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Safety and Tolerability of High-Intensity Focused Ultrasonography for Noninvasive Body Sculpting: 24-Week Data From a Randomized, Sham-Controlled Study

Mark L. Jewell, MD; Robert A. Weiss, MD; Richard A. Baxter, MD; Sue Ellen Cox, MD; Jeffrey S. Dover, MD, FRCP(C); Lisa M. Donofrio, MD; Richard G. Glogau, MD; Michael C. Kane, MD; Patrick Martin; Ira D. Lawrence, MD; and Joel Schlessinger, MD, FAAD, FAACP

Abstract

Background: High-intensity focused ultrasonography (HIFU) is a nonsurgical, noninvasive method for body sculpting in nonobese patients. The technique ablates subcutaneous adipose tissue by causing molecular vibrations that increase tissue temperature and induce rapid cell necrosis.
Objectives: The authors evaluate the long-term safety of a HIFU device for sculpting the abdomen and flanks.
Methods: Adults with subcutaneous abdominal fat ≥2.5 cm in thickness who met screening criteria were randomized to receive HIFU treatment of the anterior abdomen and flanks at 1 of 3 energy levels (3 passes per patient): 47 J/cm^2 (141 J/cm^2 total), 59 J/cm^2 (177 J/cm^2 total), or 0 J/cm^2 (no energy applied; sham control). Safety was assessed for 24 weeks and included laboratory testing, physical examinations, and documentation of adverse events.
Results: Adverse events (AE) included mild to moderate discomfort, ecchymosis, and edema, all of which were transient. There were no reports of scarring or burns and no clinically meaningful changes in lipid panel findings, inflammatory markers, or renal or hepatic function. Physical examination results were unremarkable.
Conclusions: This HIFU device exhibited an AE profile similar to that of sham treatment. There were no significant changes from baseline in laboratory values, including lipid levels.

Level of Evidence: 2

Keywords

high-intensity focused ultrasonography (HIFU), adipose tissue, fat reduction, body contouring, body sculpting, noninvasive

Body-sculpting procedures are an effective adjunct to diet and exercise for the improvement of body contour. For nonobese patients who desire a noninvasive approach to fat reduction for specific problem areas (eg, abdomen, hips, thighs), newer noninvasive body-sculpting technologies are an option. Noninvasive body-sculpting methods currently in use or development include cryolipolysis,[1] radiofrequency ablation,[2] low-level external laser therapy, injection lipolysis, low-intensity/low-frequency nonthermal ultrasonography,[3] and high-intensity focused ultrasonography (HIFU).[4-6] High-intensity focused ultrasonography ablates subcutaneous adipose tissue (SAT) by causing molecular vibrations that increase the temperature of local tissue and induce rapid cell necrosis.[7] It also has been reported to contract collagen.[8] The characteristics of HIFU make it well suited for removing

Dr Jewell is Assistant Clinical Professor of Plastic Surgery at Oregon Health Sciences University, Portland, Oregon. Dr Weiss is Associate Professor of Dermatology at Johns Hopkins Hospital, Baltimore, Maryland.

Corresponding Author:
Dr Mark Jewell, Jewell Surgery Center, 10 Coburg Rd, Suite 300, Eugene, OR 97401, USA
E-mail: mjewell@teleport.com

localized deposits of SAT while sparing surrounding and superficial tissue.[7]

At high frequencies (eg, 2 MHz), ultrasound energy is highly convergent, such that tissue damage is confined to a small focal volume[9] and the length of the lesion can be controlled by increasing or decreasing the energy dose.[7] Thus, ablation of SAT can be accomplished without damaging the dermis or other tissues outside the focal point. After the lesion is formed within the SAT, the body's normal healing process occurs. Macrophages proliferate in the treated area and remove the cellular debris, including extracellular lipids.[10] The liberation of lipids from adipocytes has not presented a safety concern; in clinical studies, there has been no increase in systemic lipid profile values or related adverse events (AE) such as fat emboli and gallstones.[4,6,11,12]

An HIFU device with user-adjustable fluence and depth (LipoSonix system; Medicis Technologies Corp, Scottsdale, Arizona) has market clearance in the United States, Canada, and the European Union. Safety and efficacy data from 2 randomized trials of a single HIFU treatment have been published. In a 12-week, randomized, uncontrolled, single-blind trial, HIFU treatment of the anterior abdomen at energy levels of 47, 52, or 59 J/cm^2, each applied in 3 passes at graduated depths, significantly reduced the least squares (LS) mean waist circumference by 2.5 cm.[6] A randomized, sham-controlled, single-blind trial evaluated the efficacy of HIFU through 12 weeks and safety through 24 weeks after HIFU treatment of the anterior abdomen and flanks with energy levels of 0, 47, or 59 J/cm^2, each in 3 passes at a single depth.[4] Both active treatments reduced LS mean waist circumference by >2 cm.[4] In both of these trials, positive aesthetic outcomes also were indicated by secondary subjective aesthetic assessments, investigator evaluation on a Global Aesthetic Improvement Scale, and a nonvalidated patient satisfaction questionnaire.[4,6] Overall, HIFU treatment was well tolerated; AE consisted mainly of mild or transient abdominal ecchymosis or redness.[4,6]

The present study documents the 24-week safety data for HIFU treatment administered in 3 passes at energy levels of 0, 47, or 59 J/cm^2.

METHODS

Study Design

This randomized, single-blind, sham-controlled study of the safety and efficacy of an HIFU device for waist circumference reduction was conducted at 9 clinical sites in the United States. The study received investigational device exemption and was approved by the Western Institutional Review Board (Olympia, Washington) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. The trial was registered on May 19, 2009 (ClinicalTrials.gov NCT00906815), and the first patient was enrolled on June 17, 2009.

Efficacy was assessed through 12 weeks posttreatment, and safety was evaluated through 24 weeks posttreatment. Detailed methods and 12-week safety and efficacy findings have been published.[4] The present study focused on the full safety data through posttreatment week 24.

Patients

Men and women (18-65 years of age) whose body mass index (BMI) was ≤30 mg/kg^2 and SAT thickness was ≥2.5 cm in the treatment region were eligible to participate. Pregnant or lactating women were excluded. Other major exclusion criteria were coagulation disorders or medications that could affect coagulation, diabetes and cardiovascular disease, prior aesthetic procedure or surgery/surgical scar in the treatment region; skin or tissue abnormality in the treatment region, and weight reduction medication or procedures. After excluding patients with these conditions, 180 qualifying men and women were included in the study. Patients were instructed to not change their normal diet or exercise routines during their participation in the study. This requirement was reinforced verbally by the study staff and by reminder cards given to the patients at each visit.

Treatment

Patients were assigned randomly, in single-blind fashion, to receive HIFU treatment of the anterior abdomen and flanks at 1 of 3 total doses of energy: 177 J/cm^2 (3 passes at 59 J/cm^2), 141 J/cm^2 (3 passes at 47 J/cm^2), or 0 J/cm^2 (3 passes at 0 J/cm^2; sham group). Each pass was applied at a focal depth of 1.3 cm below the skin to a series of 2.8 × 2.8-cm treatment grids that had been marked by the investigator beforehand. Patient discomfort was managed at the investigator's discretion (eg, oral analgesics could be administered before, during, or after the procedure). Each treatment zone took approximately 60 seconds to complete HIFU treatment. Depending on the number of zones to be treated, the zone was re-treated in 12 to 15 minutes, as the zones were sequentially treated.

Assessments

Patients returned for follow-up visits at posttreatment weeks 4, 8, 12, and 24. In addition, they received a telephone call

Dr Baxter is a plastic surgeon in private practice in Mountlake Terrace, Oregon. Dr Cox is Associate Clinical Professor of Dermatology at the University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina. Dr Dover is Associate Clinical Professor of Dermatology at Yale University School of Medicine, New Haven, Connecticut. Dr Donofrio is a dermatologist in private practice in New Haven, Connecticut. Dr Glogau is a dermatologist in private practice in San Francisco, California. Dr Kane is a plastic surgeon in private practice in New York, New York. Mr Martin is Executive Director of Clinical Affairs and Dr Lawrence is Chief Medical Officer and Senior Vice President at Medicis Technologies Corporation, Scottsdale, Arizona (the manufacturer of products discussed in this study). Dr Schlessinger is a dermatologist in private practice in Omaha, Nebraska.

at weeks 16 and 20 to assess AE and concomitant use of medication.

Patients underwent a comprehensive physical examination at screening and week 12. At each visit, patients were questioned about any changes to their diet or exercise habits, and their weight was monitored for any significant changes that might indicate changes in diet or exercise. The treatment area was examined at each visit, waist circumference was measured,[13] and diagnostic ultrasonography of the treatment area was performed at screening and posttreatment weeks 4, 12, and 24 to detect any abnormalities. During the procedure, patients rated their level of discomfort using a 4-point verbal pain assessment scale (ie, none, mild, moderate, severe). Discomfort on the first 7 days posttreatment was evaluated using a 100-mm visual analog scale (VAS; 0-4 = no pain, 5-44 = mild pain, 45-74 = moderate pain, 75-100 = severe pain).

Blood samples were obtained at baseline, within 1 hour after treatment, and at each follow-up visit and were used to analyze lipid panel values (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglyceride, free fatty acid, very low-density lipoprotein [VLDL]), inflammatory markers (erythrocyte sedimentation rate, high-sensitivity C-reactive protein [hsCRP], rheumatoid factor), coagulation (prothrombin time, partial prothrombin time, fibrinogen), and renal function (creatinine, blood urea nitrogen). These blood samples also were used to evaluate hematology (white and red blood cell counts, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, relative cell distributive width, platelet count, mean platelet volume), liver and pancreatic function (alanine transaminase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, total bilirubin, amylase, lipase, albumin, total protein), and chemistry (sodium, potassium, chloride, bicarbonate, glucose, uric acid, calcium, phosphorus, magnesium, glycerol).

Adverse events were assessed by the investigator during each visit and telephone interview. An AE was defined as serious (SAE) if it was life threatening, resulted in permanent impairment of a body function or permanent damage to a body structure, or necessitated medical or surgical intervention to preclude these outcomes. An unanticipated adverse device-related effect was defined as any serious effect on health or safety, life-threatening problem, or death associated with the device that had not been specified in the investigational plan or labeling information.

Statistical Analysis

Efficacy and safety were analyzed in the intent-to-treat (ITT) population, which comprised all treated patients. Efficacy also was analyzed in the per-protocol (PP) population, which included only the patients who had no major protocol violation. The primary efficacy end point was analyzed using analysis of covariance of the LS mean, with treatment and study site as fixed effects, and baseline waist circumference and change in weight from baseline as covariates. Least squares mean (the group mean, corrected for imbalances in other variables by holding them at the mean value) was used to help control for any changes in body weight. Safety data were analyzed using descriptive statistics.

Table 1. Patient Characteristics (ITT Population)

	Treatment Group[a]		
Characteristic	0 J/cm^2 (n = 58)	47 J/cm^2 (n = 59)	59 J/cm^2 (n = 63)
Mean (SD) age, y	41.1 (10.7)	42.2 (10.8)	42.8 (11.2)
Women, No. (%)	47 (81.0)	52 (88.1)	54 (85.7)
White, No. (%)	51 (89.9)	52 (88.1)	53 (84.1)
Mean (SD) height, cm	167.7 (9.6)	166.1 (9.3)	165.2 (8.1)
Mean (SD) weight at baseline, kg	69.8 (13.3)	70.4 (11.2)	69.6 (10.6)
Mean (SD) weight change from baseline, kg	1.10 (2.52)	1.10 (2.50)	0.64 (2.29)
Mean (SD) BMI, kg/m^2	24.6 (2.6)	25.5 (2.6)	25.4 (2.7)

BMI, body mass index; ITT, intent to treat.
[a]Treatment consisted of 3 passes at the specified energy level.

RESULTS

Patient Characteristics and Disposition

One hundred eighty patients were randomized, received treatment, and were included in the ITT population. Most patients in each study group were women and were Caucasian, and the mean age range was 41.1 to 42.8 years (Table 1). The 3 study groups were comparable with respect to weight, BMI, and height at baseline (Table 1). Of the 180 subjects, 85% were female, 15% were male, 87% were Caucasian and 13% were non-Caucasian.

Four patients did not complete the 24-week study, including 1 who withdrew from the study on the day of treatment and 3 who did not attend their scheduled 24-week visit. The PP population comprised 168 patients; 12 patients were excluded for 1 of the following reasons: a major protocol violation (failure to complete treatment owing to discomfort [n = 6], device failure [n = 1]), an exclusion criteria violation (n = 3), or exacerbation of a preexisting condition (irritable bowel syndrome [n = 1], Graves disease [n = 1]). The mean total duration of the treatment procedure appeared independent of the energy level (sham, 41.6 minutes; 47 J/cm^2, 47.4 minutes; 59 J/cm^2, 42.7 minutes). Of the 6 patients who failed to complete treatment due to discomfort, 2 were in the 47-J/cm^2 group and 4 were in the 59-J/cm^2 group.

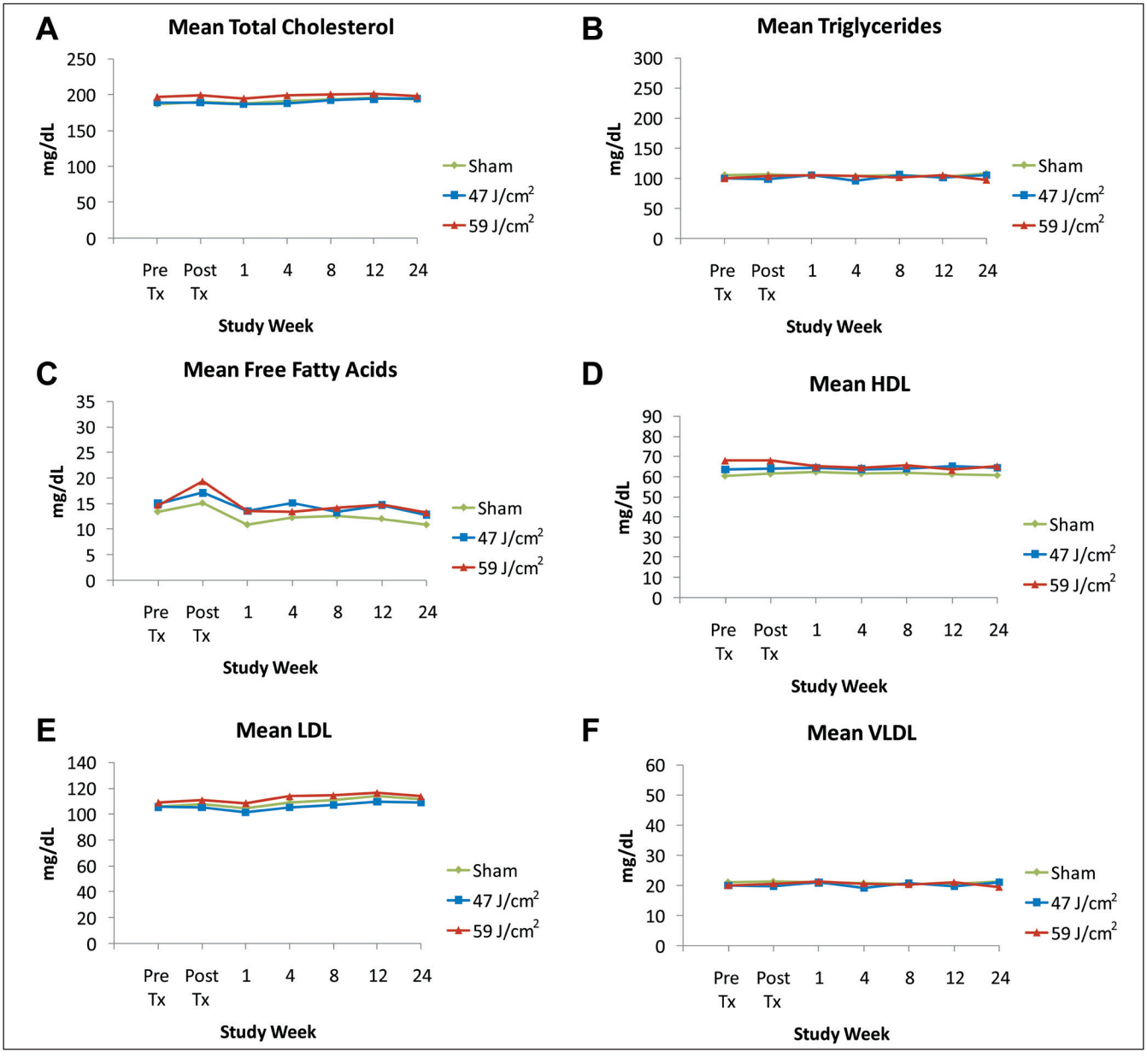

Figure 1. Mean lipid panel results through posttreatment week 24: (A) total cholesterol, (B) triglycerides, (C) free fatty acids, (D) high-density lipoprotein (HDL), (E) low-density lipoprotein (LDL), and (F) very low-density lipoprotein (VLDL). Pre Tx, immediately before treatment; Post Tx, immediately after treatment.

Safety

Physical Examination. Physical examination findings were unremarkable. There were no reports of dimpling, indurations, burns, or changes in skin laxity. Diagnostic ultrasonography showed no abnormalities in the treated areas at any visit.

Laboratory tests. Lipid panel results showed overall stable mean levels of total cholesterol, triglycerides, HDL, LDL, VLDL, and free fatty acids over the 24 weeks, with negligible differences between the study groups (Figure 1). Overall, mean levels of markers of inflammation also were stable throughout the study; the only exception was transient elevation of mean hsCRP levels in the 59-J/cm^2 group at week 8 (Figure 2). The hsCRP level was unusually high in 2 patients; 1 of them was diagnosed with streptococcal pharyngitis, and the other had no abnormal clinical findings. One patient in the 47-J/cm^2 group had elevated alanine transaminase, aspartate aminotransferase, and γ-glutamyl transpeptidase at week 24 only.

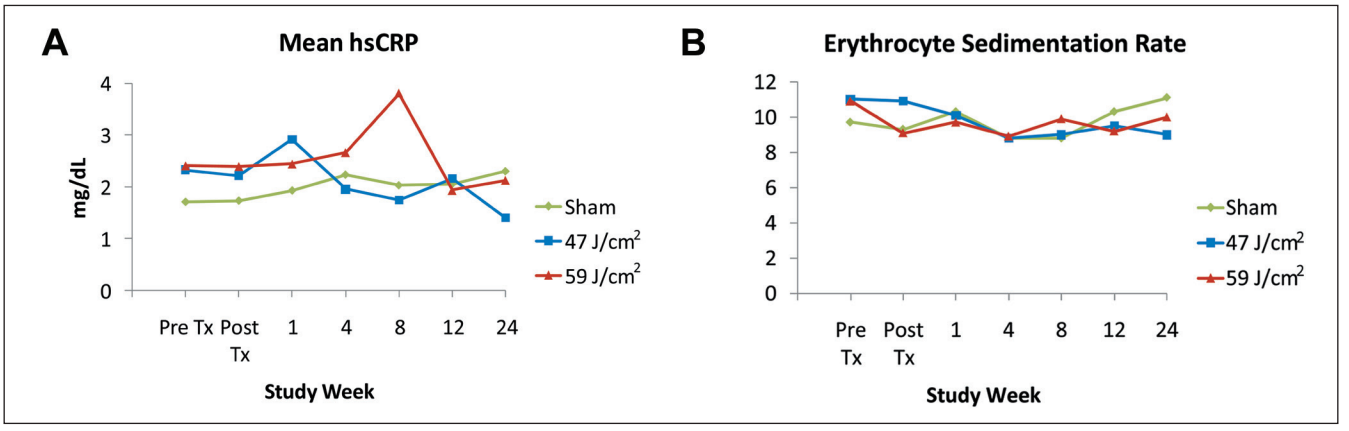

Figure 2. Mean levels for markers of inflammation through posttreatment week 24: (A) high-sensitivity C-reactive protein (hsCRP) and (B) erythrocyte sedimentation rate. Pre Tx, immediately before treatment; Post Tx, immediately after treatment.

Table 2. Common Treatment-Related Adverse Events Through Posttreatment Week 24

	Treatment Group[a]			
Event	0 J/cm^2 (n = 58)	47 J/cm^2 (n = 59)	59 J/cm^2 (n = 63)	Active-Treatment Groups Combined (n = 122)
Procedural pain	7 (12.1)	50 (84.7)	60 (95.2)	110 (90.2)
Postprocedure pain	8 (13.8)	36 (61.0)	33 (52.4)	69 (56.6)
Ecchymosis	0	39 (66.1)	42 (66.7)	81 (66.4)
Swelling	0	5 (8.5)	6 (9.5)	11 (9.0)

Values are presented as No. (%).
[a]Treatment consisted of 3 passes at the specified energy level.

Laboratory findings for liver and pancreatic function, including mean total bilirubin levels, did not change throughout the study, and the between-group differences in these parameters were minor. There were no clinically meaningful fluctuations in renal function, coagulation, hematology, or chemistry and no substantive differences between the study groups.

Adverse Events. The most common AE deemed related to treatment were procedural pain, postprocedure pain, ecchymosis, and swelling (Table 2). Most patients had mild or moderate pain during the procedure. Three patients (5%) in the 47-J/cm^2 group and 6 patients (10%) in the 59-J/cm^2 group reported severe pain. After the procedure, no patient reported severe pain. All pain resolved within 7 to 10 days after the procedure. Among the active-treatment population, 60 patients (49%) experienced mild ecchymosis, 20 (16%) had moderate ecchymosis, and 1 (<1%) had severe ecchymosis. The average times to resolution in the 47-J/cm^2 and 59-J/cm^2 groups (respectively) were 12 and 14 days for ecchymosis, 13 and 16 days for swelling, and 8 and 10 days for postprocedural pain.

Discomfort directly after treatment, as measured by the 100-mm VAS, was greater for active-treatment patients (47 J/cm^2, 23.5 mm; 59 J/cm^2, 32.5 mm) than for sham controls (3.0 mm). Mean VAS scores remained higher with active treatment (range, 2.4-32.5 mm vs ≤4 mm for sham) at all assessments until day 5, at which time the mean score was 3.9 mm in the 47-J/cm^2 group and 7.4 mm in the 59-J/cm^2 group. Ratings (verbal scale) of no or mild pain (VAS 0-44), moderate pain (VAS 45-74), and severe pain (VAS 75-100) during treatment were given by 54% (32 of 59), 41% (24 of 59), and 5% (3 or 59) of patients in the 47-J/cm^2 group (respectively); by 29% (18 of 63), 60% (38 of 63), and 11% (7 of 63) of patients in the 59-J/cm^2 group; and by 98% (57 of 58), 2% (1 of 58), and 0% of sham controls. On posttreatment day 1, the percentage of patients who rated their pain as none/mild, moderate, or severe was 79% (46 of 58), 19% (11 of 58), and 2% (1 of 58) in the 47-J/cm^2 group; 67% (41 of 61), 23% (14 of 61), and 10% (6 of 61) in the 59-J/cm^2 group; and 96% (54 of 56), 4% (2 of 56), and 0% in the sham group. By posttreatment day 5, the mean VAS scores reflected mild pain (score <10) for all groups.

At the discretion of the treating investigator, some patients (22%; 40 of 180) received an oral analgesic before, during, or after the procedure. Analgesia use increased with energy level: sham, 7 of 58 patients (12%); 47 J/cm^2, 13 of 59 patients (22%); and 59 J/cm^2, 20 of 63 patients (32%). Analgesics were most frequently administered before the procedure (sham, 10.3%; 47 J/cm^2, 20.3%; 59 J/cm^2, 28.6%) as opposed to during the procedure (sham, 5.2%; 47 J/cm^2, 13.6%; 59 J/cm^2, 20.6%) or after it (sham, 6.9%; 47 J/cm^2, 11.9%; 59 J/cm^2, 22.2%). Most analgesics were nonsteroidal anti-inflammatory drugs such as acetaminophen, ibuprofen, and naproxen; all were administered orally.

No AE reported after week 12 was determined to be treatment related. There were 2 SAE: community-acquired pneumonia and breast cancer. Both were deemed unrelated to HIFU treatment. No unanticipated device-related AE occurred at any time during the study.

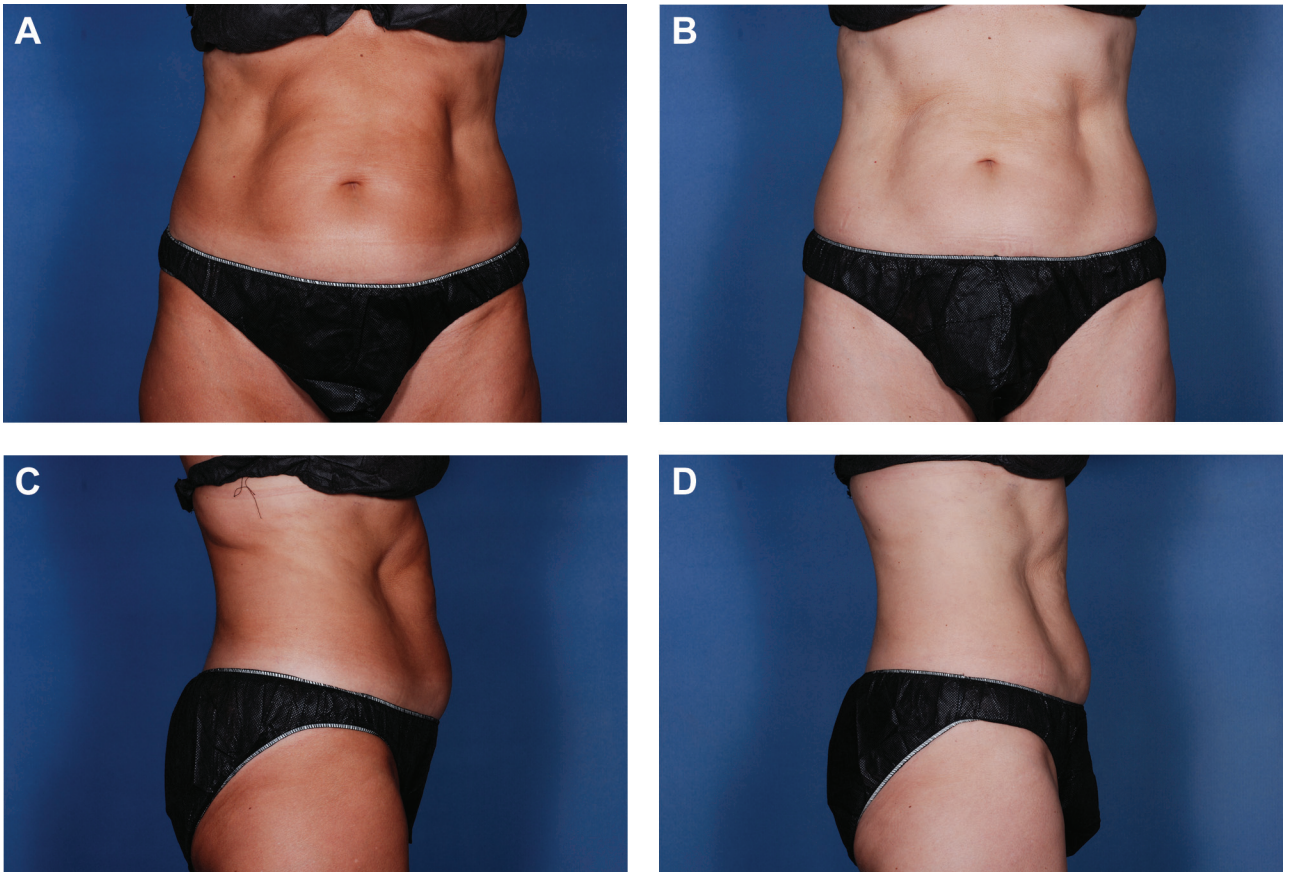

Figure 3. (A, C) This 42-year-old woman presented for treatment with high-intensity focused ultrasonography. (B, D) Twelve weeks after treatment with 3 passes of 59 J/cm^2. From baseline to 12 weeks posttreatment, her waist circumference decreased by 3.1 cm and her weight decreased by 0.3 kg.

Clinical results are shown in Figures 3 and 4.

DISCUSSION

In this randomized, sham-controlled, single-blind trial, the safety profile of total HIFU doses of 141 J/cm^2 and 177 J/cm^2 (3 passes each of 47 J/cm^2 or 59 J/cm^2, respectively) applied to the anterior abdomen and flanks was similar to that of sham treatment (3 passes at 0 J/cm^2). Active treatment was generally well tolerated through 24 weeks posttreatment. There were no burns or other skin AE and no meaningful changes in laboratory tests, including lipid profile, inflammatory markers, liver function, or renal function.

Previous clinical reports of HIFU treatment for body sculpting, which included follow-up to ≤16 weeks, consistently demonstrated mild transient AE such as edema, ecchymosis, and pain.[4,6,14] Safety findings of the current report, the first randomized trial to assess safety through 24 weeks posttreatment, are consistent with those data. Common treatment-related AE that were more common with active treatment (vs sham) were procedural and postprocedural pain, ecchymosis, and swelling, none of which persisted beyond 16 days posttreatment. No new treatment-related AE occurred after the initial 12 weeks of follow-up. In a report of the efficacy and safety of HIFU during the initial 12 weeks of this study, we noted that pain during the first week posttreatment (VAS) was mild (on average) and resolved within 7 to 10 days after treatment; 22% of the overall study population used analgesics before, during, or after the procedure.[4] During the 24-week follow-up, there were no treatment-related SAE or unanticipated adverse device-related effects.

There were no reports of skin dimpling, indurations, or increased skin laxity in the current study. The absence of skin damage, such as burns and scars, is consistent with the properties of HIFU, which, at the frequency used (2 MHz), consist of highly convergent energy that produces a tissue effect only within the focal volume, with preservation of surrounding and superficial tissues.[9] Compared with the lower HIFU frequencies used in low-intensity nonthermal focused ultrasonography (0.2 MHz),[15] 2-MHz waves are attenuated faster, reducing the likelihood of the mechanical process of acoustic cavitation, which can lead to irregular lesions and adversely affect overlying tissue.[7]

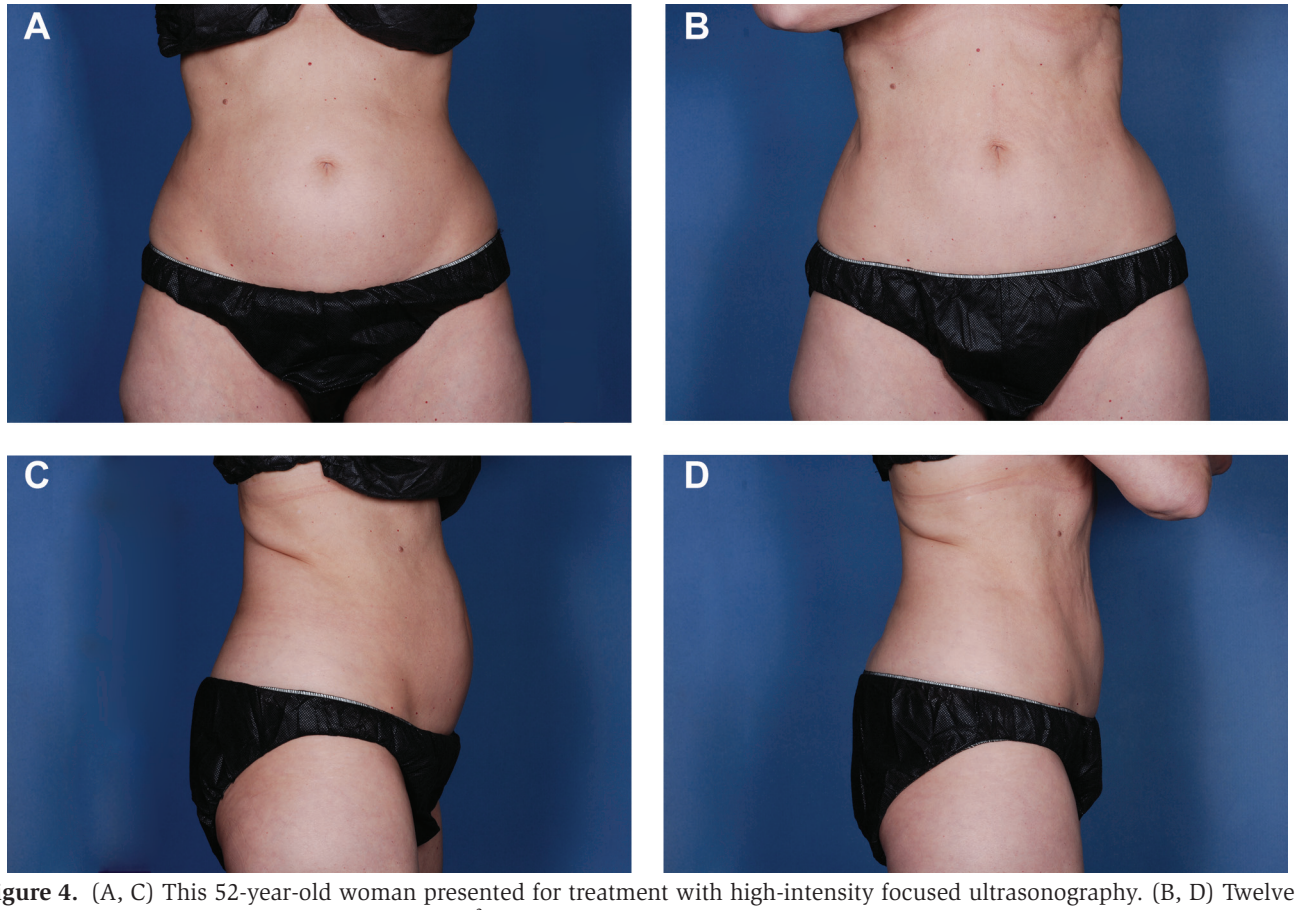

Figure 4. (A, C) This 52-year-old woman presented for treatment with high-intensity focused ultrasonography. (B, D) Twelve weeks after treatment with 3 passes of 59 J/cm^2. From baseline to 12 weeks posttreatment, her waist circumference decreased by 2.5 cm and her weight increased by 0.8 kg.

At 2 MHz, the tightly focused transducer of the system used in this study produces lesions that are approximately 1 mm wide and 10 mm long.[7] In pilot studies, gross pathologic and histologic findings of patients undergoing HIFU treatment before abdominoplasty repeatedly demonstrated discrete regions of coagulative necrosis of adipocyte tissue spatially isolated from the dermis and epidermis, consistent with focal depth of the ultrasonic energy.[8,10,11] Resorption of the damaged tissue was observed between 8 and 16 weeks posttreatment, with no dystrophic calcification, fat necrosis, sterile abscess, or fistula.[11,16] Computed tomography and magnetic resonance imaging showed no skin or intra-abdominal organ damage.[11] We excluded patients who had underlying abnormalities of the skin or soft tissues of the abdominal wall (eg, hernia) in the areas to be treated, in an effort to reduce the potential for treatment-related complications in those regions; this practice should be mandatory.

During the 24 weeks of follow-up, there were no clinically meaningful changes or trends from baseline in lipid panel findings, liver function, renal function, or inflammatory markers in any study group. This was expected given the mechanism of action of HIFU, whereby lesion formation is followed by a normal healing process in which macrophages remove free lipids. Histologic studies in patients who received HIFU treatment have shown a mild tissue response 7 days after treatment consisting primarily of macrophages, and macrophages containing released lipids have been seen 8 to 12 weeks posttreatment.[10,11] There was no indication that the lipids liberated from HIFU treatment had been released directly into the systemic circulation. Similarly, a preclinical study of HIFU treatment showed no fatty liver changes or other systemic abnormalities.[16] Moreover, pilot clinical studies of HIFU treatment for body sculpting showed no clinically significant changes from baseline in findings on lipid panels, metabolic panels, amylase, lipase, or hematology.[11,16,17] Thus, the 24-week safety results for the present study were consistent with those of preclinical and early pilot studies of HIFU and with the 12-week data for the current study.[4]

CONCLUSIONS

In this randomized, sham-controlled study of noninvasive sculpting of the abdomen, the 24-week safety profile of HIFU was similar to that of sham treatment. The procedure

was generally well tolerated at total doses of 141 J/cm^2 and 177 J/cm^2. The most common treatment-related AE were pain, ecchymosis, and swelling. No burns or scarring occurred, and there were no clinically meaningful changes in lipid findings or inflammatory markers.

Disclosures

Dr Jewell has served as a paid consultant for Allergan, AorTech International PLC, Medicis, and Sound Surgical Technologies. He has received grants for clinical research from Allergan, Medicis, and Mentor Worldwide, LLC, and has received grants for educational activities from Medicis. Dr Weiss has received grant/research support from Medicis, Palomar Medical Technologies, Ultrashape (Syneron), and Zeltiq Aesthetics. He has served as a consultant for Cooltouch Corporation, and Medicis, has been on speaker bureaus for Allergan, Colbar Lifescience, LTD, Cooltouch Corporation, Johnson & Johnson, and Palomar Medical Technologies; and owns stock in Cooltouch Corporation. Dr Baxter has served as a consultant to Allergan, Lifecell Corporation, and Medicis. Dr Cox has received grants for clinical research from Allergan, and Medicis, has served as a principal investigator for Allergan, Medicis, and Revance Therapeutics, has served as a consultant to Allergan, Medicis, Johnson & Johnson, and Merz Pharmaceuticals LLC, and has served as an adviser for Allergan, and Medicis. Dr Dover has served as an adviser or consultant for Iridex Corporation, Zeltiq Aesthetics, Lumenis, Medicis, Shaser, and Solta Medical, has received grants for clinical research from Allergan, Cynosure, Lumenis, Medicis, Merz Pharmaceuticals LLC, OpusMed, Palomar Medical Technologies, Shaser, Syneron, and Solta Medical, and owns stock, stock options, or bonds in CVS/Skin Effects, and Shaser. Dr Donofrio has received grant or research support from Allergan, Cynosure, Medicis, Mentor Worldwide LLC, and Merz Pharmaceuticals LLC, has served as a consultant for Medicis, Niadyne Pharma, and Vichy Laboratories, has been on speaker bureaus for Mentor Worldwide LLC, and Vichy Laboratories, and has served on an advisory board for Medicis. Dr Glogau has served as an adviser or consultant for Allergan, Medicis, Revance Therapeutics, LipoSonix (Medicis Technologies), and Lumenis, has received grants for clinical research from Allergan, Medicis, Revance Therapeutics, and LipoSonix (Medicis Technologies); and does not own stock, stock options, or bonds in any of these companies. Dr. Kane has served as an adviser or consultant for Allergan, BioForm Medical (now Merz Pharmaceuticals LLC); Medicis, QMed AB, and Stiefel Laboratories, has served as a speaker or a member of a speaker bureau for Allergan, Medicis, QMed AB, and Sanofi-Aventis US, has received grants for clinical research from Coapt Systems, Medicis, and Revance Therapeutics, and owns stock, stock options, or bonds in Allergan, Medicis, and Revance Therapeutics. Mr Martin and Dr Lawrence are employees of Medicis, the study sponsor. Dr Schlessinger has served on an advisory board or as a consultant to Abbott Laboratories, Allergan, Amgen, Artes (now Suneva Medical), Dermik Laboratories, Galderma SA, Genentech, GSK/Stiefel, Kythera Biopharmaceuticals, Medicis, Mentor Worldwide LLC, Merz Pharmaceuticals LLC, Novartis Pharmaceuticals Co, Obagi Medical Products, and Ortho-McNeal Pharmaceuticals (division of Johnson & Johnson), has served as a researcher for 3M Pharmaceuticals (3M CO), Abbott Pharmaceuticals, Allergan, Amgen, Astellas Pharm US, Barrier Therapeutics, Biogen IDCE, Centocor Ortho Biotech, Clay-Park Labs, CollaGenex, Connetics Corporation (now Stiefel), Dermik Laboratories, Dow Pharmaceutical Sciences, Lumenis, Galderma SA, Genentech, GSK/Stiefel, Glenmark Pharma, HealthPoint Ltd, Immunex, Kythera Biopharmaceuticals, Medicis, Mentor Worldwide LLC, Merz Pharmaceuticals LLC, Novartis Pharmaceuticals Co, Novum Pharmaceutical Services, Nucryst Pharmaceutical, Ortho Pharma (Johnson & Johnson), Penederm Pharma, Perrigo, Pfizer, QLT USA, Regeneratio Pharma AG, Sandoz, Schering-Plough, Stiefel, and owns stock in Allergan, Revance Therapeutics, exCel Cosmeceuticals, Medicis, and Obagi Medical Products.

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