Ultrasound tightening of facial and neck skin: A rater-blinded prospective cohort study

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Background: Nonablative skin tightening technologies offer the prospect of reduction of wrinkles and skin sagging with minimal downtime, discomfort, and risk of adverse events. The excellent safety profile is mitigated by the limited efficacy of such procedures.

Objective: We sought to assess the efficacy of ultrasound skin tightening for brow-lift in the context of a procedure treating the full face and neck.

Methods: This was a rater-blinded, prospective cohort study at a dermatology clinic in an urban academic medical center. Subjects were medicated with topical anesthetic and then treated with an investigational focused intense ultrasound tightening device to the forehead, temples, cheeks, submental region, and side of neck using the following probes: 4 MHz, 4.5-mm focal depth; 7 MHz, 4.5-mm focal depth; and 7 MHz, 3.0-mm focal depth. Standardized photographs of front and side views were obtained at 2, 7, 28, 60, and 90 days; rating scales of pain, adverse events, physical findings, and patient satisfaction were also completed. Primary outcome measure was detection of improvement in paired comparison of pretreatment and posttreatment (day 90) photographs by 3 masked expert physician assessors, cosmetic and laser dermatologists, and plastic surgeons who were not authors. Second primary outcome measure was objective brow elevation as quantitated by a standard procedure using fixed landmarks. Secondary outcomes measure was patient satisfaction as measured by a questionnaire.

Results: A total of 36 subjects (34 female) were enrolled, one subject dropped out, and 35 subjects were evaluated. Median age was 44 years (range 32-62). On the first primary outcome measure, 30 of 35 subjects (86%) were judged by the 3 masked experienced clinician raters to show clinically significant brow-lift 90 days after treatment (P = .00001). On the second primary outcome measure, mean value of average change in eyebrow height as assessed by measurement of photographs at 90 days was 1.7 mm.

Limitations: Limitations of this study include the inability to quantitatively measure lower face tightening because of the lack of fixed anatomic landmarks in this area.

Conclusion: Ultrasound appears to be a safe and effective modality for facial skin tightening. A single ultrasound treatment of the forehead produced on average brow height elevation of slightly less than 2 mm. Most treated individuals responded, commonly with accompanying transitory mild erythema and edema. (J Am Acad Dermatol 2010;62:262-9.)

Key words: lifting; nonablative; tightening; ultrasound.

The visible signs of facial skin aging include not only surface irregularities, such as mottled red-brown dyschromia and fine wrinkling, but also coarser textural changes, such as sagging and wrinkling of facial skin. In recent years, laser, light, and other energy procedures have been modified to treat skin wrinkling and sagging in a so-called nonablative manner.

Epidermal injury is minimized, and thermal energy is directed into the reticular dermis and subcutis, where immediate tissue contraction and delayed remodeling are believed to collectively cause tightening.

The attractive features of nonablative skin tightening are limited postprocedure healing time, ability to return to work or social engagements, reduced risk of adverse events compared with ablative resurfacing or rhytidectomy, and less need for physician oversight. For all these reasons, more patients are appropriate candidates for nonablative skin tightening than for ablative or surgical skin tightening.[1]

Limiting factors that have prevented nonablative tightening and lifting from replacing comparable invasive procedures are the relative lack of efficacy, persistence, and reliability of these procedures.[2,3] Face-lifting continues to provide a greater degree of improvement than nonablative tightening, and arguably, the benefit lasts longer. And some nonablative tightening recipients experience little or no visible tightening at all, with there being no set of demographic or patient-specific criteria that can be used to predict and hence prevent such lack of results. Further, there remains a need for precise, accurate 3-dimensional imaging instruments that may reliably assess subtle changes in the volume, draping, and tightening of skin over the middle aspect of the face; once these are available, and validated against blinded expert observation, it may be easier to document modest but significant visible tightening after nonablative treatments.

Given the promise and limitations of nonablative skin tightening, emerging refinements aim to retain the tolerability and safety of the procedure while enhancing its efficacy and persistence. Numerous broadband light devices, monopolar and bipolar radiofrequency devices, and hybrids of these are now on the market.[4] One technology that is yet to be approved for this indication but may be particularly suitable is focused ultrasound.

This article describes an investigation of focused intense ultrasound for tightening facial skin. The purpose of this study was to assess both the safety and efficacy of this treatment.

CAPSULE SUMMARY

- A single ultrasound treatment of the face and neck resulted in clinically significant brow elevation as determined by 3 masked clinician raters 90 days after treatment.

- The average change in eyebrow height assessed by photographic measurements relative to fixed anatomic landmarks was 1.7 mm.

- Most subjects experienced mild transitory erythema and edema. There were no serious adverse events.

METHODS

Patient selection

A total of 36 adult patients of either sex who provided informed consent were enrolled at an urban university-based dermatology department. Subjects were recruited from the study site's patient database. Exclusion criteria included: active systemic or local infections; local skin disease that might alter wound healing; scarring in the test areas; diagnosed psychiatric illness; history of smoking; and insertion of soft-tissue augmentation materials or application of ablative or nonablative laser procedures within the previous 6 months.

Equipment used

Investigational device. The investigational focused intense ultrasound device (Ulthera System, Ulthera Inc, Mesa, AZ) incorporated both: (1) ultrasound imaging capability for visualizing skin and subcutis (Fig 1); and (2) a therapeutic ultrasound module configured to create small (approximately 1 mm^3) zones of thermal coagulation. The thermally induced zones result from selective absorption of focused ultrasound energy in the region of the geometric focus of the beam (Fig 2). Adjustable parameters included the source energy (0.5-1.2 J) from the probes. The depth and volume/size of the thermally induced lesions were characteristics determined by the preset focus depth and frequency of a given probe, respectively, and by the intrinsic characteristics of the tissue being treated (Fig 3). Probes used in this study were: 4 MHz, 4.5-mm focal depth (source energy 0.75-1.2 J); 7 MHz, 4.5-mm focal depth (source energy 0.75-1.05 J); and 7 MHz, 3.0-mm focal depth (source energy 0.4-0.63 J). Higher-frequency probes were associated with more superficial tissue effect than lower-frequency probes. On activation and firing, each probe delivered a series of ultrasound pulses along a 25-mm long exposure line. The pulse duration for each individual exposure ranged from 25 to 40 milliseconds. Prior work[5-8] in which the facial skin tissue was excised after exposure to the intense ultrasound device has shown that the zones of thermal coagulation are wedge shaped and are consistent in size and depth. In each case the epidermis was spared after ultrasound energy exposure.
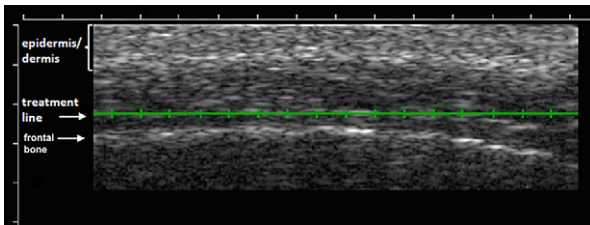
Fig 1. Before treatment, therapeutic ultrasound image can be generated to verify flush apposition of probe to epidermis. Image permits ascertainment of combined depth of epidermis and dermis at point being treated, and location of fascia and bony interface.

Skin thickness and geometry of probe-induced thermal injury zones. A number of studies report measurement of skin thickness (epidermis, dermis, and subcutaneous tissue) at different facial locations using direct histologic methods in full-thickness biopsy samples from cadavers, or using ultrasound imaging.[9-12] Despite the specimen-to-specimen variability of skin thickness, in general, the skin is thickest at the cheeks, followed by the forehead. The skin in the neck region is relatively thin. The nominal measured thickness of the skin in the forehead region is 3.5 to 5 mm; temple is 6 mm; and cheek is 5 to 8 mm. In addition, at facial sites, soft tissue beneath the skin includes fascia and muscle that comprise another several millimeters, on average 3 to 3.5 mm.

During probe use, thermally induced zones resulted from selective absorption of focused ultrasound energy in the region of the geometric focus of the beam (Fig 2). Each individual thermal coagulation zone had an inverted conical shape, point down. Cone width at the point of maximal breadth (superior pole) was 0.5 to 0.75 mm for all probes, and relatively wider for the 7-MHz probes than the 4-MHz probes. Vertical length of the coagulation zones was 0.75 to 1.5 mm. For the 3-mm probe, the deepest point of the cone was approximately 3 mm from the skin surface; for the 4.5-mm/7-MHz probe it was 4 to 4.5 mm; and for the 4.5-mm/4-MHz probe it was approximately 4.5 mm. These results have been previously reported in various contexts: in vitro and in vivo porcine with bioacoustic simulations[7]; cadaver skin[6,8]; and treat-and-resect human clinical studies.[5]

Photographic setup. A custom-designed Canfield photographic system (Canfield Scientific, Inc, Fairfield, NJ) was used for pretreatment and posttreatment photography of subjects' face and necks. The apparatus included a digital single-lens reflex camera attached to a fixed base and a semicircular table with a ratcheting arm that permitted the camera to be rotated to obtain either frontal or 45-degree patient photographs.
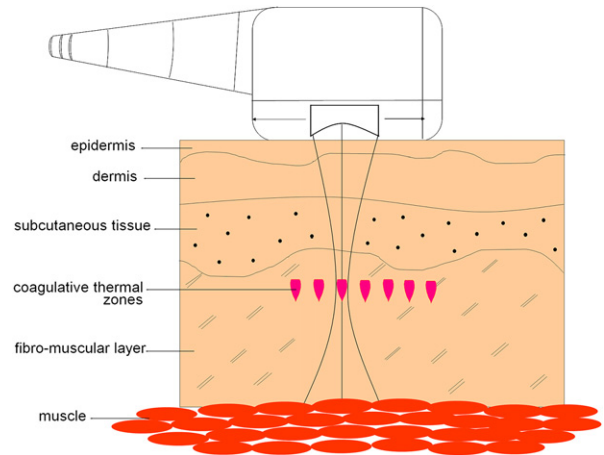

Fig 2. Schematic view of ultrasound device applied to skin. Note I-shaped focused ultrasound beam emanating from probe and penetrating into dermis. In study, coagulative zones were formed in dermis and subcutis, but they can theoretically be deeper, in fascia, as shown here.

A patient positioning device permitted vertical and horizontal adjustment of facial position, and included separate attachments to permit unobstructed photography of the face and of the neck. A dedicated computer using Canfield Mirror software enabled downloading and secure storage of photographic images, each of which was automatically tagged with a specific label (metadata) that cannot be edited by the user.

Experimental design

The study was a rater-blinded, prospective, cohort study. Approval to perform the study was obtained from the university institutional review board and the trial was registered with clinicaltrials. gov before enrollment of patients.

Experimental procedures

Pretreatment preparation. Topical anesthetic ointment (7%/7% lidocaine-tetracaine; Central Avenue Pharmacy, Pacific Grove, CA) was applied to the face and neck areas to be treated for 45 minutes before the procedure. The anesthetic was washed off with mild soap and water immediately before energy delivery.

Selection of probes and areas treated. Areas treated included the forehead, temples, cheeks, submental region, and side of neck. Skin within the orbital rim was not treated. Neck skin, expected to be relatively thinnest, was treated with the 7-MHz, 3.0-mm probe or the 7-MHz, 4.5-mm probe; forehead and temple skin was treated with the 7-MHz, 4.5-mm probe; and cheek skin, expected to have the
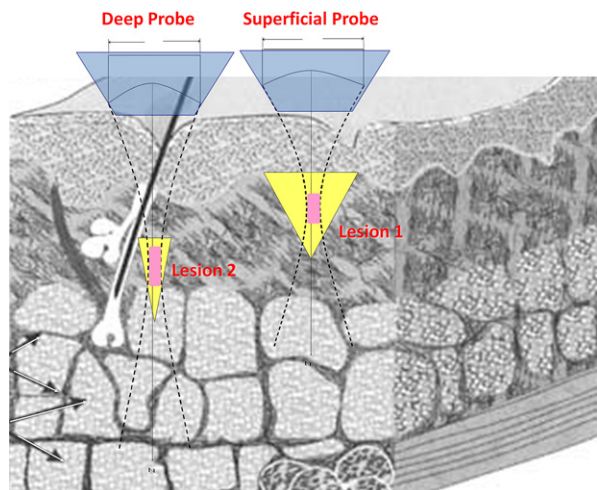
Fig 3. Shallow and deep probes both create triangular zones of thermal coagulation but at different depths in dermis.

greatest soft-tissue thickness, underwent treatment with the 4-MHz, 4.5-mm probe.

Treatment settings. The spacing of pulses within each exposure line was set at 1.5 mm, allowing 17 thermal coagulative zones to be created along each line. The operator moved the probe almost parallel to first exposure line, placing the second row of ultrasound exposures 3 to 5 mm away from the first line. This permitted a gridlike distribution of thermal coagulative zones, with closer spacing along each exposure line than between parallel exposure lines.

Ultrasound exposure protocol. Ultrasound gel was applied to the skin. Then the probe was placed firmly on the targeted skin surface, and pressed uniformly so it was coupled to the skin surface. The ultrasound imaging functionality was used to confirm that the probe was acoustically coupled to the skin tissue and that the geometric focal depth for therapy was in the mid-to-deep reticular dermis. If necessary, the probe was readjusted by further scanning of the region with imaging to satisfy these two conditions. Treatment exposure was initiated, with a line of individual ultrasound pulses being delivered over approximately 2 seconds. The probe was then slid to the next location, and repositioned 3 to 5 mm laterally, such that it was adjacent and parallel to the previous treatment line. The energy delivery sequence was repeated. On average, 110 exposure lines were placed using the focused ultrasound system on the face and neck of each subject (Fig 4). Because facial size varied, the total number of lines was adjusted to ensure consistent density and spacing. Complete treatment of the face and neck required 15 to 25 minutes.

Posttreatment care. Ultrasound gel was wiped off. Patients were instructed that mild redness and
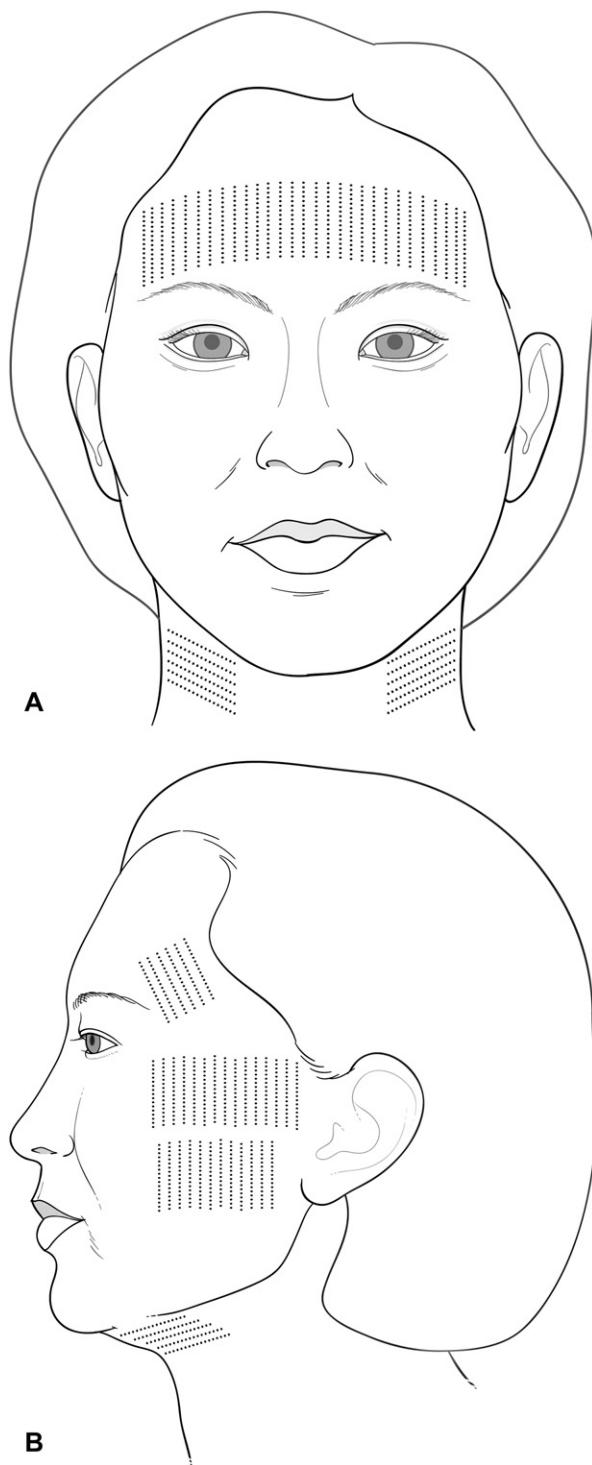

Fig 4. Placement of exposure lines on subject as seen in front view of forehead and neck (**A**), and side view of temple, cheeks, preauricular, and submental areas (**B**). All marked sites were treated in each patient.

swelling might persist for several days, but that if they encountered any other effects they should contact the investigator promptly.

Outcome measures

Standardized photography. Frontal and 45-degree still digital photographs of the face and neck were obtained before treatment, within 30 minutes after treatment, and at 2, 7, 28, 60, and 90 days. Photographs were taken per protocol using the Canfield photography system described above.

Rating scales. After treatment, patients were asked to grade intraprocedure pain on a visual analog scale from 0 to 10, with 0 denoting no pain and 10, the most pain possible. Edema, erythema, ulceration/erosion, hypopigmentation, and hyperpigmentation were each graded by the investigator on a scale from 0 to 4 (0 = absent; 1 = trace; 2 = slight; 3 = moderate; 4 = prominent). Pain and physical findings measures were obtained for each treated anatomic area (forehead, temples, preauricular, cheeks, neck) separately. Any adverse events or serious adverse events were noted, recorded, and reported to the institutional review board. The above-mentioned measures were again obtained at follow-up visits on days 2, 7, and 30, and month 3.

Photographic analysis process. To ensure uniform assessment of change in eyebrow elevation, the following protocol was used (Fig 5).

1. Photographs were adjusted and matched for uniformity. The preoperative photograph at 0 degrees (frontal view) was rotated to position the medial canthi exactly on the horizontal axis and used as baseline reference. Postoperative 0-degree images were matched to the adjusted preoperative image using the match orientation function of Canfield Mirror software, which adjusted for lateral flexion discrepancies as well as for other extension and flexion discrepancies by matching the frontal view parameters. Postoperative 45-degree views were matched to the corresponding preoperative images using the match orientation function of Canfield Mirror software, keeping the lateral canthi and earlobes as reference points.

2. Eyebrow height was assessed using a standard measurement technique.[13,14] In the 0-degree views for each eye, 5 measurements of distance in millimeters were obtained from the line connecting both medial canthi to the top edge of the eyebrow by moving from the medial canthus laterally in 8-mm increments along the line horizontally bisecting the medial canthi. The maximum height and the average eyebrow height thus obtained were recorded.

To compare the upper and lower side views of the face, all before and after images were magnified by 140%.

Masked clinician assessment. Three masked, experienced clinicians evaluated paired pretreatment and posttreatment (day 90) photographs of 35 subjects in a randomized fashion (pretreatment and posttreatment not identified as such) to determine if a discernable clinical improvement (ie, improvement) was noted. Specifically, if a particular masked reviewer detected a change, the reviewer was asked to identify the posttreatment image. If the correct image was identified as the posttreatment image, then the assessment from the reviewer was considered an improvement; if the reviewer identified the wrong image as the posttreatment image, the assessment from the reviewer was considered a worsening. If the reviewer reported no difference across the two photographs, the assessment was considered indicative of no change. Once each of the 3 reviewers had separately examined the 35 sets of photographs, the results were compiled in tabular form and majority opinion was considered definitive. Thus, if two or more reviewers noted improvement, the patient was said to have improved; if two or more noted worsening, the patient was said to have worsened; and if two or more noted no change, then it was determined that no change had occurred. In the event of 3 different responses (ie, improvement, no change, and worsening) from the 3 reviewers with regard to a given patient, the intermediate response of no change was accepted.

By definition, if any improvement in eyebrow position between a set of pretreatment and posttreatment photographs was identified by a majority of the masked clinicians, this change was considered clinically significant. The proportion of subjects found to be improved was calculated. This approach for masked clinician assessment of eyebrow position improvement is similar to that used for assessment of periorbital wrinkles,[15] and eyebrow elevation after botulinum toxin treatment or surgical brow-lift.[16-23]

A calibrating analysis of photographs that preceded the masked assessment described above revealed that the threshold for discernable clinical improvement in eyebrow position was consistent with an absolute change of at least 0.5 mm.

RESULTS

A total of 36 subjects (34 female) were enrolled, one subject dropped out, and 35 subjects were evaluated. Median age was 44 years (range 32-62). All subjects developed at least trace or slight (1-2 on a 4-point scale) erythema and edema immediately after treatment, two patients had moderate erythema and edema (3 on a 4-point scale) immediately after treatment, and none had prominent erythema or edema. In all cases, erythema and edema had
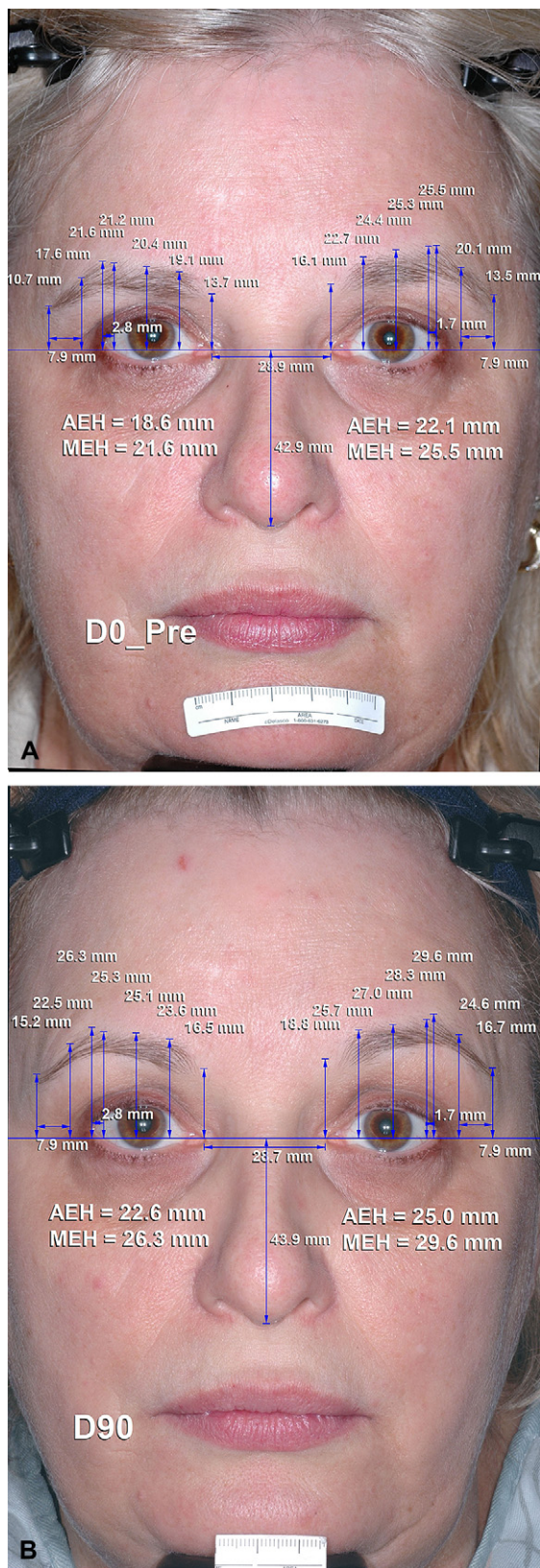
Fig 5. Frontal view of representative patient before (**A**) and 90 days after (**B**) treatment. Note superimposed lines and numbers that are used to objectively measure brow position. *AEH,* average eyebrow height; *MEH,* maximum eyebrow height.

resolved by the day-7 follow-up visit, and in 78% of cases complete resolution had occurred by the day-2 follow-up visit. Ulcerations/erosions, hypopigmentation, and hyperpigmentation were not seen in any patients at any time points. Pain scores on the day of treatment were 3 to 4 on a 10-point scale. Five patients reported more than 7 of 10 on the pain scale, but all were able to complete treatment. Pain was not reported by any patients at any of the follow-up visits. No other adverse events, including but not limited to nerve/muscle dysfunction, treatment-stopping pain, or bruising/bleeding, were observed. There were no serious adverse events.

Two early subjects developed elevated white linear striations of the neck after treatment with the 3.0-mm probe. These were treated with high-potency topical steroids and resolved without sequelae, including no pigmentary or textural abnormalities, within 1 week. Subsequent to these events, only the 7-MHz, 4.5-mm probe was used on the neck.

On the first primary outcome measure for efficacy of eyebrow-lift, 30 of 35 subjects (86%) were judged by the 3 masked experienced clinician raters to show clinically significant improvement 90 days after treatment. Based on the binomial theorem, this was a statistically significant finding at $P = .00001$.

On the second primary outcome measure for efficacy of eyebrow-lift, mean value of average change in eyebrow height as assessed by measurement of photographs at 90 days was 1.7 mm, and mean value of maximum change in eyebrow height was 1.9 mm.

DISCUSSION

Ultrasound appears to be a safe and effective modality for facial skin tightening. A single ultrasound treatment of the forehead produced on average brow height elevation of 1.7 to 1.9 mm. This effect was seen in more than 83% of treated patients and was preserved 3 months after treatment. Side effects were limited to transient redness and swelling, which are common to all laser, light, and other energy treatments.

Significant intraoperative pain was noted by 5 patients. Interestingly, all of these were among the minority of subjects who had never before received a laser, intense light, radiofrequency, chemical peel, or energy treatment to the skin. We suspect that these patients were unaccustomed to the mild discomfort associated with cosmetic procedures. Conversely, patients who had previously undergone cosmetic procedures may have been more acclimated to the treatment-associated discomfort

common with laser and other nonablative procedures, and hence reported lower pain scores.

Whitish wheals/striations were noted in two patients during the early use of the 3.0-mm focal depth probe on the neck. We hypothesize that the 3.0-mm focal depth probe, which deposits energy more superficially compared with the deeper 4.5-mm focal depth probes, was possibly not coupled adequately to the skin during operation. The transient apparent injury to the dermal collagen recovered after application of topical steroids. Subsequent use of the 4.5-mm probe with appropriate acoustic coupling resulted in no further occurrences of this type. This reassured us that the 4.5-mm probe was directing energy deeper into subcutis, beyond the more papillary dermis that appeared vulnerable to injury.

Skin tightening by nonablative energy delivery offers the promise of reduction of wrinkles and sagging with minimal downtime, and no scars or serious adverse effects. Intense light, lasers, and radiofrequency energy are among the modalities currently used to tighten skin. Based on the work reported in this article and recent feasibility studies,[5,6] ultrasound may be added to the list.

Ultrasound energy has specific characteristics that may increase its suitability for skin tightening. First, it is widely believed that energy delivery to the deeper subcutaneous layers of the face, or even the superficial musculoaponeurotic system, is most effective in inducing skin tightening.[24-29] Further, to the extent that this delivery can be divorced from secondary scatter and absorption in the epidermis and dermis, the risk of inadvertent cutaneous injury can be reduced. Apart from ionizing radiation, ultrasound is the only type of inducible energy that can be delivered arbitrarily deeply into tissue in a selective manner.

Intense ultrasound works as follows: an ultrasound field vibrates tissue, thus creating friction between molecules, which absorb mechanical energy that leads to secondary generation of heat. Overall, selective coagulative change is effected within the focal region of the beam but other tissue proximal and distal to the focal region of the ultrasound field is preserved.[5-8,30-34]

Notably, the intense ultrasound we investigated for skin tightening is different from ultrasound devices designed for lipolysis. The skin tightening ultrasound penetrates 4 to 5 mm into the facial skin and delivers focal, intense pulses (20-50 milliseconds long) that cause localized thermal injury (thermal coagulation zone ~1-mm^3 volume), and instigate the tissue repair cascade.[5-8,35-37] Ultrasound for lipolysis is predicated on delivery of focal energy to much larger regions (>100 mm^3) so as to induce tissue coagulation in the fat tissue 10- to 30-mm deep. The goal is to "debulk" fat tissue during each treatment session.[38,39] Also, the system for facial tightening includes an ultrasound imaging capability that allows the user to assess the skin and soft-tissue interfaces before the therapeutic ultrasound system is activated.[7] The imaging of the deeper tissue layers imparts added safety to the ultrasound treatment procedure. When ultrasound is used for lipolysis, pretreatment imaging is not typically available.

Our study has limitations. Because it was designed to assess both safety and efficacy, and because, to our knowledge, it was the first ultrasound skin tightening study on live patients in whom the treated skin was not immediately resected, we used modest treatment parameters. As such, it is possible and likely that efficacy was not optimized. More optimized exposure parameters (eg, higher energy densities, more passes, and different focal depths) may have induced greater tissue tightening. That being said, clinically and statistically significant eyebrow elevation was evident in this study. Of course, it is also theoretically possible that more energy and passes may result in more adverse events.

Another weakness of the study was that lower face tightening was difficult to evaluate systematically. Unlike brow-lift, jowl tightening is not amenable to measurement relative to fixed landmarks. This is a problem faced by all studies that assess cosmetic interventions to the lower face, and hopefully future methodological and measurement advances will provide a solution.

Future work could use intense ultrasound probes focused deeper into the tissue to achieve greater tightening efficacy. Higher resolution diagnostic ultrasound imaging would provide better intraoperative visualization of the facial tissue layers, thus facilitating precise treatment. In particular as demonstrated in an earlier cadaveric study,[6] if "suture like" points of thermal injury could be delivered at the level of the superficial musculoaponeurotic system, shrinkage and retraction at that level may be achieved with minimal risk to the facial nerve.[40] Although this sort of energy-mediated facelift may seem fanciful at present, it remains a goal for which to strive.

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