

Clinical Pilot Study of Intense Ultrasound Therapy to Deep Dermal Facial Skin and Subcutaneous Tissues

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Objective: To evaluate the clinical safety of intense ultrasound in the treatment of the dermis and subcutaneous tissues of the face and neck in terms of skin inflammation, pain, adverse events, and histologic features.

Design: In an open-label, phase 1 study, patients scheduled to undergo a rhytidectomy were enrolled into immediate (face-lift surgery within 24 hours of intense ultrasound treatment) and delayed (face-lift surgery 4-12 weeks after treatment) treatment groups. Intense ultrasound treatments were performed as a series of several linear exposures delivered 1.5 to 2.0 mm apart with the use of 1 of 3 available handpieces with different focal depths. Subject pain ratings and standardized digital photographs were obtained at uniform points. Photographs were blindly rated for inflammation. Histologic evaluation of treated tissues was performed with nitroblue tetrazolium chloride viability stain.

Results: Fifteen subjects with a mean \pm SD age of 53 ± 7 years were enrolled. Seven subjects were nonrandomly assigned to the immediate group and 8 were in the de-

layed group. On histologic examination, thermal injury zones were consistently identified in the dermis at exposure levels greater than 0.5 J as focal areas of denatured collagen. At this threshold level or above, most patient exposures were associated with transient superficial skin erythema and slight to mild discomfort on a standardized pain scale. No other adverse effects were noted in any case. Thermal injury zones were produced in the expected linear pattern and were consistent in size and depth from zone to zone. Increasing source power did not increase the depth of the epicenter of the thermal injury zone. Epidermis was spared in all cases.

Conclusion: In this first clinical study of intense ultrasound therapy to facial tissues, the intense ultrasound system allowed for the safe and well-tolerated placement of targeted, precise, and consistent thermal injury zones in the dermis and subcutaneous tissues with sparing of the epidermis.

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VARIOUS NONINVASIVE DEVICES have been developed in an effort to treat facial rhytids.¹ These devices can be grossly categorized as either ablative skin resurfacing (ASR) or nonablative skin rejuvenation (NSR). The ASR modalities (microdermabrasion, chemical peels, and carbon dioxide and erbium-YAG laser therapy) work by removing the superficial layer of the epidermis and inducing thermal injury to the dermis. All these ASR modalities have demonstrated superior efficacy in treating superficial rhytids in the aging face. However, because of the removal of the epidermis, patients treated with ASR can have prolonged erythema, infections, and permanent pigmentary changes.

The NSR devices (intense pulsed light and light-emitting diode, radiofrequency, Nd:YAG, and pulsed dye lasers) have been designed to selectively induce thermal injury within the dermis while sparing the overlying epidermis.^{2,3} This controlled dermal heating incites a "wound-healing" response through the liberation of several cytokines that stimulate fibroblasts to synthesize and lay down new collagen. The lack of epidermal damage with NSR techniques has significantly reduced the treatment-related side effects seen with ASR, yet the overall treatment efficacy, especially with superficial rhytids, has been suboptimal when compared with ASR.⁴⁻⁶

Intense ultrasound (IUS) is an energy modality that can propagate through

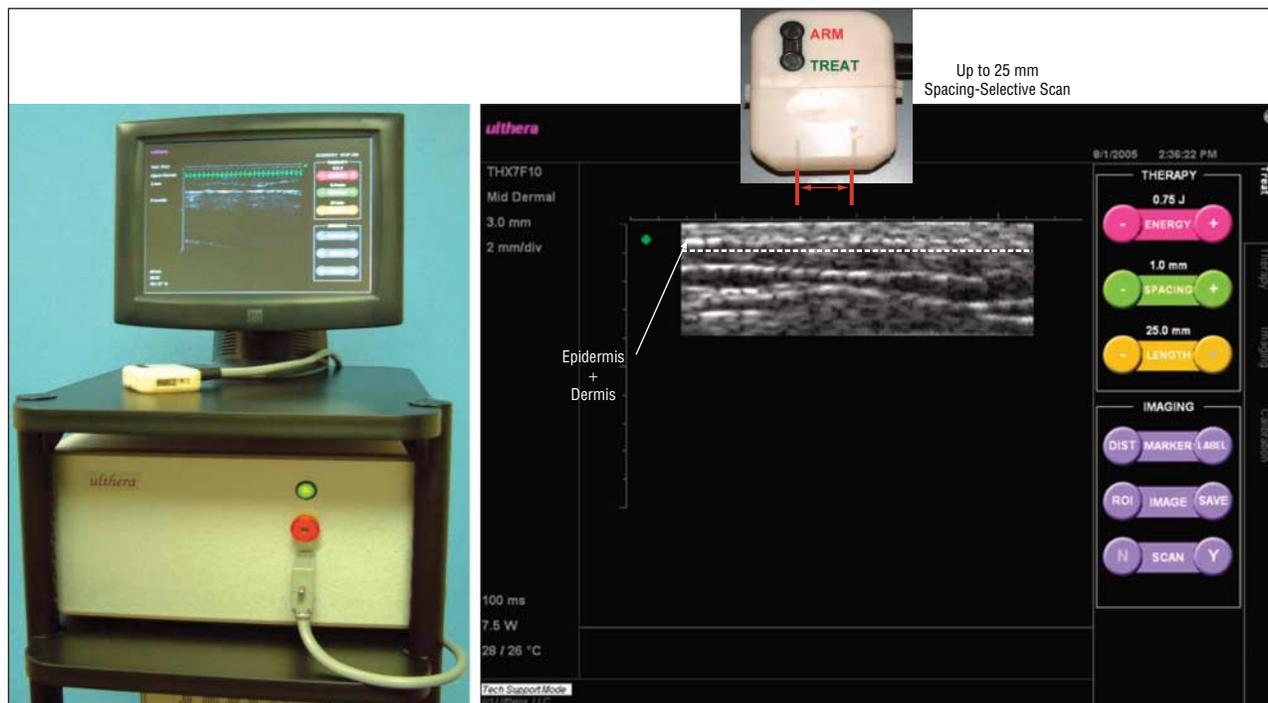


Figure 1. Intense ultrasound system. Imaging and treatment are possible with the same handpiece.

tissues, resulting in selective thermal coagulative change within the focal region of the beam while leaving the remaining regions unaffected.⁷ Ultrasound waves induce a vibration in the composite molecules of a given tissue, and the friction developed between the molecules is the source of the generated heat. It has been well established in the literature that IUS fields transcutaneously directed into whole-organ soft tissue can produce coagulative necrosis resulting primarily from thermal mechanisms.⁸⁻¹⁰ During the past decade, the clinical use of focused IUS has been investigated as a noninvasive surgical tool to treat whole-organ tumors, such as liver, breast, and uterus. To our knowledge, this technology has not been previously applied to human facial tissue.

Working in conjunction with the manufacturer (Ulthera Inc, Mesa, Ariz), we have developed a novel IUS device capable of creating thermal injury zones (TIZ) at depths up to 6 mm. This device is able to focus energy within tissue to produce a 25-mm line of discrete TIZs spaced 0.5 to 5.0 mm apart. Furthermore, both imaging and targeted energy exposure can be accomplished with the same handpiece. Preclinical studies conducted in our department, with human cadaveric facial tissues, have demonstrated that the IUS system can reliably create small, well-defined TIZs in the subdermal soft tissue and deeper superficial musculoaponeurotic system layers while preserving immediately adjacent soft tissue and structures.^{8,11}

In summary, the IUS system is a novel device designed to target and deliver focused energy to a specific skin layer. The purpose of this study was to evaluate the clinical safety of the IUS in the treatment of the face and neck, using skin inflammation, patient-reported pain, and histologic evaluation of injury as the primary end points after IUS exposure over a range of energy levels and source conditions.

METHODS

STUDY DESIGN

We conducted an open-label, prospective, pilot phase 1 human study to determine skin tissue response after exposure to an investigational ultrasound device (the IUS system). This study was approved by the Massachusetts Eye and Ear Infirmary Institutional Review Board for Human Studies.

Adult patients scheduled to undergo a limited rhytidectomy (mini-face-lift) procedure who provided informed consent were eligible for the study. Exclusion criteria included the following: active systemic or local infections; systemic or local skin disease; previous facial surgery (including rhytidectomy, lesion removal, laser or other skin resurfacing, radiofrequency treatments, and injections of filler materials); scarring of any etiology in the planned treatment areas; psychiatric illness; and inability to provide informed consent.

Subjects were assigned by preference for timing of their rhytidectomy into 1 of 2 groups: (1) patients who would receive a surgical mini-face-lift within 24 hours after IUS exposures (immediate group), and (2) patients who would receive a mini-face-lift 4 to 12 weeks after IUS exposures (delayed group).

IUS DEVICE

The prototype IUS device used in this study (UltraSite GT; Ulthera Inc) was specifically designed for facial soft tissues to create TIZs at certain depths with specified patterns. This device consists of a central power unit, a computer, and a delivery handpiece (**Figure 1**). The same handpiece enables sequential imaging (to evaluate layers and structures and to target treatment) and delivery of the ultrasound energy. The console allows for multiple source settings to be controlled, including power output, exposure time, length of exposure line, distance between exposure zones, and time delay after each exposure.

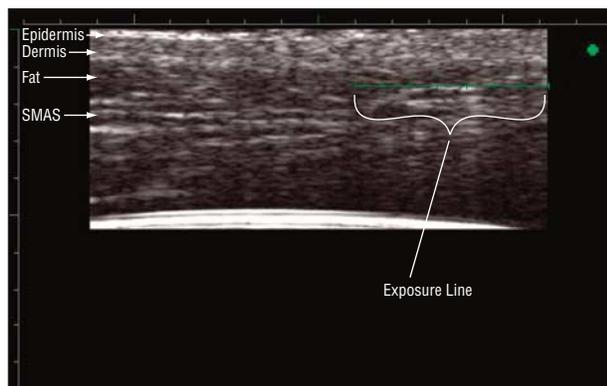


Figure 2. Ultrasound image of the left preauricular region in patient 8. Imaging allows identification of tissue layers (epidermis, dermis, subcutaneous fat, and superficial musculoaponeurotic system [SMAS]). This assessment can help to guide source settings and ensure that the handpiece is coupled to the tissue. Also, the selected length of the treatment line and pulse spacing is displayed onscreen.

Previous studies performed in our laboratory in porcine and human cadaveric tissues have demonstrated that higher-ultrasound-frequency handpieces have shallower focal depths (ie, produce TIZs more superficial in tissue), while lower-frequency handpieces have deeper focal depths (ie, produce TIZs at greater depths).⁸ Three handpieces were created specifically for this experiment: (1) superficial: 7.5 MHz, 3.0-mm focus depth; (2) intermediate: 7.5 MHz, 4.5-mm focus depth; and (3) deep: 4.4 MHz, 4.5-mm focus depth.

On the basis of our previous work in human cadaveric tissues, ultrasound exposures were administered in this study starting with the lowest ultrasound exposure (0.5 J) seen to induce TIZs in human cadaveric facial tissues by means of several combinations of power and exposure durations.

TREATMENT PROCEDURE

The surgeon (R.E.G.) first estimated the amount of periauricular skin area that was destined to be excised during the patient's limited rhytidectomy. This area was demarcated with the use of a surgical marker. Topical anesthetic cream (2.5% lidocaine and 2.5% prilocaine; EMLA; AstraZeneca, Wilmington, Del) was applied to the treatment area and left under occlusion for approximately 45 minutes.

Within each skin area to be excised during face-lift surgery, a series of paired microtattoos were placed 10 mm apart with sterile india ink to indelibly mark the positions of each of the 5 to 10 ultrasound exposure lines. The size of the skin to be excised was unique for each patient and, in some cases, limited the number of ultrasound exposure sites. The microtattoos were used to correlate the position of surface exposures to histologic examination of the tissue.

After cleansing the skin surface with an alcohol swab, ultrasound gel (Parker Laboratories, Fairfield, NJ) was applied to the skin. Each proposed area of treatment was then imaged (**Figure 2**) and the diagnostic image was stored. The IUS handpiece was positioned by alignment with a skin microtattoo pair, a diagnostic image was captured, and the treatment mode was then activated. The treating component of the handpiece mechanically moves in a straight line, at the same source conditions (power, duration) in accordance with the selected treatment variables (length of treatment, spacing of exposures) for distances up to 15 mm, generally producing 5 to 7 uniform tissue exposures per each horizontal "line" of IUS treatment. Several IUS treatments were performed according to the available tissue in each patient (ie, tissue planned for subsequent exci-

sion). This allowed the comparison of multiple source settings from each side of the patient's face after treatment on both sides.

High-resolution digital photography of the periauricular skin areas was performed with a digital single-lens-reflex camera (Nikon D-70; Nikon USA, Melville, NY). Standardized conditions for distance (same f-stop) and lighting were used for photography. Photographs were taken of both the left- and right-side profiles of the face at the following time points: at the screening visit, after microtattoo placement just before IUS treatment, immediately after IUS treatment, 10 minutes after IUS treatment, 48 hours' follow-up (in the delayed group), and just before the surgical mini-face-lift. With the use of image processing software (NIH Image J; <http://rsbweb.nih.gov/ij/>), post-exposure digital photographs were compared with the pre-treatment images.

PAIN, INFLAMMATION, AND ADVERSE EVENTS

After each individual IUS exposure line, the subject was asked to rate sensation by using a 5-point scale as follows: no sensation (0); warm (1); hot, with mild transient pain (2); hot, with moderate transient pain (3); hot, with strong but transient pain (4); and hot, with strong and persistent pain (5). For dermal exposures, the gross cutaneous responses were blindly graded by a single rater (W.M.W.) from photographs taken immediately (papule formation) and 10 minutes (erythema or edema) after exposure on a scale of 0 to 3 as follows: absent (0), slight (1), moderate (2), and prominent (3). All patients were asked to report whether they had experienced any adverse events of any type at each visit.

HISTOLOGIC ANALYSIS

After surgical excision of tissue, all treatment sites were oriented in the anatomic position and placed in a freezer (-15°C). The frozen tissue was sectioned perpendicular to the horizontal IUS exposure lines and immersed in nitroblue tetrazolium chloride (NBTC) solution for 24 hours. The remaining tissue was embedded and submitted for histopathologic examination.

Thermal lesions within collagen were evaluated by the NBTC viability stain,¹² a frequently used stain to evaluate laser-induced thermal injury. Blue staining of cells on frozen section with NBTC confirms viability, and the absence of blue staining is indicative of an area of coagulative necrosis. A positive histologic finding of coagulative change is recorded when at least 3 consecutive histologic sections indicate a region of thermal necrosis. In this manner, the 3-dimensional nature of the thermal coagulative zones was confirmed.

RESULTS

Fifteen subjects were assigned to 1 of 2 treatment groups (**Table**). There were 2 males and 13 females. Mean \pm SD age was 53 ± 7 years. Seven patients underwent face-lift within 24 hours after IUS treatment (immediate group) with complete excision of the treated areas. Eight patients underwent face-lift surgery between 4 and 12 weeks (mean, 5.5 weeks) after IUS treatment (delayed group). More than 1400 individual IUS exposures were administered and evaluated in the patients.

SENSORY AND SKIN RESPONSE

As shown in the Table, patients varied in their pain response to the IUS treatments. All patients were pre-

Table. Treatment Characteristics

Patient No./Sex/Age, y	Mini-Face-lift	Side Treated	Handpiece, MHz/mm*	Energy, J	Inflammation†	Sensation‡
1/M/59	Delayed	R	4.4/4.5	0.5-2.1	0	0-4
		L	7.5/4.5	0.5-1.9	1	0-5
2/F/58	Delayed	R	4.4/4.5	0.5-2.1	0	0-5
		L	7.5/4.5	0.5-1.6	1	0-5
3/F/44	Immediate	R	7.5/4.5	0.5-1.2	0	0-1
		L	7.5/3.0	0.15-0.25	0	0
4/F/58	Delayed	R	4.4/4.5	0.5-1.5	0	0-2
		L	4.4/4.5	0.6-1.6	0-1	0-2
5/F/42	Immediate	R	4.4/4.5	0.6-1.6	0	0-3
		L	7.5/4.5	0.5-1.5	1	1-3
6/F/48	Delayed	R	7.5/3.0	0.45-1.125	0-2	2-3
		L	7.5/3.0	0.25-0.75	0	0-3
7/F/47	Delayed	R	7.5/3.0	0.45-0.90	0-1	0-4
		L	7.5/3.0	0.45-0.70	0-1	2-3
8/F/64	Immediate	R	7.5/3.0	0.45-1.0	0-2	0-3
		L	7.5/4.5	0.9-1.5	1-2	1-4
9/F/47	Immediate	R	7.5/3.0	0.75-1.125	0-2	0
		L	4.4/4.5	1.2-1.6	0	0
10/M/57	Delayed	R	7.5/4.5	0.9-1.2	0	1-3
		L	7.5/3.0	0.5-0.75	0	0-2
11/F/56	Immediate, dense pattern	R	7.5/4.5 (9)	0.9-1.05	1	2-4
		L	7.5/3.0 (9)	0.625	1	2
12/F/46	Immediate, dense pattern	R	4.4/4.5 (8)	0.45-1.6	0-1	1-2
		L	7.5/3.0 (7)	0.45	0-1	0.2
13/F/56	Immediate, dense pattern	R	7.5/4.5 (10)	1.05	0	0
		L	7.5/3.0 (8)	0.625	0	0
14/F/53	Delayed, dense pattern	R	4.4/4.5 (7)	1.6	1	1-3
		L	7.5/3.0 (7)	0.625	0	0-1
15/F/59	Delayed, dense pattern	R	7.5/3.0 (9)	0.625	1	1-2
		L	7.5/4.5 (8)	1.05	1	2-3

*In patients in whom treatment lines were performed in a denser pattern, the number of lines is in parentheses.

†On a scale of 0 to 3 as follows: 0, absent; 1, slight; 2, moderate; and 3, prominent.

‡On a scale of 0 to 5 as follows: 0, no sensation; 1, warm; 2, hot, with mild transient pain; 3, hot, with moderate transient pain; 4, hot, with strong but transient pain; and 5, hot, with strong and persistent pain.

treated with topical lidocaine. Only 1 patient required injection with local anesthetic to complete the treatments, mostly secondary to anxiety. Most patients rated the pain sensation from 0 (no sensation) to 3 (hot, with moderate transient pain) immediately after treatment, and pain was rated as 0 (no sensation) in all patients by 10 minutes after treatment. All patients in the delayed group reported no persistent pain at 48 hours after treatment.

Most patients in both immediate and delayed treatment groups demonstrated transient, mild erythema immediately after treatment. **Figure 3** demonstrates clinical photographs taken in a patient treated with the most superficial handpiece (7.5 MHz/3 mm). Here we can see persistent erythema at the 10-minute point (rated 1, slight). Erythema generally dissipated by 10 minutes in all patients treated with the superficial handpiece. In patients treated with the deeper focal probes (7.5 MHz/4.5 mm [Figure 4] and 4.4 MHz/4.5 mm [Figure 5]), a milder inflammatory response was seen. No persistent erythema was discernible at 48 hours in any patient. In 2 patients treated with the superficial 3.0-mm focal-depth handpiece at the highest energy setting (1.0 J), a linear inflammatory wheal appeared immediately after treatment but completely resolved by 48 hours. Clinically, no signs of



Figure 3. Patient 11. Clinical photographs taken before treatment with a 7.5-MHz/3-mm handpiece (A) and 10 minutes after exposure (B). Nine lines of exposure were placed at 0.625 J. Inflammation score was 1; sensation, 2. The scale is in millimeters.

epidermal disruption or slough (Figures 3, 4, and 5) or any additional delayed adverse effects (eg, persistent pain or inflammation) were seen in any patient.



Figure 4. Patient 13. Clinical photographs taken before treatment with a 7.5-MHz/4.5-mm handpiece (A) and 10 minutes after exposure (B). Ten lines of exposure were placed at 1.05 J. Inflammation score was 0; sensation, 0. The scale is in millimeters.

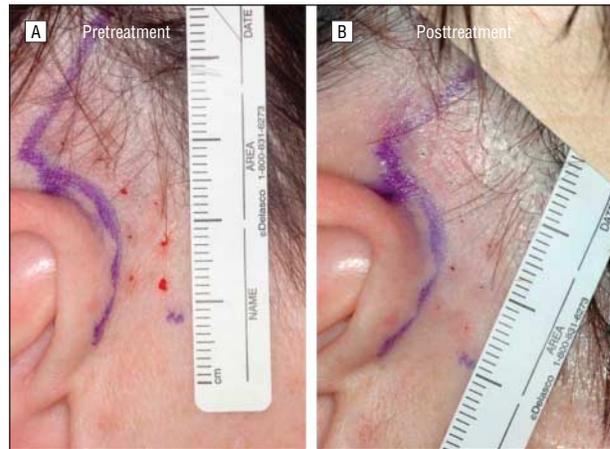


Figure 5. Patient 12. Clinical photographs taken before treatment with a 4.4-MHz/4.5-mm handpiece (A) and 10 minutes after exposure (B). Eight lines of exposure were placed at 1.6 J. Inflammation score was 0; sensation, 1 to 2. The scale is in millimeters.

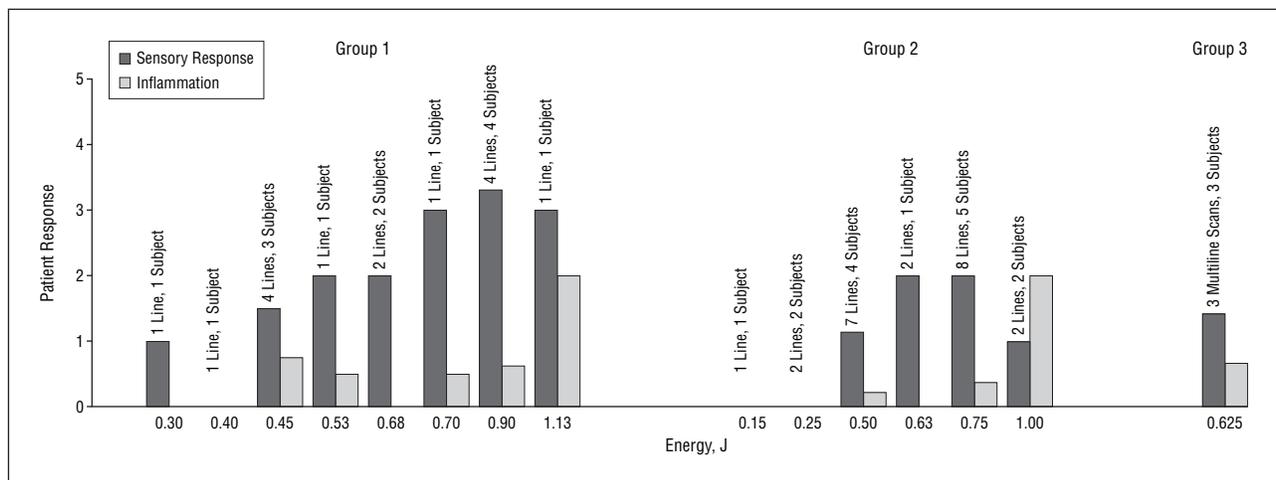


Figure 6. Patient responses to treatment with a 7.5-MHz/3.0-mm handpiece. Group 1 had high power levels (30-45 W at 0.30-1.13 J). In group 2 the power levels were kept lower (15-25 W at 0.15-1.00 J). Group 3 had dense pattern exposures (25 W, 0.625 J).

Figures 6, 7, and 8 summarize the sensory and inflammatory responses for all of the exposures with the 3 handpiece types used in the study. Each bar demonstrates average patient response, as multiple unique exposure lines were made at the same source power-time (energy) combination. For each graph (ie, each handpiece type), the data could be divided into 3 categories based on the power settings (watts) used for the IUS exposures. In each graph, the first grouping of data bars represents the higher source power (watts) settings, or “high power.” The second grouping of data bars represents lower source power (watts) settings, or “low power.” The specific power levels for each given handpiece are given in the figure legends.

From the individual graphs, it is evident that the high-power settings resulted nominally in a greater sensory response, whereas the low-power source conditions were better tolerated by the subjects. Furthermore, when the 3 unique handpieces were compared over similar source conditions, the superficial handpiece (7.5 MHz/3 mm [Figure 6]) produced less of a sensory response than did

the intermediate and deep handpieces, both of which were focused at 4.5 mm (Figures 7 and 8). However, higher-frequency handpieces (7.5 MHz [Figures 6 and 7]) tended to produce a greater inflammatory response than did the lower-frequency handpiece (4.4 MHz [Figure 8]). The average inflammatory response for all of the exposures made with the 3 IUS handpiece types did not exceed 2 (moderate inflammation) on a 0 to 3 ordinal scale.

The third grouping of data bars seen in the graphs (Figures 6-8, rightmost bars) consists of the average sensory and inflammation scores of patients after placement of a higher density of parallel IUS exposures. In this higher-density pattern, multiple consecutive parallel exposure lines were delivered at the same unique power setting, such that an array of densely spaced TIZs were deposited per unit volume of tissue. This was in contrast to the previous low-power and high-power groups, in which individual exposure lines were delivered at different source settings. These source settings chosen for the denser pattern were from the low-power source settings groups for each handpiece. Again, when densely

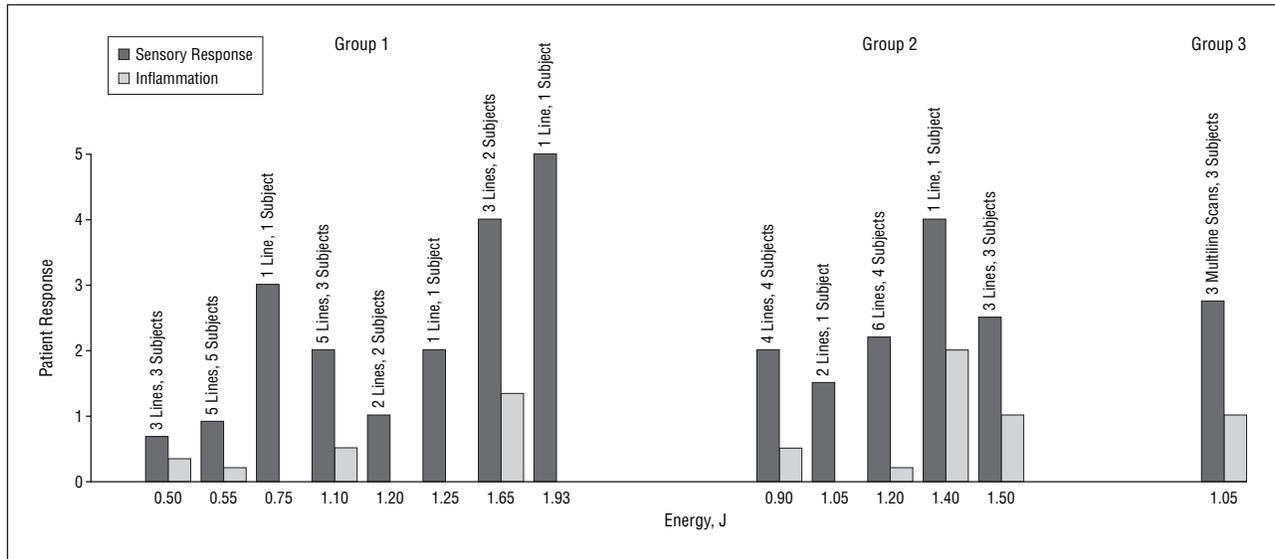


Figure 7. Patient responses to treatment with a 7.5-MHz/4.5-mm handpiece. Group 1 had higher power levels (50-60 W at 0.50-1.93 J). In group 2 the power levels were kept lower (30-35 W at 0.90-1.50 J). Group 3 had dense pattern exposures (30 W, 1.05 J).

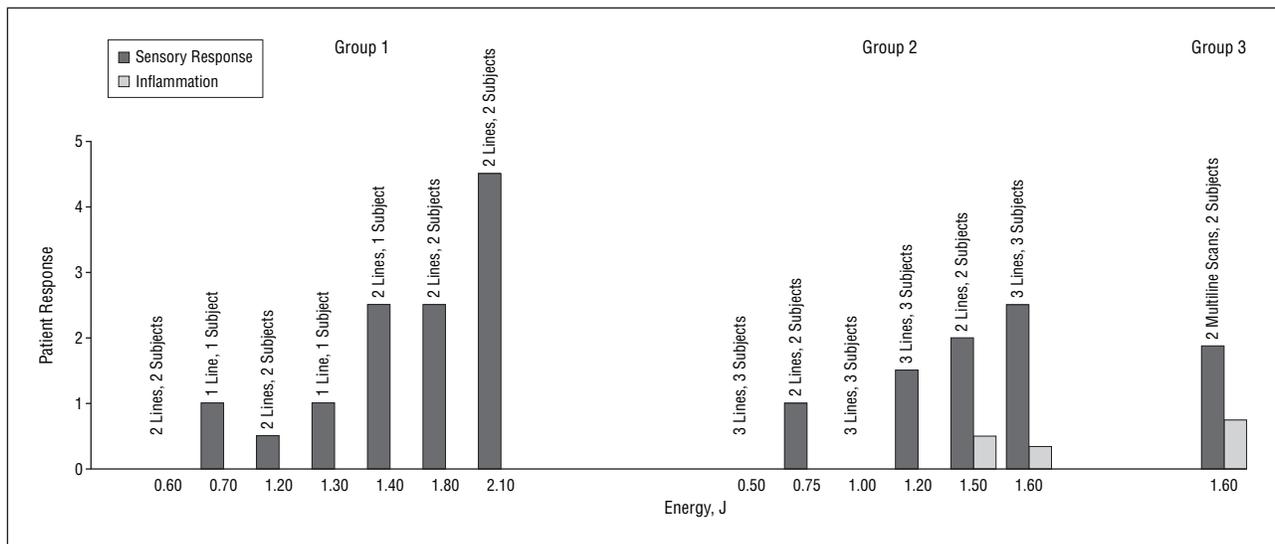


Figure 8. Patient responses to treatment with a 4.4-MHz/4.5-mm handpiece. Group 1 had higher power levels (60-70 W at 0.6-2.1 J). In group 2 the power levels were kept lower (40-50 W at 0.50-1.60 J). Group 3 had dense pattern exposures (40 W, 1.60 J).

spaced TIZs were deposited in a higher-density pattern, no clinically significant sensory discomfort or inflammation was noted (Figures 3-5).

NBTC VITAL STAINING

On gross and histologic examination, TIZs were consistently identified in the dermis (corresponding to the focal point of the exposures) as areas of collagen denaturation at exposure power levels greater than 0.5 J. At this TIZ threshold level or above, most patient exposures were associated with transient superficial skin erythema and slight to mild discomfort (average pain sensation score, 3 [hot, with moderate, transient pain]). The TIZs were reproducibly created in the expected linear pattern and were consistent from zone to zone (**Figure 9**). The depth of the TIZs was consistent from spot to spot for the same

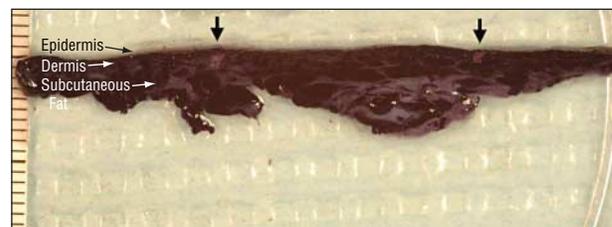


Figure 9. Nitroblue tetrazolium chloride (NBTC) staining of grossly excised preauricular tissue, sectioned perpendicularly to the lines of treatment. Two thermal injury zones can be seen by their loss of blue NBTC vital staining just below the skin surface (arrows). The treatment was performed with a 7.5-MHz/3-mm handpiece on patient 8 (scale, 1 mm per division). The scale is in millimeters.

handpiece. Increasing source power did not increase the depth of the epicenter of the TIZ (**Figures 10, 11, and 12**). The epidermis was spared in all cases.

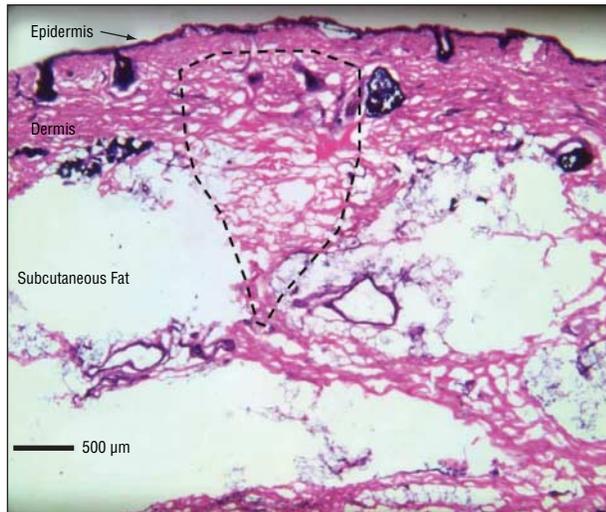


Figure 10. Digital photomicrograph of a frozen section stained with nitroblue tetrazolium chloride (NBTC) (eosin counterstain). A thermal injury zone is shown by the loss of blue NBTC vital stain and dilated collagen fibers just below the skin epidermis (dotted line). Note the complete epidermal preservation. The treatment was performed with a 7.5-MHz/3-mm handpiece (0.9 J) on patient 8 (original magnification, $\times 20$).

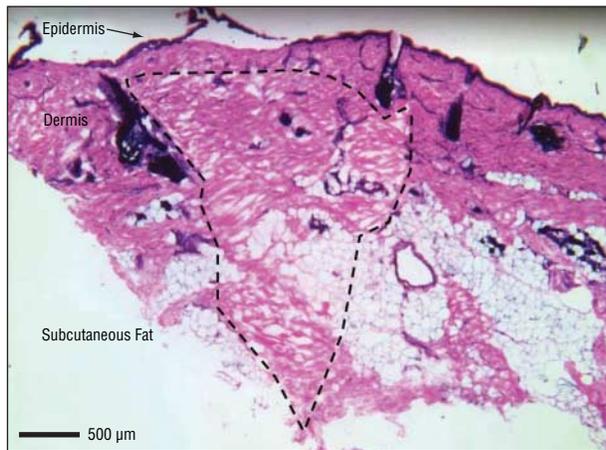


Figure 11. Digital photomicrograph of a frozen section stained with nitroblue tetrazolium chloride (NBTC) (eosin counterstain). A thermal injury zone is shown by the loss of blue NBTC vital stain and dilated collagen fibers just below the skin epidermis (dotted line). The treatment was performed with a 7.5-MHz/4.5-mm handpiece (1.2 J) on patient 8 (original magnification, $\times 20$).

COMMENT

This open-label pilot clinical trial was conducted to confirm the safety of IUS treatment to facial dermis and subcutaneous tissue. The results demonstrate that, within the range of source conditions (0.5-2.1 J) used for the clinical study, the IUS exposures were well tolerated by the subjects. Furthermore, on the exposed site, there was no detrimental change in the epidermis (Figures 3-5), as well as no delayed sequelae in the treated tissue (4-12 weeks posttreatment). During this 15-patient study, there were no findings related to a detrimental impact of the IUS exposures on the facial nerve or its branches. This negative finding was anticipated on the basis of the safe use of other energy-based cosmetic devices on which the IUS device is predicated, as well as the deeper location



Figure 12. Digital photomicrograph of a frozen section stained with nitroblue tetrazolium chloride (NBTC) (eosin counterstain). A thermal injury zone is shown by the loss of blue NBTC vital stain and dilated collagen fibers just below the skin epidermis (dotted line). Note the epidermal preservation. The treatment was performed with a 4.4-MHz/4.5-mm handpiece (1.6 J) on patient 12 (original magnification, $\times 20$).

of the facial nerve in the periauricular region¹³ compared with the depth at which the IUS system is expected to cause a tissue effect.

The purpose of most energy-delivery devices in cosmetic applications is to achieve a controlled thermal injury in the skin tissue. This damage results in an immediate contraction of the collagen tissue and initiates a repair process in which a new collagen matrix is laid down subepidermally.^{1,6,14} The IUS device is designed to achieve selective regions (on the order of 1 mm³ per individual exposure shot) of thermal coagulative change below the epidermis while sparing the epidermis, adding to the overall safety of this technique. An aim of this study was, therefore, to confirm the presence of selective regions of acute thermal microablative change resulting from exposures from various IUS handpiece types at particular source conditions. Within the range of source conditions (power-time combinations, frequency, etc) used in this study, selective thermal coagulative changes were confirmed with each of the handpiece types used (Table). The coagulative damage was identified histopathologically, by the classic lack of cellular organization in the ultrasound-exposed region, as well as the denaturation of collagen in the region. These findings are evident by the lack of vital stain (NBTC) uptake (Figures 10-12) in the thermally affected region. These histologic changes are well documented in the literature as being a result of thermal damage to the skin tissue.^{6,8,12,15} The positive findings were identified primarily in the tissue excised from the patient group undergoing an immediate mini-face-lift surgery. Once again, the epidermis was spared in all cases in this study, and the region of thermal microablative damage from the IUS exposure was particularly selective (on the order of 1 mm³).

No definitive and significant histologic change could be identified in the evaluation of tissue from the delayed patient group. The lack of significant histologic findings in the tissue from the delayed group suggests resolution of the microablative injury that was caused by the IUS exposures. A limitation of this study was the lack of electron microscopy to further evaluate collagen changes with both injury and healing.¹⁶

CONCLUSIONS

This clinical study of IUS to the face and neck demonstrated that IUS can produce targeted, consistent, and reproducible thermal injury zones in the dermis and subcutaneous tissues. The ability to both target and noninvasively treat facial tissues is unique to the ultrasound device. Treatments were associated with limited transient erythema, mild discomfort, and histologic evidence of collagen denaturation in the dermis with sparing of the overlying epidermal layer. Further studies are needed to determine the efficacy of this new treatment modality, which has important implications for facial aesthetic procedures.

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