Fractional Photothermolysis

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Introduction

Photoaging involves the loss and remodeling of collagen in the dermis, increase in vascular ectasia, and a fragmentation of elastin fibers in the dermis known as solar elastosis.[1] Clinical correlates of what is observed histologically are rhytides (both static and dynamic lines that may be fine or deeper in nature) enlargement of pore ostia, dyschromia, including telangiectatic changes of the skin and brown pigmentary unevenness, generalized loss of luster of the skin on the face, and crepiness of the skin may develop in some anatomical areas such as the neck, arms and eyelids.

The theory of selective photothermolysis was introduced in 1983 and presented a logical means of targeting particular molecular entities for laser heat-induced damage while preserving the surrounding tissue.[2] By selection of a specific wavelength unique to 1 target, heat can be delivered rapidly enough to the target before it can be diffused to the surroundings leading to the thermal damage being confined to the target. Melanin, hemoglobin, and water (in the case of photorejuvenation) are the most common molecular targets.

Photorejuvenation of the skin can be separated on the basis of the skin's reaction to the treatment. Broadly, ablative skin resurfacing methods such as the CO_2 laser or the Erbium:YAG laser, target intracellular water in the skin. The CO_2 laser heats the target within cells instantaneously to greater than 100°C leading to vaporization of tissue on the surface layer of the skin; coagulation necrosis of cells and denaturation of extracellular proteins in the next layer; and finally nonfatal cellular damage in the deeper zones of the skin.[3] Ablative lasers remove 100% of the epidermis and varying thickness of underlying dermis that results in a smoother appearance to the skin and skin tightening due to heat induced collagen shrinkage.[4]

While ablative lasers have long been the gold standard for the treatment of photodamage, the applicability of the treatment has been limited by the potential for unfavorable side effects and by the prolonged healing period and downtime patients require before returning to their routine.[4-11] Frequently, patients have posttreatment erythema, edema, burning and crusting. The erythema may last on average 4.5 months[12] and pigmentary alteration, acne flares, herpes infection/reactivation, scars, milia, and dermatitis can also occur;[12-14] however, single pass CO_2 laser resurfacing can reduce the severity of these side effects.[15] Also, off the face treatments with ablative systems have been associated with a high risk of scarring and pigmentary changes that makes nonfacial ablative treatments contraindicated in most settings.[16]

Nonablative laser treatments generally employ some method of epidermal protection, most commonly a cooling method, while injuring the dermis through selectively targeting dermal water. The wound healing response produces new collagen. Examples of traditional nonablative systems include the 1320-nm Nd:YAG and the 1450-nm semiconductor diode lasers.[17] While these systems have the advantage of much reduced or no downtime and minimal risks compared to ablative lasers, the efficacy of traditional nonablative systems is inferior and unpredictable compared to ablative lasers for repairing photodamage.[18,19]

Fractional resurfacing was introduced to meet the goals of maintaining the minimal downtime and favorable risk profile of the nonablative systems while increasing efficacy in treating photodamage.

Fractional Photothermolysis

In 2005, Khan et al reported on the use of the first fractional resurfacing device, a 1550-nm erbium-doped fiber laser system that produced microscopic columns of thermal injury surrounded by intact tissue using a handpiece that scanned across the skin up to 8 cm/sec while delivering the microarray pattern to the skin.[20] These microscopic treatment zones (MTZs) range in diameter from 50 µm to 150 µm in diameter and 250 to 800 µm in depth and are produced by varying the depth of the focused beam. Recently, it has been shown that the dimensions of the MTZ at higher treatment energies can approach 200 µm in diameter and impressively more than 1 mm in depth.[21] Tissue in these coagulated zones is not vaporized, and the epidermis and stratum corneum are left intact.

The density or inter-MTZ distance at a given fluence can be varied, for example, MTZ densities of 1600 and 6400 MTZ s/cm^2 correspond to an inter-MTZ distance of 250 µm, and 125 µm, respectively.[14] The total density delivered for a treatment is calculated by multiplying the density per pass by the total number of passes. An example would be the case where 250 MTZ/cm^2 is delivered with 50% overlap for 4 passes. The calculated treatment density would be 250 x 2 x 4 to give a total of 1000 MTZ/cm^2. The depth of the MTZ and width can be increased by increasing fluence. As the density per pass is increased at a given fluence, the potential risk of bulk heating the skin is increased. A treatment protocol increasing the number of passes at reduced densities has a greater safety profile than one at high density with few passes although the final calculated density of MTZs may be the same.

Other fractional devices for photorejuvenation have been introduced that do not use a scanning hand piece. These devices use a "stamping" approach to deliver the fractionated infrared laser beam to the skin. Stamping carries a high likelihood of posttreatment skip areas after a single pass and more artifacts (small areas of higher density treatment within the treated zone) after multiple passes.[22] In contrast, the scanning handpiece uses a specialized beam deflector and high-speed pattern generator to allow for deposition of MTZs in a random pattern through a continuous beam creating a more uniform appearance of MTZs following treatment. The use of the pattern generator leads to high-interbeam fidelity, improved reliability, and reproducibility by maintaining identical energy profiles from treatment to treatment.

The laser tip incorporates a unique optical tracking system that uses a scanning LED on a roller tip that facilitates the scanning technology. In early 2007, the roller tip replaced the need for the previously used OptiGuide Blue™ dye that was used with the older nonroller tip design.

Biology of Fractional Photothermolysis

Early *in vivo* studies of fractional resurfacing examined the effects of varying MTZ density (400, 1600, and 6400 MTZ/cm^2) on forearm skin in the absence of cooling and anesthesia at an energy setting of 5 mJ using a prototypic device.[14] For this study a 50 ms delay ensured that bulk heating did not occur. This early work led to the current understanding of the biological effects of fractional resurfacing.

The MTZ dimension was measured on histologic sections of be 300 µm in depth and 100 µm in diameter. The overlying stratum corneum is left intact, while a small split confined to the sub-basilar region overlying the zone of coagulation is evident. Clinically, the microscopic epidermal split is not observed in terms of blister formation, but rather diffuse uniform urticarial-appearing edema of the treated area is a standard outcome. The dermal portion of the MTZ contains increased mucin deposition. Re-epithelialization is completed 1 day following treatment. Healing takes place through extrusion of the damaged epidermal components, microepidermal necrotic debris (MEND). Microepidermal necrotic debris (hypercompact button-shaped structures 50 to 200 µm in diameter containing both melanin and elastin)[22] could be observed as a superficial exfoliation following treatment that imparts a fine rough sand paper-like feel to the skin and is associated with a mild bronzing color of the skin in the areas of treatment. They have been shown in 1 study to be present as early as 1 day following treatment and completely eliminated by 1 week after treatment.[23] Fractional resurfacing seemingly promotes a transepidermal elimination process in the form of extruded MEND that removes tissue from both epidermal and dermal origin. The fact that the MEND contain components of both melanin and dermal elastin likely underlies the established efficacy of fractional photothermolysis in treating resistant melasma. Indeed, it is thought that the MEND act as a melanin shuttle.

The maintained intact stratum corneum functions as a biological dressing that promotes rapid re-epithelialization and a barrier against microbial invasion. Sparing regions of skin between MTZs combined with the intact stratum corneum underlies the rapid re-epithelialization associated with nonablative fractional resurfacing, as well as its favorable safety profile, as compared to ablative resurfacing methods.

The biological response to fractional photothermolysis is characterized by a complex wound healing process.[14,23] Basal layer epidermal stem cells are transiently activated and rapidly begin proliferating to regenerate the damaged epidermis. The full continuity of the epidermis is restored after 24 to 72 hours, depending on the fluence used. Immunohistochemical studies have revealed that treatment of the skin induces increased heat shock protein-70 expression. This is likely a key early step in the wound healing response leading to upregulation of transforming growth factor-beta (TGF-ß) that enhances new collagen synthesis and dermal remodeling. After 7 days, immunohistochemistry of alpha smooth muscle actin shows the presence of myofibroblast in the dermis, which further supports a wound healing response as underlying the biological effects of fractional photothermolysis. By this time, most MEND are exfoliated off. The MTZs are completely replaced by new collagen in 3 months. A recent review has outlined a succinct time course for these biological effects.[22]

The depth of penetration can be effectively varied by altering the overall treatment energy. This method is demonstrated by histologic sections of skin treated at varied energies. Depending on the location of pathology, the treating physician can achieve a desired outcome with a particular treatment energy using histologic sections as a rough guide.

Technique

Preparation for fractional resurfacing involves thorough cleansing of the skin, followed by a degreasing step where 70% alcohol is used to prep the area. Topical anesthesia is next step; typically, lidocaine 30% in a gel base is applied for 1 hour prior to the treatment. For the majority of patients, pain during the procedure is well tolerated, but select patients will require analgesics and/or nerve blocks for the procedure. Just prior to treatment, the topical anesthetic is removed. Any anesthetic ointment must be completely removed from the skin before treating to avoid backsplash that may cloud the windows of the roller tip reducing the fidelity of the beam. Each track of the roller tip is easily visualized as each pass leaves a treatment imprint on the skin that ensures proper placement of the subsequent track.

The handpiece of the laser device makes direct contact with the skin and is rolled along the area in linear fashion. The treatment energy and treatment density can be varied depending on the application. Treatment density can be increased by increasing the number of passes and/or overlapping subsequent tracks of the laser with the previous one. Typically the direction of each pass is alternated between a superior to inferior direction and a horizontal left to right one. Forced cool air should always be used in combination with fractional resurfacing to alleviate patient discomfort during treatments and to protect the epidermis from the risk of overheating. Bulk heating can occur if vigorous treatments are done without any cooling source for epidermal protection.

It is important that the operator be attentive to the amount of total energy delivered to each area of the face so as to administer equal treatments on both sides of the face. Typically, we divide the face into cosmetic subunits. Treatment of 1 side of a particular subunit is completed followed by the other side of the same subunit before moving on to another subunit. This allows for careful delivery of equal energies to both sides of any 1 subunit. It is also important to deliver equal numbers of total MTZ density by equalizing the numbers of passes on each side of the face.

Hand speed for the device has an upper threshold above which the density of the delivered MTZs falls off. The maximum speed is inversely related to the treatment energy selected and with the selected MTZ density. For example, the maximum speed of 40 mJ treatment energy and density 264 MTZ/cm^2 is 5.5 cm/sec compared to 3.2 cm/sec at 70 mJ and 258 MTZ/cm^2, or 8.0 cm/sec at 40 mJ and 162 MTZ/cm^2. It is important to maintain a constant subthreshold hand speed to deliver the desired MTZ density evenly to both sides of the face.

A rough guide for parameter selection has been published.[24] One should consider the application of treatment, as well as the skin phototype of the patient. For scarring processes, we tend to use higher treatment energy with lower total density. For textural improvement (eg, rhytides) a medium treatment energy is selected with higher density. Dyschromias are best treated with more superficial penetration of the laser; thus a lower treatment energy at higher density. Darker skin types can be treated effectively by cutting back on total treatment density while maintaining the treatment energy for the particular application. Although fractional photothermolysis has a favorable side effect profile in all skin types, darker skin types are best approached cautiously in experienced hands. Even though the downtime associated with fractional photothermolysis treatments is negligible, the patient's social context should always be considered when choosing parameters for any 1 treatment. Lighter treatments with lower density at the same treatment energies can improve healing time dramatically and allow patients with busy social schedules to have little to no erythema for upcoming social engagements, while maintaining some treatment efficacy. The need for additional treatment should be discussed with the patient ahead of time to properly gauge expectations in such a setting.

Following treatment, the skin is erythematous and edematous. Wounding is generally not observed, although reports of superficial linear erosions that heal without scarring exist. Patients are advised to use band cleansers and a heavy moisturizer for the next few days for the duration of the healing process. As erythema wanes, a superficial exfoliation that imparts a rough sand paper-like texture to the treated area ensues. Moisturization of the skin at this point hastens the exfoliation and recovery to a smooth healthy appearing skin surface.

Clinical Applications

Rhytides, Pore Size Reduction, Textural Issues Related to Photodamage

Periorbital rhytides were treated with fractional photothermolysis in a 2004 study of 30 subjects with Fitzpatrick phototypes 2 and 3 skin.[14] Subjects had 4 treatments at a density of 2500 MTZ/cm^2 and treatment energy 6 to 12 mJ over 2 to 3 weeks. One month following treatment, wrinkling and textural quality improvement was moderate in just over half the subjects. At 3 months, 34% and 47% of subjects noted moderate improvement in wrinkling and texture. Mild to moderate improvement was present in 96% of subjects in this study. Early treatments were closely spaced compared to what is currently recommended in clinical practice; a relatively large proportion of patients (~10%) had erythema and edema persisting for 1 week. Pain was well tolerated with an average pain score of 3.2 during treatment (pain scale 1-10).

A larger more recent study of 50 subjects (Fitzpatrick phototypes 1-3) with facial and nonfacial photodamage, rhytides and dyspigmentation examined the longer term efficacy of fractional photothermolysis.[16] Three treatments 3-4 weeks apart at 2000 MTZ/cm^2 and 1500 to 2000 MTZ/cm^2 at 8 mJ for facial and nonfacial locations were done. Blinded physician assessments using a 4-point scale for improvement (0=<25%, 1=25%-50%, 2=51%-75%, 3=>75%) yielded an average improvement in facial areas of 2.23, 2.10, and 1.96; and nonfacial areas of 1.85, 1.81, and 1.70 at 3, 6, and 9 months after the last treatment, respectively. Of the facially and nonfacially treated subjects, 73% and 55% (respectively) had overall improvement at 9 months. Adverse effects were limited to short-term erythema lasting on average 2.9 days in all subjects, and edema lasting 1.6 days on average in 68% of subjects. This study supports the general long-term efficacy of fractional photothermolysis and its favorable safety profile.

One case report worth mentioning examined the treatment of poikiloderma of Civatte around the neck in a patient with Fitzpatrick skin type 2.[25] Impressively, complete resolution following a single treatment at 2000 MTZ/cm^2 at 8 mJ was noted with maintained efficacy at 2 months. This patient had only edema that resolved within 1 day; however, not all patient experiences are this impressive.

Acne Scars

Fractional photothermolysis has been impressively efficacious in the treatment of acne scarring. A large series by Alster and colleagues included 53 subjects with depressed acne scars demonstrates this well.[26] Subjects were treated with a total energy of 4 to 6 kJ delivered in 8 to 10 passes at 125 to 250 MTZ/cm^2 at a treatment energy of 8 to 16 J/cm^2. Blinded physician assessments after 1 treatment reported 25% to 50% clinical improvement in 91% of patients enrolled. The average clinical scores increased after each treatment with 87% of subjects scoring 51% to 75% improvement after 3 treatments separated by 4 weeks. Improvement was found to be maintained over time with no significant changes in clinical scores after 6 months of follow-up. This study enrolled all skin phototypes and found that side effects were mild, confirming the safety of fractional photothermolysis in all skin types. Again, care should be taken in parameter selection for each individual patient to optimize outcome.

Surgical and Other Scars

Case reports of improvement in scars are easily confirmed in clinical practice. One series of 7 subjects with Fitzpatrick phototypes 1 to 4 skin were treated for hypopigmented scars due to acne (6 subjects) and a burn scar (1 subject).[27] Physician assessments at 4 weeks following 4 treatments at 1000 to 2500 MTZ/cm^2 with treatment energy 7 to 20 mJ resulted in an average improvement of 51% to 75%, with the only side effect being erythema and edema of the treated areas lasting 2 to 4 days following treatments. All subjects reported subjective improvement. Another case report echoes these results, where after a single treatment of a hypertrophic scar at 2000 MTZ/cm^2 with treatment energy 8 mJ, similar improvement was observed.[28] An impressive improvement in post-Mohs surgery scars and multiple other types of scars following fractional photothermolysis had also been observed.

Melasma

Tannous and Astner first reported remarkable improvement in melasma following 2 treatments in a Fitzpatrick phototypes 2 to 3 in Caucasian females.[29] They reported erythema and bronzing of the skin as the only short-lived adverse effect (2-3 days) that fully resolved. A larger pilot study included 10 subjects who had 4 to 6 treatments over 1 to 2 week intervals.[30] Six out of 10 of these patients with Fitzpatrick phototype 3 to 4 had 75% to 100% symptom reduction in their melasma. Similar side effects of erythema and swelling were noted in this subgroup. One Hispanic subject with Fitzpatrick phototype 5 skin was noted to have hyperpigmentation persisting for greater than 3 months, though this was not observed in other patients in that study of similar background and skin phototype. Small linear abrasions were also noted in this study in higher density treatments, which appeared 3 to 5 days following treatments and resolved completely in 1 to 2 days. Pain scores reported for treatment energy of 6 to 12 mJ at a density of 2000 to 3500 MTZ/cm^2 were moderate. This study was instrumental in helping to establish fractional photothermolysis as a therapeutic option for resistant melasma.

Idiosyncratically, melasma may darken following fractional photothermolysis, which can be observed in any skin phototype, but may be seen more commonly in Fitzpatrick phototypes 3 and darker. Patients must be cautioned about the possibility of this reaction and about the importance of strict adherence to sun avoidance and sun protection before embarking on treatment of melasma.

Adverse Effects

Adverse effects of fractional photothermolysis range from the most common (eg, pain, erythema, edema, and xerosis) a few days following treatment to the less common findings of acneiform eruptions, and rarely, pruritus and scarring. Downtime is minimal as most patients can return to social activities in 2 days. Fisher and Geronemus examined the frequency of 14 different adverse effects using patient surveys immediately following treatments and on subsequent treatments. Subjects experienced erythema resolving within 3 days.[31] Edema was present in 82% of cases, which also resolved rapidly. Xerosis was commonly observed starting 2 days following treatments and resolved in 3 to 4 days with moisturization of the skin. A total of 75% of patients were able to return to full social activity in 2 days. Pain scores were found to average 4.6 (scale 1-10) with 8 to 12 mJ treatment energy at a density of 2000 MTZ/cm^2.

Some concern for lidocaine toxicity from topically applied anesthesia due to a compromised skin barrier during fractional photothermolysis has been expressed in the literature,[32] though alternative explanations for the few reported cases have been recently presented.[22]

Future Developments/Unresolved Issues

It is somewhat of a conundrum that fractional photothermolysis has demonstrated treatment for improving both the hyperpigmentation of melasma and the hypopigmentation of scars and other dyschromias. While it is thought that the MEND produced following treatment acts as a one-way melanin shuttles,[23] the improvement of hypopigmentation is not captured by this model. Fractional photothermolysis treatments may have more of a modulatory effect on melanin that involves machinery such as elimination of MENDs and perhaps other, as of yet undiscovered players, resulting in a therapy for dyschromia that is safer with less downtime and more efficacious than anything dermatology has yet seen.

Fractional Deep Dermal Ablation

Ablative fractional resurfacing is a new concept where an ablative CO_2 fractionated beam is used to produce microscopic zones of tissue vaporization and coagulation for the treatment of photodamage and scarring.[33] This new therapy has been showing impressive improvements in both these applications with downtime that are less than half of that associated with ablative treatments, and a much reduced risk profile as well. Future studies will quantify the efficacy and safety of this new modality that will add a new dimension to the armamentarium for photorejuvenation of the skin. It is expected that improvement is textural irregularities, dyschromia, and tightening will be realized in as few as a single treatment.

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