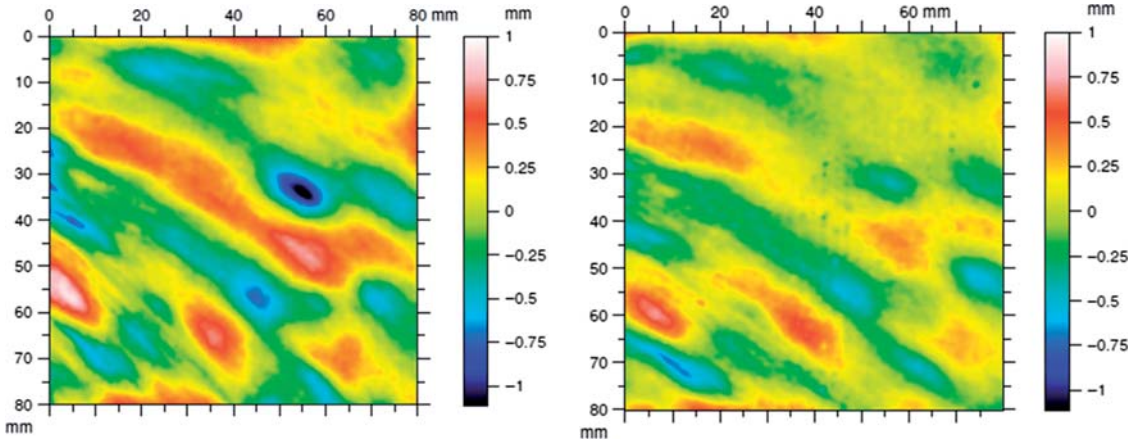

Figure 2. False colour picture covering an area of 80×80 mm^2 of the buttock of patient 04LS. Colour coding represents the height information from black for the deepest depression to white for the highest elevation. Left: baseline: Sq = 0.289 mm; Sz = 2.11 mm; Vvv = 0.0113 mm^3/mm^2; Vmp = 0.0311 mm^3/mm^2. Right: follow-up 1: Sq = 0.198 mm; Sz = 1.43 mm; Vvv = 0.00935 mm^3/mm^2; Vmp = 0.0223 mm^3/mm^2.

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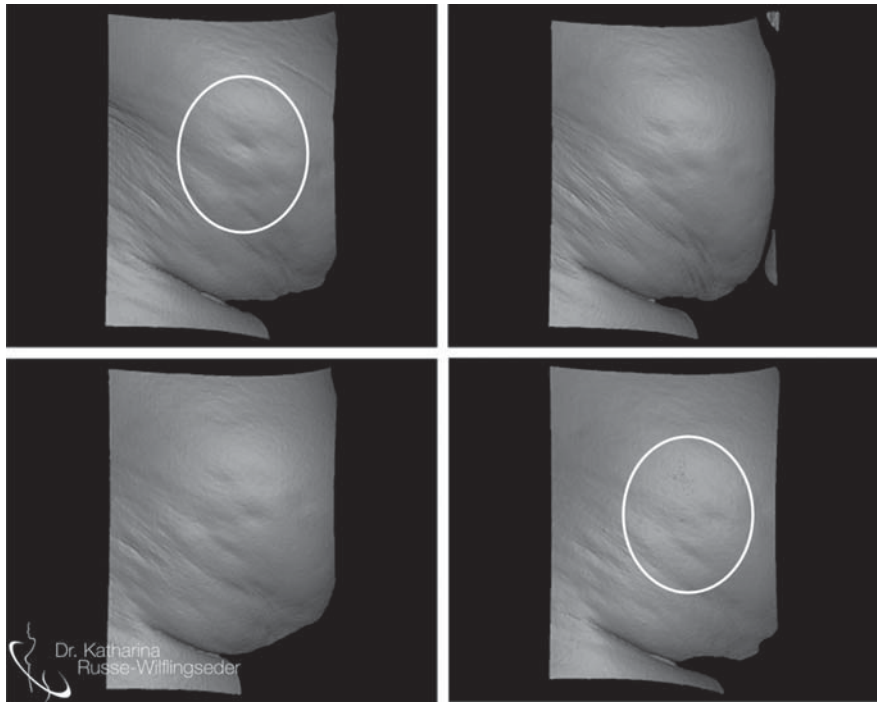

Figure 3. 2D picture of the buttock of patient 04LS. Up right at baseline, up left before the 8th treatment, down left follow-up 1 at 1 month, down right follow-up 2 at 3 month.

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which was one of the contraindications. Out of these 16 patients, 11 were randomly assigned to the verum group, whereas 5 were assigned to the placebo group. Their average age was 42.7 years (26–54, SD 7.4), the average body height was 165.3 cm (150–178, SD 5.4), the average body weight was 61.5 kg (51.5–78.6, SD 7.4), the resulting body mass index (BMI) was 22.50 (19.12–27.4, SD 1.85), the average diameter of both the left and right thigh was 55.7 cm (53–63.5, SD 2.9) and the average duration of cellulite was 17.9 years (5–40, SD 9.6).

As expected for data of cellulite patients, the raw values of the various measurements show large variations combined with outliers. In this case parametric analyses tend to be biased, especially in the case of low patient numbers as is the case in this study. Thus, a non-parametric approach should be preferred in this situation. The following table (Figure 4) shows the standardized non-parametric effect sizes of the univariate Wilcoxon tests for the demographic–anamnestic data at the baseline visit (Mann–Whitney estimator, two-sided 95% confidence intervals):

As shown in Figure 4, groups are well comparable at baseline with regard to the standardized effect sizes of age, height and BMI. With regard to duration of cellulite a more than "small" but less than "medium-sized" baseline difference was found ($MW < 0.64$); for weight and circumference of the thigh a more than "medium-sized" baseline difference was shown by the effect sizes (weight: $MW = 0.6727$; thigh: $MW = 0.6818$). Due to the small number of patients none of these baseline differences is statistically significant.

Patients' questionnaire

The patients' questionnaire asked for six different aspects which could be answered with worse (−1), equal (0) or improved (1). The following parameters were evaluated: number of dimples, depths of dimples, skin firmness, skin texture, shape of the treated area and reduction of the circumference at the treated area. The result for the verum group is given in Figure 5.

Most of the patients recognized an improvement for the first 4 parameters, whereas 6 out of 11 realized a shape improvement and 4 out of 11 could notice a reduction of the circumference. Most importantly note that no question was answered with "worse".

Three out of 11 verum patients did not like the treatment, whereas all placebo patients accepted the treatment without objection.

Photo documentation

The 2D pictures were evaluated from blinded observers using the "Modified Hexsel Scale (CSS)", which ranges from 0 points (no cellulite) to 12 points (maximum cellulite). Statistical evaluation was performed using Wilcoxon Signed Rank tests. Results are given in Table I. All four investigators recognized a statistically significant improvement of the cellulite in the verum group from the baseline to the follow-up 2. They were not able to see any difference in the placebo group.

All four examiners saw a significant decrease of the appearance of cellulite from baseline to follow-up

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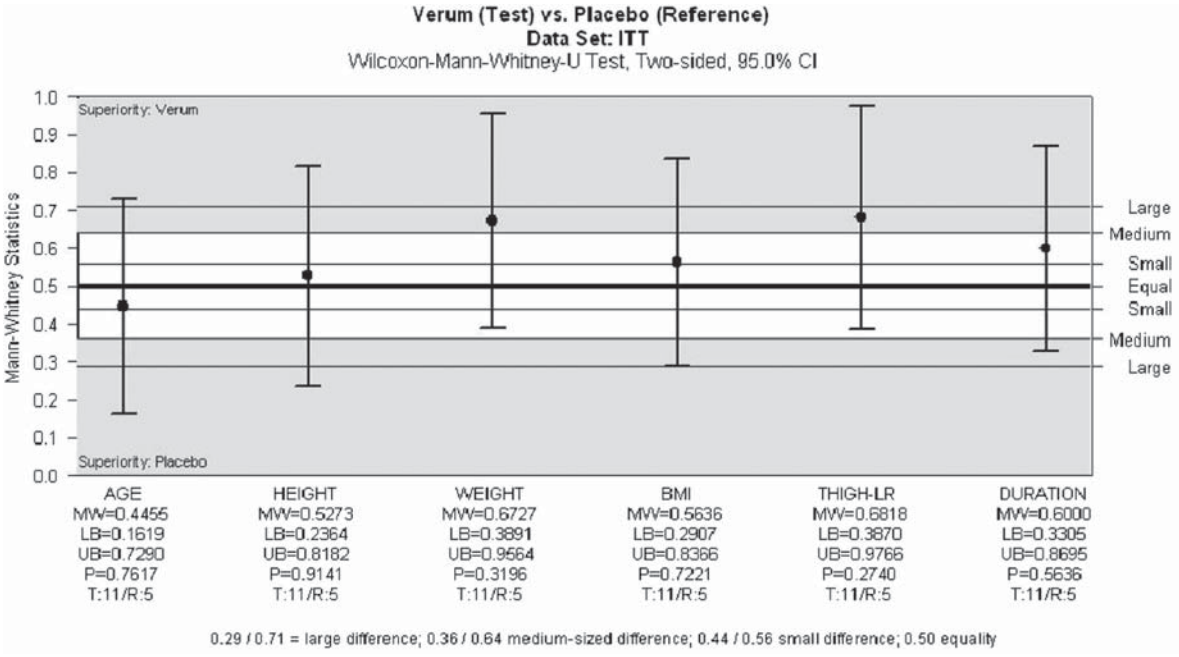

Figure 4. Demographic–Anamnestic characteristics for baseline comparability.

2 in the verum group, whereas no statistically significant decrease could be seen in the placebo group. The evidence is less significant for the comparison of the baseline with follow-up 1 (Figure 6).

3D images

The 3D images were evaluated for two different areas per patient and for three relevant time steps: baseline, follow-up 1 (xxx3) and follow-up 2 (xxx4). For the efficacy variables Sq, Sz, Vmp and Vvv the percent changes from baseline were used as effective adjustment for potential baseline differences.

As example in Figure 7, SQP3 is the difference in percentages of the root mean square (rms) height of the surface at follow-up 1 compared to baseline.

The four efficacy variables and the two follow-up visits have been combined by means of the multivariate Wilcoxon test (Wei–Lachin procedure) (12) in order to obtain more precise effect sizes in the

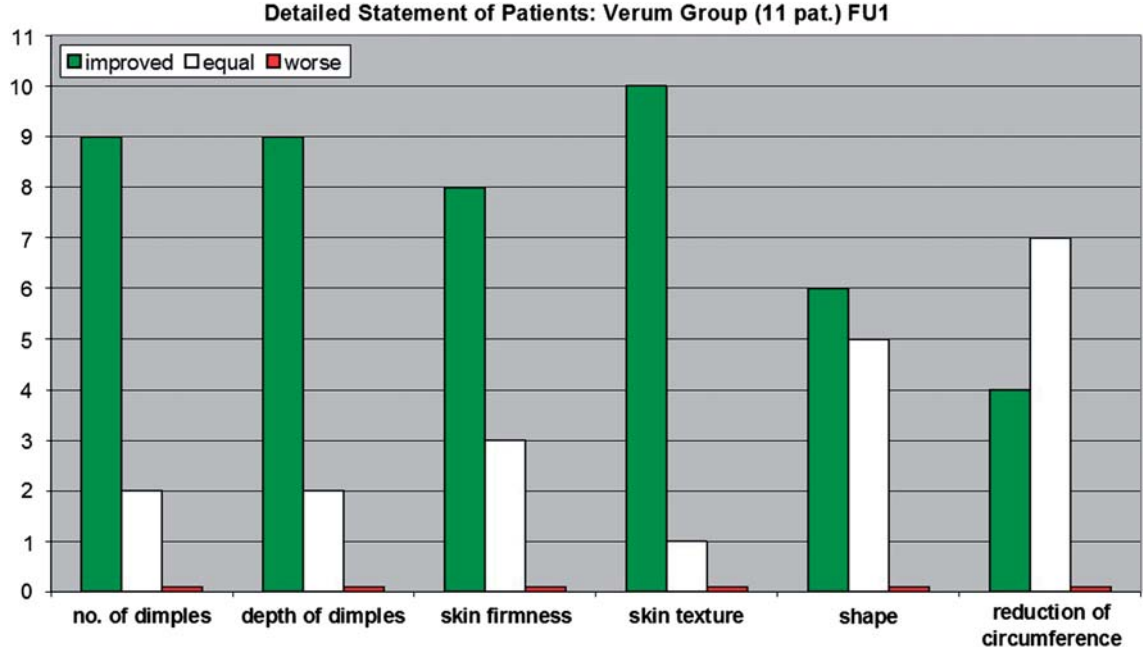

Figure 5. Result of the questionnaire for the verum group at follow-up 1. Most of the treated patients saw an improvement in the number and depth of dimples and in the skin firmness and texture. 6 out of 11 recognized a shape improvement and 4 out of 11 a reduction of the circumference.

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Table I. Four different observers ranked the pictures according to a modified Hexsel scale. Two-sided Wilcoxon Signed Rank Tests were performed. Results marked with asterix are statistically significant.

	1		2		3		4	
Observation	Placebo	Verum	Placebo	Verum	Placebo	Verum	Placebo	Verum
Baseline- >follow-up 1	0.25	0.01*	0.5	0.014*	1	0.625	0.125	0.078
Baseline- >follow-up 2	0.875	0.01*	0.813	0.01*	0.5	0.008*	0.125	0.004*

presence of low patient numbers. There were no missing values.

The following Figure 7 summarizes the overall result of the four efficacy criteria, displaying the effect sizes of the percent changes from baseline at the two points in time with their corresponding one-sided 97.5% confidence intervals (full ITT population):

As shown in Figure 7, all effect sizes except volume of depressions at the first follow-up visit (VVVP3) indicate a more than "small" superiority of the AWT treatment (MW > 0.56) and four out of the eight effect sizes indicate a more than medium-sized superiority (MW > 0.64).

The overall result (displayed at the right end of the figure) indicates a more than medium sized superiority (MW = 0.6706) and is statistically significant ($p_{\text{Wei–Lachin}} = 0.0106$, one-sided, exploratory interpretation). Thus, with regard to the overall result there is good indication for effectiveness of AWT® treatment in patients with cellulite.

As the comparison of verum and placebo at baseline showed medium-sized differences in the weight and thigh parameter (Figure 4) we decided to perform a subgroup analysis for these two parameters. We divided the patients into a low weight group with weight below the median and a high weight group with weight above the median. The division in subgroups for the thigh case was done in the same way.

Within these subgroups we made the analyses in the same way as in Figure 7 in order to check if our treatment is different for the two subgroups. The combined results for the selected subgroups are: $MW_{\text{low weight}} = 0.6417$ and $MW_{\text{high weight}} = 0.7083$.

Qualitative interactions are said to occur, when one treatment (verum) is superior for some subsets of patients and the alternative treatment (placebo) is superior for the other subsets.

The Gail–Simon test (13) indicates qualitative interactions if $p_{GS} < 0.2$. In our study we found no signs for qualitative interactions for $p_{GS} = 0.5$ concluding that our treatment effect is independent of the weight of the patient. The same result holds for the thigh parameter.

With the shown independence of the combined result (Figure 4) from the weight and thigh parameter,

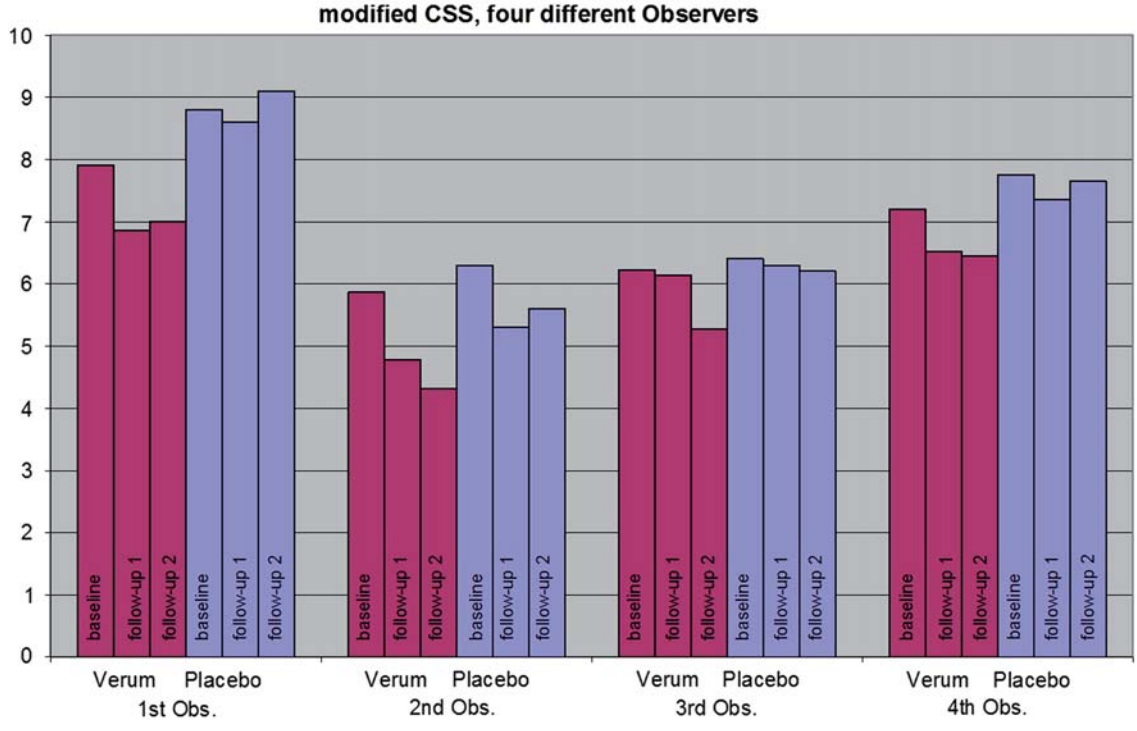

Figure 6. The results of the cellulite evaluation according to the "Modified Hexsel Scale" by four different observers are shown. Each column is the averaged value over all patients in the verum or placebo group. Wilcoxon signed rank tests were performed for each group comparing follow-up 1 and follow-up 2 with the baseline. The statistical results are shown in Table I.

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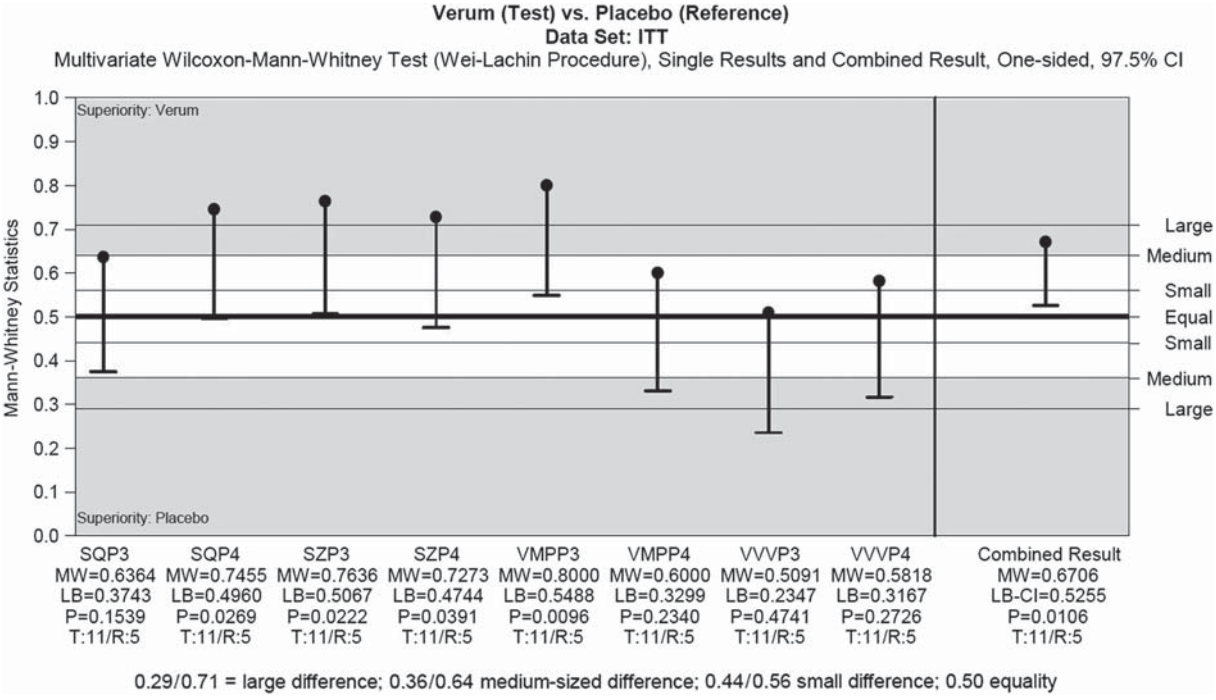

Figure 7. Percent changes from baseline of the efficacy ensemble at the two follow-up visits, Multivariate Wilcoxon Test (Wei–Lachin), single results and combined result, one-sided, 97.5% CI, ITT.

we can conclude that the differences in the demographic data at baseline should not have an effect on the overall results.

Discussion

This AWT® study was designed as a single-centre placebo controlled prospectively randomized, double-blinded clinical trial for the evaluation of the efficacy of acoustic waves in the treatment of cellulite.

Most of the treated patients in the verum group saw an improvement in the number and depth of dimples (9 out of 11) and in the skin firmness (8 out of 11) and texture (10 out of 11). Six out of 11 saw an improvement in shape and 4 out of 11 saw a reduction of the circumference of thighs.

Four blinded observers ranked the pictures of the 2D pictures photo documentation using a modified Hexsel scale. They found a statistically significant improvement in the appearance of the cellulite at the follow-up 2 at 3 months after the last treatment.

Surface 3D topography parameters dealt as an objective measure of cellulite were used as the main efficacy criteria for evaluating the effectiveness of results in acoustic wave treatment for cellulite. The changes in height and depth of dimples before and after AWT® in the verum and the placebo group was evaluated by four efficacy criteria for the waviness of the skin surface and the volume of depressions and elevations at the two follow-up visits at 1 and 3 months after the last treatment. In the verum group the two parameters for the waviness of skin surface (Sq and Sz) and the two parameters for the volume of depressions and elevation (Vvv and Vmp) evidence a significant improvement as shown in Figures 2 and 7.

The overall result (combined results of the four efficacy criteria at the two follow-up visits displayed at the right end of Figure 7) indicates a more than medium sized superiority (MW = 0.6706) and is statistically significant ($p_{\text{Wei—Lachin}} = 0.0106$, one-sided, exploratory interpretation). The placebo group revealed no statistical significance of the four efficacy criteria from baseline to the two follow-up visits. No side effects were seen. Thus, with regard to the overall result, it is a good indication for the effectiveness of acoustic wave treatment in patients for cellulite.

Conclusion

AWT® is a local therapy, non-invasive and free of side effects. The improvement in the appearance of cellulite increases continually up to 3 months and can be considered at least as temporary. The surface topography parameters used in this study are seen as an objective measurement for the evaluation of cellulite and evidenced only in the verum group a statistically significant improvement. This indicates the efficacy and safety of AWT® for patients with cellulite.

Declaration of interest: The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

The authors Gerd Haller, Dr Pavel Novak, Alexander Krotz are employees of Storz Medical

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Notice of Correction

The version of this article published online ahead of print on 21st May 2013 contained an error in authorship on page 1. The original authorship "KATHARINA RUSSE-WILFINGSLEDER[1], JOHANNES C. VESTER[2], GERD HALLER[3], PAVEL NOVAK[3] & ALEXANDER KROTZ[3]" should have read "KATHARINA RUSSE-**WILFLINGSEDER**[1], **ELISABETH RUSSE**[1], JOHANNES C. VESTER[2], GERD HALLER[3], PAVEL NOVAK[3] & ALEXANDER KROTZ[3]". The error has been corrected for this version.

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