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Fractional Nonablative Laser Resurfacing: Is There a Skin Tightening Effect?

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BACKGROUND Fractional photothermolysis, an approach to laser skin resurfacing that creates microscopic thermal wounds in skin separated by islands of spared tissue, was developed to overcome the high incidence of adverse events and prolonged healing times associated with full coverage ablative laser procedures.

OBJECTIVE To examine whether fractional nonablative laser resurfacing induces skin tightening.

MATERIALS AND METHODS A literature review was performed to evaluate the clinical and histologic effects of fractional nonablative laser resurfacing and full coverage ablative resurfacing procedures.

RESULTS Fractional nonablative lasers produce excellent outcomes with minimal risk and morbidity for a variety of clinical conditions, including photodamaged skin, atrophic scars, surgical and burn scars. Efforts to induce robust fibroplasia in histologic specimens and skin tightening in the clinical setting have yielded inconsistent results.

CONCLUSION A better understanding of the histology of fractional laser resurfacing will help to optimize clinical outcomes.

The author has indicated no significant interest with commercial supporters.

The definition of the term skin "tightening" remains elusive. In rhytidectomy surgery, it is synonymous with excising redundant skin with or without anchoring the underlying fascia and muscle, to essentially shrink and thereby smooth the skin envelope. This type of tightening is a mechanical one in nature; the skin envelope is reduced in size without changing the volume of contents beneath, leading to a smoother skin surface with fewer wrinkles and less laxity, and giving the skin a tighter appearance. Photodamaged or atrophic skin also appears tighter when injectable fillers or dermal stimulators are implanted into the subcutis, submuscular or supraperiosteal plane to reinflate or expand a lax skin envelope by restoring lost volume. Injectable fillers placed directly in the dermis or subcutis induce new collagen production and restore the integrity to a lax skin envelope or focal areas of atrophy such as scars. Full-coverage ablative carbon dioxide laser resurfacing rejuvenates facial skin and improves wrinkles and laxity by means of formation of a new epidermis and the robust induction of fibroplasia that replaces the photodamaged dermis.

The clinical improvement and tightening effect achieved with full coverage ablative carbon dioxide laser resurfacing serves as a standard for all other laser and device-based treatment of photoaging and atrophic skin conditions.[1–4] The benefits of fully ablative laser procedures, however, come at the expense of prolonged recovery times, with open exudative wounds requiring intensive wound care for up to 2 weeks, and a risk of infection, transient and long-term pigment changes, and scarring.[5] Full-coverage ablative laser procedures are limited to facial skin because of the reduced ability of the adnexal-poor skin of the trunk and extremities to reepithelialize, and their use is generally restricted to Phototype I to III skin because of the high risk of long-term

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alteration in skin pigment. To avoid these risks, clinicians turned to full-coverage nonablative lasers that use midinfrared wavelengths to coagulate a layer of dermal tissue while preserving an intact epidermis by means of simultaneous skin cooling. Histologic examination[6] after full-surface nonablative midinfrared lasers emitting at 1,320, 1,450, and 1,540 nm, in conjunction with active skin cooling, demonstrates a band-like pattern of thermal injury at approximately 150 to 500 μm in the dermis. The deep boundaries of this band are dependent on pulse energy and pulse number. After 8 weeks, biopsies show dermal fibroplasia roughly correlating to the band of immediate dermal thermal damage. These procedures are very safe but they do not repair the epidermis, and they provide little clinical benefit for wrinkles and atrophy.

Fractional Photothermolysis

Fractional photothermolysis,[7] an approach to laser skin resurfacing that creates microscopic thermal wounds and specifically spares tissue surrounding each wound, was developed to overcome the high incidence of adverse events and prolonged healing times associated with full-coverage ablative laser procedures and the limited efficacy of full-coverage nonablative laser treatment. Based on a concept developed by Manstein and Anderson[7] and termed fractional photothermolysis, fractional nonablative lasers create an entirely different injury pattern in skin. They use water-absorbing midinfrared wavelengths to produce a 3-dimensional wound by generating a pattern of microscopic columns of coagulated tissue, termed microthermal zones (MTZs), and measuring 100 to 200 μm in diameter, to depths up to 1,600 μm, that are oriented perpendicularly to the skin surface, while maintaining the integrity of the epidermis. The pattern of the wound can be manipulated by changing the density of the microbeams, and the microbeam fluence controls the depth of tissue coagulation. The intervening zones of unaltered tissue between the coagulated tissue columns and intact epidermis enable rapid healing of the treated skin. These procedures are well tolerated with the application of a topical anesthetic cream, and after treatment, patients experience erythema and edema for 2 to 4 days, followed by 2 to 3 days of exfoliation of the microcrusts that result from transepidermal elimination of the necrotic tissue debris. Because the integrity of the epidermis is not compromised, there are no specific wound care requirements, and, unlike full-coverage ablative laser procedures, nonablative fractional laser resurfacing is safe to perform on the trunk and extremities and in all skin photoypes. Fractional nonablative lasers[8] improve photodamage-associated dyschromia, actinic keratoses, burn scars, surgical scars, acne scars, and striae distensae but the reported results for wrinkles and skin laxity have been somewhat disappointing. Notwithstanding, tightening of photodamaged skin, acne scars, and striae has been described in some studies. The question of whether nonabalative fractional lasers can induce skin "tightening" remains controversial.

Technology

The first fractional nonablative laser created based on the principle of fractional photothermolysis was an optically scanned 1,550-nm erbium-doped fiber laser (Fraxel Re:Store; SoltaMedical, Hayward, CA).[1,4,5] This was followed by the development of stamping technology with the 1,540-nm erbium glass (Palomar Lux 1,540; Cynosure Inc., Westford, MA) and 1,440 nm lasers (Affirm; Cynosure Inc., Westford, MA), and stamped scanning technology with the 1,565-nm fiber laser (ResurFX; Lumenis, Yokneam, Israel). Water is the chromophore for these midinfrared wavelengths, and when the laser interacts with tissue, the water content is heated to a point of dermal denaturation. The concept of fractionation has also been applied to radiofrequency technology (eMatrix; Syneron, Yokneam, Israel). The device uses bipolar radiofrequency in a fractional manner through an applicator with an array of multi-electrode pins; it delivers heating in the areas of pin contact and spares the areas in between. All of these devices create similar damage patterns in tissue and produce varying degrees of clinical improvement for photodamage, scars, and other skin conditions, depending on the choice of parameters and number of treatment sessions. Because of differences in

technology, it is important to note that parameters from one device are not transposable to another technology. Practitioners should be knowledgeable about the tissue effects of and range of parameters for their individual system.

Skin Tightening with Resurfacing Lasers

The best example of laser-induced skin tightening is seen with multiple-pass, full-coverage ablative carbon dioxide or long-pulsed erbium:yttrium aluminum garnet laser resurfacing.[1–4] These wounds have limited depths of ablation (approximately 100 μm) with large zones (>200 μm) of residual thermal damage (RTD) after multiple laser passes, and produce excellent improvement in epidermal skin changes, coarse and fine wrinkles, as well as tightening of atrophic skin. The skin tightening observed after full-coverage ablative laser resurfacing is a result of the induction of deep zones of fibroplasia and long-term wound contraction that result in increased skin stiffness and elasticity. Carbon dioxide laser-treated wounds produce a dense lichenoid infiltrate, with neutrophils predominating, present along the transition zone separating the coagulated collagen and normal dermis below. At 1 month after laser treatment, the depth of fibrosing granulation tissue is twice that of equivalent depth short-pulse erbium:YAG laser wounds, and the depth of fibroplasia remains twice the depth of the erbium:YAG laser wounds at 3 months. In addition, elastophagocytosis is evident in the deeper layers of the granulation tissue in full-coverage carbon dioxide laser-treated skin. In contrast, equivalent depth procedures with short-pulse (250 microseconds) erbium:YAG lasers produce deeper zones of ablation (>200 μm) and thin zones (<50 μm) of RTD after multiple laser passes, resulting in less fibroplasia and less tissue shrinkage. After treatment, a patchy mixed infiltrate is present beneath the zone of coagulation, and there is no elastophagocytosis. Even when the total depth of ablation plus coagulation creates the same total depth of tissue damage as the resurfacing carbon dioxide and long-pulse erbium:YAG lasers, clinical efficacy for wrinkles and atrophy or laxity is less with the high-ablation, low-coagulation pattern of injury. When deeper ablation through the reticular dermis is performed with short-pulse erbium:YAG lasers, increased efficacy is observed, but at the expense of a higher incidence of adverse events including long-term scarring and depigmentation, similar to that observed with deep mechanical dermabrasion. There is a considerable body of literature examining the laser–tissue interactions and histology for full-coverage ablative resurfacing, and it is clear that the degree of improvement in wrinkles and skin laxity is dependent on the depth of RTD rather than the total depth of tissue damage (ablation plus coagulation). With either of these treatments, however, the total depth of tissue damage is limited to approximately 500 to 600 μm, precluding effective treatment of deep dermal lesions. It was initially believed that fractional photothermolysis would improve outcomes compared to fully ablative procedures because of the ability to safely coagulate even greater volumes of tissue, with depths of thermal wounds extending to 1 to 1.5 mm, but these suppositions have not been borne out by clinical data.

Studies characterizing the histology or molecular changes in wound healing after nonablative fractional resurfacing are few, and many of these reports examine single treatments or single-pass, low-density or low-energy treatments. Fractional nonablative treatments are performed at higher energies and densities in clinical practice, and as a series of procedures. In addition, the follow-up times in some studies are often too short (less than 6 months) to permit fair comparisons with data on wounding after full-coverage ablative resurfacing, which is usually performed as a single stand-alone procedure, rather than as a series of 4 to 6 treatments, typically performed at monthly intervals.

Histology and Wound Healing After Fractional Nonablative Laser Treatment

The immediate histologic effects after nonablative fractional photothermolysis were examined[9] after a single treatment of human abdominal skin before abdominoplasty. Pulse energies of 6 to 20 mJ were used with 4 passes at 250 MTZs/cm^2 or 16 passes at 125 MTZs/cm^2 to achieve final densities of 1,000 and 2,000 MTZs/cm^2. The stratum corneum remained intact after treatment, and at 24 hours there was vacuolar change in the epidermis overlying the

MTZs, with repopulation of keratinocytes and melanocytes at the basal layer. Clefting of the dermal-epidermal junction (DEJ) occurred just above the zone of dermal coagulation, and a spheroid collection of necrotic debris and melanin was present overlying each column of coagulated dermal tissue and is termed as microepidermal necrotic debris (MENDs). There was a complete loss of cell viability within the MTZ as assessed by lactose dehydrogenase (LDH) staining. Dermal content was observed in the vacuoles by positive staining with Gomori trichrome and antihuman elastin antibody, demonstrating that in addition to the damage and replacement of the affected epidermis, fractional photothermolysis creates microthermal lesions that allow transport and extrusion of dermal content through a compromised DEJ. This transepidermal elimination of necrotic epidermal and dermal debris creates a biological skin resurfacing.

Clinical and histologic responses to a fractional 1,500-nm diode laser treatment were examined[10] in an in vivo study of forearm skin over a 3-month duration. A single laser treatment was performed using a pulse energy of 5 mJ at a density of 1,600 MTZ/cm^2. Serial biopsies were obtained and evaluated with hematoxylin and eosin (H&E), Elastica van Gieson stain, and LDH cell viability testing. There was complete epidermal regeneration at 7 days, and complete shedding of the MENDs at 7 days. The induction of a wound-healing response was confirmed by immunohistochemistry analysis showing expression of heat shock protein 70 (HSP70) at 24 hours and smooth muscle actin (indicating the presence of myofibroblasts) at 7 days. Heat shock proteins are a group of proteins called chaperons that are expressed after sublethal thermal stress in human tissue. Heat shock proteins stabilize the 3D-folding of proteins in damaged cells, which would otherwise undergo apoptosis. Heat shock protein 70 also induces growth factors such as transforming growth factor beta (TGF-beta), which is involved in the wound-healing response and fibrogenic process. Heat shock protein 70 was elevated in the tissue surrounding the MTZ, indicating that the dermal wound-healing process was stimulated in the zone of sublethally damaged dermis adjacent to the MTZs. Despite the deep zones of coagulation produced in the dermis, there was no evidence of dermal fibrosis at 3 months after treatment. It is important to note that these results were obtained after a single laser treatment at very low pulse energy, which could explain the lack of fibroplasia.

Similar results were observed in a histologic evaluation[11] of in vivo abdominal skin treated with a fractional 1,540-nm erbium glass laser fitted with a microlens array and a simultaneously cooled sapphire glass window held at 17°C. The microlens array creates a pattern of 100 microbeams per centimeter square with a 1-mm pitch, through a 10-mm aperture. Microbeam energies of 18 to 100 mJ at pulse widths of 10 to 30 milliseconds were examined after single-pass and multi-pass treatment. Multi-pass treatment consisted of either performing a sequential series of 2 to 3 successive passes of contiguous stamped laser pulses to the treatment area, or treating repeatedly over a single spot 3 to 10 times with rotation of the handpiece by approximately 45°C. After a single treatment pass, H&E and trichrome staining of specimens showed coagulated columns of tissue ~250 μm in diameter separated by ~800 μm of unaffected tissue. The depth of coagulation increased linearly with increasing pulse energy by roughly a factor of 100 to 150 μm per 10 mJ of energy. Vacuolization of the basal layer was present in all specimens, but the integrity of the stratum corneum was maintained. The higher-pulse energies used in this study confirmed previous findings with the fractional 1,550-nm laser that increased disruption of the DEJ is observed with higher-pulse energies and multi-pass treatments. In addition, with higher pass treatment, some of the columns overlapped and blended, causing a random pattern of coagulation throughout the dermis, nonuniform coagulation around the DEJ, and larger zones of epidermal clefting. Even in these areas of overlapping MTZs, the stratum corneum remained intact.

The effect of varying MTZ density was evaluated with a fractional 1,550-nm laser in an in vivo forearm study over a period of 3 months.[7] Laser treatment using a low-pulse energy of 5 mJ was performed with low (400 MTZs), medium (1,600 MTZs), and high

(6,400 MTZs) densities. Post-treatment erythema resolved for the low and medium densities within 1 week but was still present at 3 months after high-density treatment. There was immediate whitening of the skin after high-density treatment with oozing and crusting and measurable transepidermal water loss for up to 2 weeks, correlating with the epidermal separation observed in biopsy specimens. At low and medium treatment density, there was no or little inflammatory infiltrate or granulation tissue. In contrast, high-density treatment produced marked inflammation around the MTZs and granulation tissue. Although this high-density treatment was clearly too aggressive, the results suggest that either higher volumes of tissue coagulation or greater epidermal damage will trigger a different pathway of wound healing.

In a study[12] examining the molecular mechanisms of improvement after fractional 1,550-nm laser treatment, high-energy/low-density and low-energy/high-density treatments were compared. Only 1 treatment session was performed on forearm skin, and serial biopsies taken over a 28 days' time course were examined. There was an initial inflammatory response with the induction of proinflammatory cytokines, including interleukin-1 beta and tumor necrosis factor alpha. This was followed by matrix remodeling, with the induction of several matrix metalloproteinases, and Type I collagen production and remodeling. No significant differences were observed between the high-energy/low-density and low-energy/high-density treatments, suggesting that the total energy applied to the skin and the extent of thermal damage, rather than the 3-dimensional configuration of the damage may be more predictive of clinical efficacy. Drawbacks of this study are that only 1 laser treatment session was performed, excluding the possibility of cumulative effects from multiple sessions, and that the final time point for evaluation was only 4 weeks after laser treatment.

It is difficult to draw definitive conclusions about the ability of fractional nonablative lasers to induce fibroplasia based on the histologic studies in the literature. Fractional treatment produces well-delineated columns of coagulated tissue and minimal DEJ disruption with low-to-moderate energy and single-pass treatment. Multi-pass treatment, which is a standard practice in all fractional nonablative treatments, produces greater damage to the DEJ. Higher-pulse energies (>20 mJ) also produce increased epidermal separation at the DEJ. Skin temperature control is another important variable in nonablative FP. The diameter of the MTZs is increased with an increase in skin temperature.[10] Bulk heating can be prevented using more aggressive skin cooling, or increasing the time interval between successive lasers' passes to allow heat to be dissipated by thermal diffusion and blood perfusion. The cooling systems vary for each of the different laser systems, and bulk cooling with ice is a common practice during and immediately after treatment. In addition, most nonablative fractional treatments are delivered as a series of monthly procedures. Controlled histologic studies of high-energy, high-density multiple session fractional laser treatment are lacking, and the variables in fractional procedures are even greater in number than in full-coverage ablative resurfacing.

Evidence for Skin Tightening With Nonablative Fractional Photothermolysis

There are scattered clinical trials and collective anecdotal evidence demonstrating that fractional nonablative lasers can induce tissue tightening[13] in some circumstances. Several retrospective and randomized controlled trials of acne scar treatment[14,15] have shown long-term improvement in skin texture after nonablative fractional photothermolysis. Nonablative fractional lasers produce long-term collagen remodeling in burn scars and surgical scars.[16,17] A retrospective study of eyelid treatment using multiple treatment sessions showed improvement in eyelid tightening and an increase in eyelid aperture.[18] The author has observed generalized skin tightening in some patients receiving multiple sessions of high-energy, high-density fractional nonablative laser treatment.

Tissue shrinkage was evaluated in the initial clinical studies of the prototype fractional 1,550-nm laser, where the authors reported significant improvement in periorbital rhytides and skin texture.[7] Tattoos were

placed in the treatment areas to evaluate skin shrinkage over time. A linear pattern of shrinkage was found along the sides of tattooed treatment sites, suggesting that the pattern of wounding produced tissue shrinkage and wound contraction. One week after treatment, there was statistically significant shrinkage, followed by relaxation at 1 month, and tightening was again observed at 3 months, a sequence reminiscent of that seen with ablative laser resurfacing.

The ability of nonablative and ablative fractional laser treatment to produce tissue shrinkage was compared in a rat study,[19] where 2- × 2-cm squares were tattooed on the abdomens. Nonablative and ablative treatments were performed with the same total energy and were delivered in 4 sessions with a treatment interval of 3 weeks. Immediate skin shrinkage (11.5%) occurred with the ablative but not the nonablative treatment. At 4 months, there was a 4.3% reduction in surface area of nonablative laser-treated skin and a 9% shrinkage reduction in surface area of ablative laser-treated skin. Regenerated collagen, arranged in parallel alignment to the epidermis was noted in both ablative and nonablative laser-treated skin. Type I and III collagens were upregulated and present in normal ratios. These studies indicate that some degree of tissue tightening after fractional nonablative treatment is measurable at 3 months but may be undetectable at 1 month, emphasizing the need for longer-term follow-up in studies.

Conclusion

Definitive evidence of skin tightening after fractional nonablative laser treatment is lacking, but clinical evidence suggests that this it does occur. There is a large body of literature on the characterization of wound healing after traditional ablative carbon dioxide and erbium:YAG laser resurfacing, but the dynamics of laser–tissue interaction remain poorly understood. Fractional wounds are inherently more complex to study because of the variability in geometry of the wounds, and the modulating effects of pulse energy, MTZ density, and skin temperature. Additionally, the parameters used in most of the histologic studies of fractional nonablative laser resurfacing are much less aggressive than those used in clinical practice,[8,20] undermining some of their validity. Based on what we do know, how can we potentially optimize fractional nonablative laser treatment to consistently produce skin tightening? We recognize that broad zones of middermal coagulation, without any epidermal damage, as seen in full-coverage nonablative laser treatments produce almost no inflammation. Patchy inflammatory infiltrates are present in full-coverage ablative wounds with minimal coagulation, as in short-pulse erbium:YAG laser treatment, and produce modest fibroplasia. Very dense inflammation, with neutrophils predominating, is present in full-coverage ablative laser procedures with dense zones of coagulation. These wounds produce the greatest degree of fibroplasia and long-term skin tightening. Data examining the wounds from fractional nonablative laser treatment seem to collectively indicate the following: increasing MTZ density and pulse energy will increase epidermal clefting, peri-lesional inflammation, granulation tissue formation, and prolong post-treatment erythema. Carefully planned prospective studies evaluating these variables independently and in combination may help us achieve more consistent results while preserving the safety profile of this revolutionary approach to skin resurfacing.

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