Recent Advances in Fractional Laser Resurfacing: New Paradigm in Optimal Parameters and Post-Treatment Wound Care

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Background: Laser plays an increasingly prominent role in skin rejuvenation. The advent of fractional photothermolysis revolutionizes its application. Microcolumns of skin are focally injured, leaving intervening normal skin to facilitate rapid wound healing and orderly tissue remodeling.

The Problem: Even with the popularity of fractional laser devices, we still have limited knowledge about the ideal treatment parameters and postlaser wound care.

Basic/Clinical Science Advances: Many clinicians believe that higher microbeam energy in fractional laser devices results in better clinical outcome. Two recent studies argue against this assumption. One article demonstrates that lower fluence can induce comparable molecular changes with fewer side effects. Another study corroborates this by showing that lower-density settings produce similar clinical outcome in scar remodeling as higher-density ones, but with fewer side effects. To shed light on the optimal post-treatment wound care regimen from fractional ablative resurfacing, another paper shows that platelet-rich plasma (PRP) can reduce transepidermal water loss and skin color changes within 1 month after treatment.

Clinical Care Relevance: For fractional nonablative resurfacing, lower settings in fluence or density may produce similar dermal remodeling as higher settings and with a better side-effect profile. Moreover, autologous PRP appears to expedite wound healing after fractional ablative resurfacing.

Conclusion: Lower microbeam energy in fractional laser resurfacing produces similar molecular changes and clinical outcome with fewer side effects. The findings might portend a shift in the paradigm of treatment parameters. Autologous PRP can facilitate better wound healing, albeit modestly. Long-term follow-ups and larger studies are necessary to confirm these findings.

BACKGROUND

REJUVENATION OF AGED SKIN has been a goal for many millennia. Recently, lasers have played a prominent role in attempts to improve the appearance of sun-damaged skin. In 2004, Manstein *et al.* introduced the concept of fractional photothermolysis

(FPT) for this application.¹ Their concept was to heat columns of skin to high enough temperatures to induce injury, which would result in wound healing with subsequent dermal remodeling and improved appearance. These zones of injury are microscopic in nature and separated from each

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Abbreviations and Acronyms

AR = ablative resurfacing

FAR = fractional ablative resurfacing

FNAR = fractional nonablative resurfacing

FPT = fractionated photothermolysis

MMP = matrix metalloproteinases

NAR = nonablative resurfacing

PRP = platelet-rich plasma

TEWL = transepidermal water loss

other by areas of undamaged skin, allowing for rapid healing. This differs from the two previous paradigms of laser skin rejuvenation: ablative resurfacing (AR) and nonablative resurfacing (NAR).

AR was the first paradigm. With this method of laser treatment, skin is treated with long-wave lasers and is heated to above 100°C, resulting in vaporization of a portion of the treated area.² The tissue ablation results in removal of abnormal pigmentation and reduction of wrinkles. This method of rejuvenation is widely considered to be the most effective, but also the riskiest. NAR heats skin to lower temperatures, resulting in thermal injury without vaporization of skin.³ This method, though much safer, suffered from significantly reduced efficacy.⁴

TARGET ARTICLES

1. Orringer JS, Rittie L, Baker D, Voorhees JJ, and Fisher G: Molecular mechanisms of nonablative fractionated laser resurfacing. *Br J Dermatol* 2010; **163**: 757.

2. Lin JY, Warger WC, 2nd, Izikson L, Anderson RR, and Tannous Z: A prospective, randomized controlled trial on the efficacy of fractional photothermolysis on scar remodeling. *Lasers Surg Med* 2011; **43**: 265.

3. Na JI, Choi JW, Choi HR, Jeong JB, Park KC, Youn SW, *et al.*: Rapid healing and reduced erythema after ablative fractional carbon dioxide laser resurfacing combined with the application of autologous platelet-rich plasma. *Dermatol Surg* 2011; **37**: 463.

CLINICAL PROBLEM ADDRESSED

Fractionated resurfacing attempted to bridge the divide between high-risk efficacious procedures and low-risk poorly efficacious ones. Lessons were learned from experiences with both AR and NAR. Studies with AR devices demonstrated that increasing depth of thermal damage is associated with higher efficacy for treatment of rhytides and solar elastosis.⁵ In lieu of these data, NAR based treatment efficacy upon damaging deeper dermis while cooling the epidermis from injury. The lasers used for NAR do in fact penetrate much deeper than the AR devices and also exhibit far greater safety. Unfortunately, without epidermal injury, their efficacy was significantly limited.⁴

FPT attempts to overcome the disadvantages of these two other classes of devices. Unlike both AR and NAR devices, which attempt to uniformly damage skin at varying depths, FPT induces pixilated microscopic columns of thermal injury.¹ It leaves normal undamaged intervening tissue around the damaged columns. Unlike NAR, the advantage of fractionated energy delivery is that the fluence can be turned high enough to cause local cell necrosis and collagen denaturation; the necrotic cells can be quickly regenerated from the immediate surrounding undamaged skin. For this reason, complications from FPT are less than those from AR. However, the trade off is reduced efficacy and requirement for increasing number of treatments.

Efficacy of FPT for a variety of indications including photoaging, periorbital rhytides, scars, and perhaps, some pigmentary disorders has been established in clinical trials.^{1,6–10} What is unknown is what the ideal treatment parameters should be or even what the ideal postlaser care should be. With higher-density treatments come increasing pain, edema, prolonged erythema, and incidence of postinflammatory hyperpigmentation.¹ Whether these increased side effects come with increased efficacy or they are reducible with wound care regimens is the issue our chapter concerns itself.

RELEVANT BASIC SCIENCE CONTEXT

Adaptation of FPT in NAR and AR creates two of the most popular laser systems today, the fractional NAR (FNAR) and fractional AR (FAR). Little is known about the molecular changes occurring after FNAR or FAR. Histologic examination of skin after FNAR reveals a rapid re-epithelialization with inflammatory infiltrates followed by dermal remodeling.^{8,11} Studies in skin treated with NAR or CO₂ AR show variable degree of elevation in inflammatory cytokines, type I procollagen, type III procollagen, growth factors, and matrix metalloproteinases (MMPs)-1, -3, -9, and -13.^{12–15} This pattern of molecular change is expected in most wound healing process.¹⁶

EXPERIMENTAL MODEL OR MATERIAL: ADVANTAGES AND LIMITATIONS

Human skin is a highly accessible organ and ideally lends itself to experiments involving direct visual inspection, tissue manipulation, and tissue acquisition for molecular analysis. The three target

articles each take a different approach to study the efficacy of FPT or FPT-induced wound healing. Orringer *et al.* examined changes in expression of chosen genes and proteins in selected time points after high- or low-fluence FNAR.¹⁷ Lin *et al.* described a prospective, randomized, controlled trial on clinical efficacy of FNAR in scar remodeling.¹⁸ Na *et al.* evaluated the potential of autologous platelet-rich plasma (PRP) to expedite wound healing after FAR.¹⁹

Disadvantage of *in vivo* human experimental models are that they are typically expensive and involve risks for the study participants. These two inherent problems tend to keep study numbers small, which makes reaching statistically significant conclusions difficult. In the case of laser studies, technology changes rapidly. By the time clinical trials of specific laser systems are complete and finally published, new laser systems have often been introduced, making clinically relevant findings more difficult to apply. Also, FNAR is used for many indications; findings from these studies may not be generalizable for all uses.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Studies with AR devices demonstrated that increasing depth of thermal damage is associated with higher efficacy for treatment of rhytides and solar elastosis.¹ Consequently, many clinicians hold the prevailing view that higher fluence or higher-density FNAR produces superior clinical outcome.^{1,4,7} With higher settings, more side effects are expected.⁷ Herein, we reviewed two recent articles concluding that low-fluence or low-density FNAR can produce comparable results with fewer side effects. In addition, we also review a recent article on the use of PRP to facilitate better wound healing after FAR.

Low-fluence FNAR produces similar molecular changes compared with high-fluence FNAR

To better define optimal FNAR parameters, Orringer *et al.* examined changes in expression of chosen genes and proteins in selected time points after high- (70 mJ) and low-fluence (15 mJ) FNAR treatments.¹⁷ Fluence is defined as energy per focal spot area. Photodamaged forearms of subjects were treated, and serial skin biopsies were obtained at baseline and at selected time points up to 28 days after FNAR treatments. Specimens were subjected to histological evaluation, immunohistochemistry, and real-time polymerase chain reaction.

With increasing energy settings, the dermal depths and dermal column widths of laser microbeam are increased proportionally. However, the authors report a decreased number of columns per section, or density, based on laser's software design in their experiment. The 70 mJ FNAR produced a more intense inflammatory response. Interestingly, both treatments produced similar patterns of molecular changes, and only minimal differences were observed between lower and higher microbeam energy settings. This suggests that clinical results might also be similar, though this needs to be verified with more studies.

Low-density FNAR has similar clinical outcomes compared with high-density FNAR for treatment of scars

Similarly, optimal parameters for induction of scar remodeling by FNAR have not been clearly defined. Lin *et al.* performed a prospective, randomized, controlled trial on this topic.¹⁸ Linear hypertrophic scars were randomized to internal control halves and treatment halves in 20 subjects. The treatment halves were further randomized to higher (26% coverage: Treatment level 9) or lower density (14% coverage: Treatment level 5) FNAR. Scars were treated every 2 weeks for four treatments, and clinical response was assessed at 1 and 3 months after last treatment.

Overall, blinded dermatologists found greater improvement of scars at 3 months when compared with 1 month after FNAR. In higher-density FNAR, significant improvement over control was found only at 1 month following FNAR. In lower-density FNAR, significant improvement over control was seen at both 1 and 3 months post-FNAR. The control halves were scored better than higher-density FNAR halves in three subjects at 3 months post-FNAR. The majority of subjects from both arms perceived improvement in their scars. However, a lower percentage of higher-density FNAR treatment arm perceived improvement. Overall, there were more side effects in higher-density FNAR treatment arm. Moreover, stratification of data based on age of scars demonstrated that younger scars respond better to FNAR.

Autologous PRP facilitates better wound healing after FAR

In comparison to FNAR, FAR is believed by many to have better clinical efficacy, but also with increased risk for scarring and infection. PRP is a high concentration of platelets in a small volume of plasma, and it contains growth

factors and cytokines previously shown to expedite healing of acute wounds or chronic ulcers. To investigate PRP's benefit in post-FAR wound healing, Na *et al.* treated 25 subjects with FAR (either 10 or 20 mJ) on the bilateral inner arms.¹⁹ PRP prepared from 10 mL of whole blood or saline were randomly applied to one of two arms after FAR. Transepidermal water loss (TEWL) and skin color were measured.

Overall, the PRP-treated side had greater average reduction of TEWL than the control side, but only reached statistical significance on days 14 and 21. There was less erythema with the 10 mJ treatment and also with PRP treatment. Statistically significant reduction in erythema was seen in the PRP-treated 10 mJ arm versus control on day 1. Melanin index was used to assess skin darkness and thus the potential for postinflammatory hyperpigmentation. The PRP-treated arms had a statistically significant lower-average melanin index on day 3 in comparison to control. There was less erythema and better and thicker epidermis after PRP treatments. It remains uncertain whether the difference in melanin index on day 3 has any real clinical significance.

INNOVATION

The major innovation from the two FNAR articles comes from the findings that lower-energy FNAR with a more favorable side-effect profile can have similar efficacy as higher-energy FNAR. The optimal parameters for dermal remodeling by FPT are an area of active investigation. Many clinicians believe that higher microbeam energy in FPT result in better clinical outcome.^{1,4,7} Previous studies with AR devices popularize the thinking

that increasing thermal damage is associated with higher efficacy for resurfacing. We reviewed two recent articles that cast doubt on this assumption. The study by Orringer *et al.* is one of the first studies to demonstrate that a single FNAR treatment can induce a wound-healing reaction resulting in dermal remodeling. Lin *et al.* showed that low-density FNAR has similar, if not better, clinical outcome, comparing to high-density FNAR. Both findings may portend a new paradigm shift in FPT parameters.

The advent of FAR significantly reduced post-treatment downtime and wound care. Nevertheless, complications from FAR remain higher than from FNAR. Na *et al.* investigated the efficacy of PRP in reducing these side effects.¹⁹ PRP was found to reduce TEWL, erythema, and hyperpigmentation in the study. It is a promising new addition to the standard post-FAR wound care regimen.

SUMMARY ILLUSTRATION

This figure compares the concepts of AR, non-ablative dermal remodeling/NAR, and FPT. **(A)** AR removes the epidermis and causes residual thermal damage within the dermis. Re-epithelialization is delayed because of relative long migratory path lengths for keratinocytes that repopulate from skin appendages. **(B)** NAR creates a layer of thermal damage below the surface without causing epidermal removal or damage. It is not as efficacious as AR. **(C)** FPT is the distribution of microscopically small volumes of thermal damage within the skin. Epidermal repair is fast because of small wounds and short migratory paths for keratinocytes. It has the best risk-to-benefit ratio. Reprinted by permission from Manstein *et al.*¹

CAUTION, CRITICAL REMARKS, AND RECOMMENDATIONS

Orringer *et al.* demonstrated that the patterns of molecular changes are comparable between high and low fluence. The study uses a laser system that has a fixed percentage surface area of coverage. Thus, increasing energy levels decrease the density of individual microbeams for a given selected treatment level. Future experiments with fixed density will be critical. In addition, this study did not address the cumulative molecular effects of multiple treatments on dermal remodeling. It also examined a limited number of genes known to be involved in wound healing. A follow-up study addressing these issues will be highly informative.

Lin *et al.* demonstrated that low-density FNAR has similar clinical outcome as high-density FNAR. The study relies primarily on analyzing scars by blinded dermatologists using just a single modality of photography. Several subjects have higher-rated control side than the treatment side. Continuing scar remodeling could explain this phenomenon. The study includes subjects with a wide range of scar ages. Thus, it does not have enough power to stratify data by analyzing only young scars. Moreover, the current standard for the laser treatment of hypertrophic scars is to allow 6–8 weeks for the dermal remodeling phase of wound healing to complete before applying another treatment. Scars were treated every 2 weeks in the study, raising the concern that inadequate time was given for high-density FNAR to show clinical benefits.

Na *et al.* investigated the efficacy of PRP in reducing side effects of FAR. In the study, PRP was found to reduce TEWL, erythema, and hyperpigmentation. The preliminary results are modest based on the parameters tested. The clinical significance of the tested parameters, such as the melanin index, is not known. In addition, long-term clinical efficacy has not been established. The study did not compare occlusive ointment, the standard of care, to PRP. Instead, saline was used as a control, which may be much more drying than PRP. A follow-up study comparing ointment and PRP or a combination of both would be informative.

TAKE-HOME MESSAGE

Basic science advances

- Fractional nonablative resurfacing creates microcolumns of thermal injury enough to denature collagen and induce cellular necrosis without damaging the epidermis.
- Fractional ablative resurfacing vaporizes microcolumns of epidermal and dermal tissues.
- After fractional laser therapy, there is variable degree of elevation in inflammatory cytokines, type I procollagen, type III procollagen, growth factors, and MMPs-1, -3, -9, and -13. Similar molecular events are observed after ablative and nonablative resurfacing.
- Single fractional nonablative resurfacing treatment can induce a wound-healing reaction resulting in dermal remodeling.

Clinical science advances

- FPT induces pixilated microscopic columns of thermal injury. These devices leave normal undamaged intervening tissue around the damaged columns.
- Efficacy of indications including photoaging, periorbital rhytides, scars, and perhaps some pigmentary disorders has been established in clinical trials.
- With increasing energy settings, the dermal depths and dermal column widths of laser microbeam penetration increased proportionally.

Relevance to clinical care

- Lower fluence in fractional nonablative resurfacing may produce similar dermal remodeling as higher fluence, with better safety profile.
- Lower-density fractional nonablative resurfacing produces similar scar remodeling as higher density, with better side-effects profile.
- Autologous PRP facilitates better wound healing after fractional ablative resurfacing.

FUTURE DEVELOPMENT OF INTEREST

Both articles on FNAR provide intriguing new insights into the optimal parameters for dermal remodeling by FNAR. The findings are in contrast to popular theory and anecdotes. One intriguing hypothesis is whether the FNAR at 1550 wavelength confers some unique properties that do not extend to lasers of other wavelengths. Additional long-term and larger studies are necessary to confirm these findings.

With modest improvements, Na *et al.* introduced a novel way to reduce side effects of FAR. Isolating the active molecular components of the PRP, such as employing high-performance liquid chromatography, may facilitate the development of new wound healing agents. Alternatively, known components of PRP can be tested in the same experimental design for their ability to improve post-FAR complications.

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