Non-sequential fractional ultrapulsed CO$_2$ resurfacing of photoaged facial skin: Preliminary clinical report

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NON-SEQUENTIAL FRACTIONAL ULTRAPULSED CO₂ RESURFACING OF PHOTODAMAGED FACIAL SKIN: PRELIMINARY CLINICAL REPORT

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Abstract
This study evaluates results, adverse side effects and downtime of the protocol ‘ActiveFX’ for photodamaged facial skin. A non-sequential fractional ultrapulsed CO₂ laser with specific settings is used in addition to a new computer pattern generator (CPG). From September 2006 to March 2007, 55 patients underwent this new ‘soft’ single-session, single-pass and full-face ablative fractional treatment. The patients were evaluated at baseline and 1 and 3 months after the treatment using a five-point scale. Seven aspects of photodamaged skin were recorded: global score, fine lines, mottled pigmentation, sallow complexion, tactile roughness, coarse wrinkles and telangiectasias. The results were compared with a non-parametric statistical test, the Wilcoxon’s exact test. Eight patients received a double-pass treatment on the crow’s feet regions and the improvement of the coarse wrinkles was analyzed with a quartile grading scale. Significant differences (p<0.05) between baseline and 1 and 3 months post-treatment were observed for all features except telangiectasias. Coarse wrinkles presented a good improvement only in the regions submitted to a double-pass. Minimal and isolated adverse side effects were noted and the downtime was very low. Non-sequential fractional ultrapulsed CO₂ light treatment (‘ActiveFX’) can be considered an excellent alternative for photodamaged facial skin.

Key words: Fractional CO₂ laser, fractional resurfacing, photodamaged skin

Introduction
Over the past two decades ultrapulsed CO₂ resurfacing was considered the ‘gold standard’ for the treatment of rhytids and photodamaged facial skin (1–9). However, the prolonged postoperative recovery, the delayed return to normal activities and the high incidence of adverse side effects made patients reluctant to accept this method (10–13). Therefore, patients and physicians continue to look for less invasive techniques to improve rhytids and photodamaged skin. As a result, the market for non-ablative techniques is growing fast and many devices claim to be efficient for wrinkle reduction and photodamaged skin improvement. After critical review of recent literature, however, all these non-ablative methods are not comparable with ablative skin resurfacing in terms of efficacy (14–16). With non-ablative treatments, physicians and patients may have to accept a delicate, incremental and gradual improvement. A relatively high proportion of non-responders is also reported (17). Additionally, these methods often need multiple treatments, are time-consuming and sometimes painful, which makes them less attractive than originally intended. Last but not least, these devices with modest efficacy are often very expensive for the physician.

Despite these considerations, a positive trend in non-ablative methods can be observed from 2004 to 2006, according to American Society for Aesthetic Plastic Surgery (ASAPS) statistics. The total percentage of non-ablative procedures increased from 85.9% of all skin resurfacing in 2004 to 87.8% in 2005 and to 93.2% in 2006 (18). Contrary to this trend, in our practice laser resurfacing has experienced a comeback in the last 2 years as more patients come to the realization that non-ablative approaches are unable to produce their desired results. Excluding our experience, how can we understand this worldwide ambiguity? On the one hand we have indeed seen better results with ablative lasers, but on the other hand patients seem to select treatments associated with poorer, unpredictable results. Probably the answer is that patients prefer...
procedures with low downtime and low risks. This situation has stimulated the search for methods, technologies and protocols that can provide good results with low downtime and minimal or no risks. Device manufacturers have responded with the fractional resurfacing. Comparing the non-ablative fractional devices with ablative devices is not the aim of this study. Rather, by considering the higher immediate collagen shrinkage and the greater delayed new collagen formation using a CO2 laser versus an erbium laser (19–28) we decided to evaluate a new fractional non-sequential ultrapulsed CO2 laser.

Materials and methods

The device

The term ‘ActiveFX’ means a particular protocol of soft superficial resurfacing obtained with a new non-sequential fractional ultrapulsed CO2 laser (Ultrapulse Encore, Lumenis Ltd, Santa Clara, CA, USA). This new device is a radiofrequency excited ultrapulsed CO2 laser with a new computer pattern generator (CPG). The important differences between this new device and the old ultrapulsed CO2 are: a spot of 1300 µm instead of 2500 µm (the treated surface changes from 3.97 mm² to 1.3 mm²) and the fractional non-sequential feature of the energy emission. Leaving intact tissue bridges between spots results in faster healing time, as healing originates not only from the skin adnexa but also from these skin bridges. Reducing the spot diameter (and so also the surface) allows less heat to build up around each scanned spot. This leads to less post-treatment erythema. Finally, modifying the energy sequence emission from sequential to non-adjacent allows for thermal relaxation of each spot before the next spot is placed.

The hits are not laid down adjacent to each other, but are ‘randomly’ placed within the pattern; thus, there is less heat build up and less thermal injury. This energy emission feature is called ‘Cool Scan’ and results in reduced erythema and edema (Figure 1). The old CPG caused a tiger stripe effect because of its serpentine pattern. With the old system, the laser emission placed several adjacent spots at each corner (two or three on the row above and two or three on the row just below), which caused significant heat accumulation. Therefore, there was additional heat build-up on the edges of each pattern. The tiger stripe effect was determined by the overheating of two adjacent pattern margins. With the new CPG this problem is solved.

Treatment

After an occlusive application of an anesthetic cream (Ortodermina cream [lidocaine 5% cream]; Sofar SpA, Milano, Italy) for 1 hour the patients were subjected to the treatment. For patients who were afraid or of poor compliance (12 patients – 22.64%) 0.7 mg/kg of diazepam drops were administered half an hour before the treatment. The anesthetic cream was first carefully removed and then, to obtain a completely dry skin surface, alcohol was used to degrease the skin. Eyes were protected with eye shields. A full-face, single-pass treatment was then performed with no overlapping of the shots. The parameters used were: CPG settings = 3-6-3; fluence = 100 mJ (corresponding to energy density of 7.5 J/cm²); frequency = 100 Hz. With these parameters the ablation depth is about 80 µm and the depth of the residual thermal damage is 200 µm. Instead of reducing the parameters, along the hairline and the jaw-line, the handpiece of the laser was held at a 45° angle to the skin. This results in oval ablation instead of circle ablation, which spreads energy over a larger area to blend the treated and non-treated areas. Another advantage of this technique is faster treatment time. On the eyelids all parameters were modified as follows: CPG settings = 3-4-2; fluence = 60 mJ; frequency = 75 Hz. We always use the Cool Scan and a repeat delay of 0.5 seconds. The main duration of the treatments

Figure 1. (A) The ‘old’ sequential CPG spot delivery; (B) the new non-adjacent ‘random’ fractional CPG spot delivery.
was 25 minutes. Immediately after the shot there is a distinct stippled gray fractional epidermolysis pattern that aids in visualization of treatment progress. We never remove little eschars because these serve as a completely bio-compatible wound dressing. All treatments were performed by a single physician (MTC). After a thorough discussion with and consent from the patient, a second pass on crow’s feet was performed in eight patients. This increased the regional downtime but was done to obtain better results on coarse wrinkles. Immediately after the procedure wet cold gauzes were applied to the treated surface. These were continuously kept wet and cold using cold saline solution. At 20–30 minutes after the treatment or when the pain or burning sensation decreased, a layer of Vaseline was applied to the treated surface.

Patients

From September 2006 to March 2007 55 patients (mean age 47.3 years, range 35–73 years) with severely photodamaged skin were enrolled in this study. All patients were Caucasian with skin type II or III and gave written informed consent prior to entry. The criteria for exclusion from the present study were: (i) utilization of any kind of topical treatment (e.g. topical retinoids, depigmentation creams, azelaic acid creams, topical steroids) in the previous 3 months; (ii) surgical aesthetic treatments in the previous 6 months; (iii) local injective therapies (e.g. fillers, botulinum toxin, hyaluronic acid and vitamins injections) or other cosmetic procedures (e.g. peels) in the previous 6 months; (iv) other lasers or IPL treatments in the previous 12 months (e.g. IPL photorejuvenation or ALA photodynamic photorejuvenation); (v) pregnancy; (vi) lactation; (vii) history of keloids; (viii) history of severe herpes infections; (ix) likelihood of poor compliance; and (x) presence of an active infectious disease or other inflammatory or neoplastic skin diseases.

All patients were clinically and photographically evaluated at baseline (T0), 1 month (T1) and 3 months (T2) after the treatment. UV photos were also taken to help the reviewers with evaluations (Figure 2). A post-treatment follow-up was also performed 1, 3, 5 and 21 days after the treatment. Starting the night before the treatment, and in accordance with more recent guidelines for ablative treatments (29,30), all patients took antibiotics (Cefixoral 400 mg × 1; Menarini, Firenze, Italy) and antiviral (Talavir 1000 mg × 2; Sigma-Tau, Roma, Italy) drugs and continued them for 5 and 14 days, respectively. Cleansing was allowed only with a gentle cleanser (Cetaphil; Galderma, Agrate Brianza, Italy) starting from 36 hours after the treatment. Before leaving the office all patients were instructed to repeatedly apply petrolatum ointment for the next 3–5 days and advised against picking or scrubbing the skin. All patients were also strictly instructed to repeatedly apply topical sun-block preparations for 40 days after the treatment.

The degree of photoaging and the efficacy of treatment were evaluated using a five-point scale (Table I) derived from that suggested by Dover et al. (31). A global score was recorded as well as that of six photodamage variables: fine lines, mottled pigmentation, sallow complexion, tactile roughness, coarse wrinkles and telangiectasias. For each patient the results were separately collected by two physicians and a nurse with no access to the previous results. To help authors quantify the results, standard photographs and UV photographs were taken at T0, T1 and T2 (Figure 3). Standard

Figure 2. A 53-year-old patient. UV photo (A) before treatment and (B) 3 months later.
photographs were also taken at day 1, day 3 (Figure 4) and day 5 to demonstrate the healing progression. Clinical scores were then compared using a non-parametric statistical test, the Wilcoxon’s test. All patients gave a pain quantification using a 10-point scale in which 0 was no pain and 9 was intolerable pain. At days 5 and 21 the erythema was quantified using a five-point scale (0=no erythema, 1=slight erythema, 2=mild erythema, 3=moderate erythema, 4=severe erythema). At T2 (3 months after the procedure) the patients also rated the overall progress on a quartile grading scale from ‘no improvement’ to ‘excellent improvement’ as follows: 0–25% (no or minimal improvement); 26–50% (fair improvement); 51–75% (good improvement); and 76–100% (excellent improvement).
improvement). Finally, the patients were asked whether or not they would recommend this treatment to others.

In eight patients we performed a second pass in the crow’s feet region and a quartile grading scale, similar to that just described, was used at T2 (3 months after the treatment) by two blinded independent physicians and a nurse to evaluate the results on coarse wrinkles (Figure 5).

Results

A total of 53 patients completed the study. The mean pain sensation felt during the treatment was 3.1 while the burning sensation felt for 15–20 minutes after the treatment was 4.5. All patients reported no pain after these 15–20 minutes and none of them took analgesic drugs during the hours or days after the treatment. All patients reported gradual desquamation of ablated epithelium starting 3 days after the treatment. All of them referred to a total absence of the fine crusts 6 days after the treatment. No swelling or oozing was reported during the days or weeks after the procedure. On day 5 only three patients (5.66%) referred to the presence of some fine crusts (in all cases near the hair-line and/or in the preauricular region). At day 5 the mean erythema was 2.6 but this value decreased to 0.7 at day 21. The mean healing time was 3.3 days and the erythema lasted for a mean of 13.6 days.

The global score for photoaging improved from $3.65 \pm 0.52$ at baseline to $2.45 \pm 0.60$ at T1 and $2.07 \pm 0.57$ at T2. The score for fine lines was $3.40 \pm 0.50$ at baseline, $2.30 \pm 0.43$ at T1 and $1.87 \pm 0.37$ at T2. The score for mottled hyperpigmentation was $3.35 \pm 0.49$ at baseline, $1.35 \pm 0.38$ at T1 and $1.32 \pm 0.40$ at T2. The score for sallowness was $3.00 \pm 0.58$ at baseline, $2.23 \pm 0.57$ at T1 and $1.40 \pm 0.45$ at T2. The score for tactile roughness was $3.60 \pm 0.66$ at baseline, $2.22 \pm 0.44$ at T1 and $1.74 \pm 0.44$ at T2 (Table II). For all of these variables the Wilcoxon’s test showed a statistical difference between scores at baseline and scores at T1. A statistical difference was also present between T1 and T2 for the global score, the fine lines, the sallowness and the tactile roughness but not for the hyperpigmentation. At T1 and T2 the scores for coarse wrinkles and telangiectasias remained statistically unchanged in comparison to baseline. In only one case did we observe some fine, round hyperpigmentations in the preauricular region that appeared 32 days after the treatment and spontaneously disappeared after 15 days. Of note, this patient related an improper and inconsistent application of sun protection after the treatment. In another case, the post-treatment erythema lasted 33 days.
Infections, milia, scars or other adverse side effects were not observed.

At T2, 40 patients (75.47\%) noted they would recommend this treatment to others because they had obtained an overall improvement greater than 75\%. Two patients (3.77\%) referred to having obtained a similar improvement but also said they would not recommend the treatment due to the amount of recovery time needed before returning to normal activities. Eight patients (15.09\%) referred to an overall improvement between 50\% and 75\% and would recommend this treatment to others while three patients (5.66\%) referred to an overall improvement between 25\% and 50\% and would not recommend the treatment to others.

In the eight patients treated twice in the crow’s feet region, the results at T2 were: three patients presented improvement in coarse wrinkles between 75\% and 100\%, three patients improved between 50\% and 75\%, and two patients improved between 25\% and 50\%. The mean healing time was 8 days with a mean post-treatment erythema of 17 days. No adverse side effects were observed.

**Discussion**

CO\(_2\) or erbium resurfacing are well-established methods to treat rhytids and photoaging; however, both the CO\(_2\) and the ‘hot’ erbium:YAG lasers can be associated with prolonged postoperative healing, to include delayed re-epithelialization, persistent erythema, delayed and permanent hyper- and hypopigmentation, and the potential for scarring. If no adverse side effects occur, these methods still result in a delayed return to normal activities. Even if the ablative effect and its clinical advantage is well understood, despite vast progress in laser medicine the exact mechanism by which ablative resurfacing achieves clinical wrinkle reduction remains poorly understood (28).

The most attractive theories are based on heat delivery. Both erbium:YAG used in a thermal sub-ablative mode and CO\(_2\) laser generate heat (29). This heat results in an immediate tightening because of shrinkage and denaturation of type I collagen. Fibrillar type I collagen undergoes helix-coil transition, which forcefully shortens the fibers by 30\%.

The collagen subsequently undergoes denaturation and acts as a matrix for newly formed collagen (19,33). Despite the excellent results, the higher incidence of adverse effects and prolonged downtime of traditional resurfacing result in a loss of interest by both the physicians and the patients.

The non-ablative methods are therefore now pre-eminent in utilization, but they have never reached, nor are they ever likely to reach, the same end results as their predecessors, the CO\(_2\) and erbium:YAG lasers (14–16). In order to bridge the gap between available results and the demand by both patients and physicians for low downtime and low risks, the research has recently lead to the development of multiple fractional devices. These devices create microscopic or small columns of thermal injury in the dermis surrounded by islands of normal tissue, resulting in faster healing processes and minimal risks. By obtaining very good results the fractional resurfacings are therefore gaining popularity all over the world.

The aim of this study is not to evaluate different fractional technologies but to understand if a new far infrared non-sequential fractional ultrapulsed CO\(_2\) laser can obtain good results on photoaged facial skin with low downtime and minimal to no risks. The procedure is fast and simple to perform and covers 80\% of the entire surface during each session. The Wilcoxon’s exact test results demonstrate that very good improvement can be achieved in fine lines, mottled pigmentation, sallow complexion, tactile roughness and the global score. In contrast, coarse wrinkles and telangiectasias have demonstrated only a slight improvement. For coarse wrinkles very good results can be obtained only by using a double pass resulting in higher heat generation. The statistical difference between T0 and T1 is probably due to immediate ablative effect and to the immediate shrinkage of the dermis, whereas the statistical difference between T2 and T1 is probably due to new collagen formation. The immediate ablative effect accounts for very good results in mottled pigmentation at T1 and explains why this result is almost the same at T2. The statistical results are confirmed by the patients’ evaluation: nearly 90\% of the patients would recommend this treatment to others. In addition, 75\% of those patients referred to

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global score</td>
<td>3.65 ± 0.52</td>
<td>2.45 ± 0.60*</td>
<td>2.07 ± 0.57**</td>
</tr>
<tr>
<td>Fine lines</td>
<td>3.40 ± 0.50</td>
<td>2.30 ± 0.43*</td>
<td>1.87 ± 0.37**</td>
</tr>
<tr>
<td>Mottled pigmentation</td>
<td>3.35 ± 0.49</td>
<td>1.35 ± 0.38*</td>
<td>1.32 ± 0.40</td>
</tr>
<tr>
<td>Sallowness</td>
<td>3.00 ± 0.58</td>
<td>2.23 ± 0.57*</td>
<td>1.40 ± 0.45**</td>
</tr>
<tr>
<td>Tactile roughness</td>
<td>3.60 ± 0.66</td>
<td>2.22 ± 0.44*</td>
<td>1.74 ± 0.44**</td>
</tr>
<tr>
<td>Coarse wrinkles</td>
<td>2.94 ± 0.48</td>
<td>2.75 ± 0.49</td>
<td>2.65 ± 0.61</td>
</tr>
<tr>
<td>Telangiectasias</td>
<td>2.84 ± 0.56</td>
<td>2.74 ± 0.73</td>
<td>2.71 ± 0.79</td>
</tr>
</tbody>
</table>

*p < 0.05 versus baseline; **p < 0.05 versus T1 (Wilcoxon exact test).
an overall improvement greater than 75%. All these results can be achieved with a mean healing time of 3.3 days and a mean post-treatment erythema of 13.6 days. We observed a transitory post-inflammatory hyperpigmentation in only one case, which spontaneously resolved in about 2 weeks. We ascribed this adverse effect to a discontinuous, incorrect application of the prescribed sun protection.

The study also demonstrates that very good results can be obtained on coarse wrinkles in those patients willing to endure a longer downtime and prolonged post-treatment erythema. By modifying the parameters and the number of passes similar or improved results can be achieved compared with the traditional ultrapulsed CO₂ resurfacing. For example, the first pass may be performed with CPG settings of 3–9–6 and a fluence of 90 mJ; the second one may be performed with CPG settings of 3–9–5 and a fluence of 80 mJ, while the third one (only for very thick skin and coarse wrinkles) may be performed with CPG settings of 3–9–5 and a fluence of 80 mJ.

The literature is very scarce about clinical results obtained with these kind of devices. Only recently, several papers on the subject were presented at the 27th Annual Meeting of the American Society for Laser Medicine and Surgery. All of them report very good results with low downtime and low risks. Rahman et al. (34) reported using a new 30 W fractional CO₂ laser (Reliant Technologies, Mountain View, CA, USA) on 30 patients for moderate to significant improvement in the appearance of rhytids, pigmentation and laxity of the face in greater than 75% of the treated patients. They also reported a significant transient post-treatment erythema which resolved by 3 months. Weiss et al. (35) used the same device and reported a median improvement in rhytids of 50–75%. They also reported minimal pain and a post-treatment erythema varying from 4 to 6 days. In a study conducted on 32 subjects, Levy et al. (36) reported systematic wrinkle reduction using a fractional CO₂ laser (Quanta Medical, France) delivering a pattern of 300 µm spots spaced 2400 µm apart. Using various energies (120–240 mJ) they histologically demonstrated restored epithelium in 5 days, dermal fibrosis of 200–550 µm around the cones of altered collagen and neocollagenesis at 30 days. Adding these results to the results presented in this paper permits us to affirm that fractional CO₂ lasers are very promising for the treatment of photodamaged facial skin (Figure 3).

Conclusions

Very good results on photodamaged facial skin can be obtained using this new non-sequential fractional ultrapulsed CO₂ laser. The superficial resurfacing called ‘ActiveFX’ can obtain good results in all aspects of photoaged skin excluding coarse wrinkles. Coarse wrinkles can be treated by increasing the number of passes and, therefore, the heat delivered to the skin, if the patient is willing to accept a longer downtime and higher risk of adverse side effects, by increasing the number of passes and therefore the heat delivered to the skin. In conclusion, this new device can bridge the wide gap between the different potentials of ablative and non-ablative devices and, with the ‘ActiveFX’ protocol, can offer patients the best compromise position between downtime and results.

References