Ablative Fractional Lasers (CO₂ and Er:YAG): A Randomized Controlled Double-Blind Split-Face Trial of the Treatment of Peri-Orbital Rhytides

Syrus Karsai, MD, ¹ Agnieszka Czarnecka, MD, ¹ Michael Jünger, MD, PhD, ² and Christian Raulin, MD, PhD, ^{1,3}*

¹Laserklinik Karlsruhe, Kaiserstr. 104, D-76133 Karlsruhe, Germany

Background and Objective: Ablative fractional lasers were introduced for treating facial rhytides in an attempt to achieve results comparable to traditional ablative resurfacing but with fewer side effects. However, there is conflicting evidence on how well this goal has generally been achieved as well as on the comparative value of fractional $\rm CO_2$ and $\rm Er:YAG$ lasers. The present study compares these modalities in a randomized controlled double-blind split-face study design.

Study Design/Materials and Methods: Twenty-eight patients were enrolled and completed the entire study. Patients were randomly assigned to receive a single treatment on each side of the peri-orbital region, one with a fractional CO₂ and one with a fractional Er:YAG laser. The evaluation included the profilometric measurement of wrinkle depth, the Fitzpatrick wrinkle score (both before and 3 months after treatment) as well as the assessment of side effects and patient satisfaction (1, 3, 6 days and 3 months after treatment).

Results: Both modalities showed a roughly equivalent effect. Wrinkle depth and Fitzpatrick score were reduced by approximately 20% and 10%, respectively, with no appreciable difference between lasers. Side effects and discomfort were slightly more pronounced after Er:YAG treatment in the first few days, but in the later course there were more complaints following CO_2 laser treatment. Patient satisfaction was fair and the majority of patients would have undergone the treatment again without a clear preference for either method.

Conclusions: According to the present study, a single ablative fractional treatment session has an appreciable yet limited effect on peri-orbital rhytides. When fractional CO_2 and Er:YAG lasers are used in such a manner that there are comparable post-operative healing periods, comparable cosmetic improvement occurs. Multiple sessions may be required for full effect, which cancels out the proposed advantage of fractional methods, that is, fewer side effects and less down time. Lasers Surg. Med. 42:160–167, 2010. © 2009 Wiley-Liss, Inc.

Key words: skin aging; laser surgery; fractional photothermolysis; comparative study

INTRODUCTION

The procedural volume of laser treatment of skin aging (rhytides, telangiectasias, and pigmentation) has substantially increased during the past decade: Tierney and Hanke [1] estimated a 330% increase of non-ablative skin rejuvenation procedures and a 66% increase of ablative ones in the USA between 2001 and 2007. These data clearly show a trend towards more tolerable non-invasive methods; however, compared to skin resurfacing, non-ablative laser devices have so far failed to achieve equivalent effects. Furthermore, controversy persists regarding the optimal laser treatment of rhytides.

Carbon dioxide (CO₂) and erbium:yttrium-aluminumgarnet (Er:YAG) laser ablation are accepted and widely employed methods of skin rejuvenation [2]. In contrast to CO₂ lasers (10,600 nm), the Er:YAG laser has a technical benefit because its wavelength of 2,940 nm is much closer to an absorption maximum of water (3,000 nm) [3-5], thus allowing for high precision yet superficial skin ablation. With the selection of appropriate parameters, however, the biophysics of CO2 and Er:YAG laser-tissue interaction creates similar injuries and cosmetic results [4-7]. Conceivably, the shortcomings of both methods are very similar: while they produce clinically efficacious results, the intensity and depth of the thermal injury may require anesthesia and result in unwanted effects such as hypo-or hyperpigmentation, prolonged wound healing and even scarring [1,6,8,9]. Extended downtime and long lasting side effects are obvious drawbacks for patients undergoing these procedures. On the other hand, the effect of

²Department of Dermatology, University of Greifswald, Ferdinand-Sauerbruch-Strasse, D-17475 Greifswald, Germany ³Department of Dermatology, University of Heidelberg, Voβstr. 2, D-69115 Heidelberg, Germany

Conflict of interest: None of the authors of the study has financial interests of any kind or is in any way related to the manufacturers, wholesalers or retailers of the devices under investigation.

Funding: Both devices under investigation were provided by the German distributors at no cost. No funding has been received in relation to the trial.

^{*}Correspondence to: Christian Raulin, MD, PhD, Laserklinik Karlsruhe, Kaiserstr. 104, D-76133 Karlsruhe, Germany. E-mail: info@raulin.de

Accepted 27 October 2009 Published online 1 December 2009 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/lsm.20879

non-ablative methods is generally only moderate and typically requires 5-6 treatment sessions to be accomplished [10].

Fractional methods have the potential to provide great efficacy in treating rhytides while minimizing downtime and side effects [11]. The findings about ablative fractional photothermolysis of rhytides that have been published so far are encouraging, but they are inconsistent in detail as far as study design and the respective efficacy of different laser modalities are concerned. Whereas several studies claim encouraging results of erbium lasers (e.g., [12–14]), the same holds true for fractional CO₂ ablation [15–17]. There is very little evidence on the comparative safety and efficacy of both methods, but the limited scope of the literature to date suggests a roughly equivalent status [18], just as it does for non-fractional applications [4-7]. However, claims that the fractional CO₂ laser is superior to fractional Er:YAG [19] call for evidence-based scrutiny, as do the extremely encouraging results of fractional erbium lasers [14,20]. No systematic comparative studies of both fractional modalities have been published, according to a recent MEDLINE research. Furthermore, data that have been generated with traditional ablative lasers cannot necessarily be attributed to ablative fractional devices due to different laser-tissue interactions.

The issue of comparative effectiveness and safety is of major relevance in the clinical setting where economical considerations play a considerable role for both patient and surgeon. Since devices for fractional Er:YAG therapy might be more economical than those for fractional CO₂ laser treatment—both in terms of equipment acquisition (US \$60,000–70,000 vs. US \$120,000–150,000 for the devices used in the present study) and maintenance, Er:YAG would be an attractive option, assuming the results are comparable. This study therefore attempts to compare both methods in terms of:

- the effect of a single treatment session on the Fitzpatrick wrinkle score and the profilometric wrinkle depth;
- side effects and tolerability;
- patient satisfaction.

MATERIALS AND METHODS

Study Design

The study was performed as a randomized controlled double-blind trial in a split-face design. Based on the results of previous studies [7,21], the sample size was calculated with the statistical sign test [22] using the following parameters: probability of first-order error = 0.05, probability of second-order error = 0.20, expected percentage of improvement according to the Fitzpatrick wrinkle score [23] = 30-60%, likelihood of a significant difference = 0.75-0.86. Depending on the scope of these parameters, the required sample size for a split-face design was 25-30 patients. The randomization table was generated by an external statistician not otherwise involved in the study after the sample size calculation.

Patients

Patients were recruited for the trial between August and October 2008 in a private practice for cosmetic laser surgery. To be eligible for enrollment, patients of either sex had to be between 40 and 55 years of age with mild to moderate peri-orbital rhytides ("crow's feet") at rest (Class II according to Fitzpatrick [23]; see Table 1).

Exclusion criteria included: (1) unrealistic expectations; (2) inability to meet follow-up criteria; (3) Fitzpatrick skin phototype > III [24]; (4) coagulation disorders or anticoagulant treatment; (5) allergy to lidocaine or tetracaine; (6) oral isotretinoin within the last 6 months; (7) any active skin disease within the treatment area (e.g., cancer or autoimmune disease); (8) synthetic implants in the treatment area; (9) facial cosmetic procedures affecting the treatment area (e.g., blepharoplasty, botulinum toxin, dermabrasion, chemical peeling, laser surgery, or face-lift) within the last 6 months; (10) photosensitizing medications (e.g., tetracycline or gold); (11) history of keloid formation; (12) pregnancy.

Informed consent (oral and written) was obtained from all patients. The study met Good Clinical Practice criteria and the principles of the Declaration of Helsinki. The protocol was approved by the Institution's Human Research Review Committee and registered with Clinical-Trials.gov (identifier: NCT00990431).

Overall, 45 patients were considered during the study period, 33 of which met the study criteria. Two patients were enrolled but dropped out prior to the study due to disease, and three withdrew their consent because of the anticipated downtime. The 28 remaining patients were predominantly female (n=26;92.9%) and on average 46.1 ± 4.0 years of age.

TABLE 1. Fitzpatrick Wrinkle Score and Its Application in the Study*

Class	Wrinkling	Score	Degree of elastosis
I	Fine wrinkles	1-3	Mild (fine textural changes with minimal skin lines)
II	Fine to moderate depth wrinkles, moderate number of lines	4–6	Moderate (distinct elastosis with yellow discoloration of individual papules)
III	Fine to deep wrinkles, numerous lines (with or without redundant skin folds)	7–9	Severe (marked confluent elastosis with thickened, multipapular and yellowed skin)

^{*}The score is based on depth first and foremost and then takes into account the number of lines. All investigators were instructed to take the deepest wrinkle as the basis for their scoring.

162 KARSAI ET AL.

TABLE 2. Patient Evaluation

	Method						
Time	Fitzpatrick wrinkle score	Profilometry	Side effects	Patient satisfaction questionnaire			
Before treatment	\checkmark	✓					
1 day after treatment			✓	\checkmark			
3 days after treatment			✓	\checkmark			
6 days after treatment			✓	\checkmark			
3 months after treatment	\checkmark	√	✓	\checkmark			

Treatment

Technical data. Treatment parameters were chosen according to the manufacturers' recommendation, the published evidence (e.g., [15,18]) and an estimated downtime of 4–5 days for both methods. Both procedures were limited to a single treatment session.

The Er:YAG laser used in this study has a fractional handpiece (MCL 30 Dermablate, Asclepion Laser Technologies GmbH, Jena, Germany). By means of a microlens array the laser beam is divided into 13×13 small spots with 250 µm diameter each, spread over an area of 13×13 mm². A coverage of 5% of the skin is achieved with a single pass. The pulse duration is 400 µseconds. In this trial, we performed four passes (resulting in coverage of 20% of the treated skin) with a total fluence of 60 J/cm² and six stacked pulses to optimize thermal exposure [25].

The CO_2 laser (Fraxel Re:pair, Solta Medical, Inc., Hayward, CA) employs disposable tips with a diameter of 7 and 15 mm, the smaller being used for the peri-orbital region. The laser beam is delivered through multiple deflective and refractive elements; it is focused to a spot size of approximately 120 μ m in diameter at incidence to the skin to deposit an array of laser beams across the surface. Pulse energy varies from 5 to 70 mJ and density from 5% to 70%. The pulse duration is 10 milliseconds. In the present trial, patients received two passes at 15 (1st pass) and 20 mJ (2nd pass), respectively, with a total density of 20%. The skin coverage is slightly below the manufacturer's recommendation (of up to 40%) due to the following considerations:

- We employed pinpoint bleeding and a slight serosanguinous exudate as established and well-accepted clinical end points for ablative resurfacing.
- Ablative fractional resurfacing is far from being free of side effects. Serious side effects have been reported

[26,27] and the manifest risk of scarring demands great caution when ablative fractional resurfacing is applied to delicate regions such as the peri-orbital area or the neck [28].

Treatment protocol. Four weeks prior to the treatment, patients were advised to avoid direct UV light exposure and to apply sun-blocking lotions on a daily basis regardless of the weather. Immediately before starting the procedure, any creams and cosmetic residues were meticulously removed with saline solution. On the side of the face that was designated for CO₂ laser treatment, a topical anesthetic gel (23% lidocaine and 7% tetracaine in LipoThene 133TM, LipoThene, Inc., Pacific Grove, CA) was applied and left for 30 minutes; the contralateral (Er:YAG) side received no anesthetic. The differential application of the topical anesthetic in this study corresponds to the daily routine where sites treated with the short-pulsed Er:YAG laser are generally not numbed.

The patients were advised to keep their eyes closed, and the eyes were covered with a moist gauze held in place by an assistant during the entire procedure.

The fractional lasers were applied without overlapping or gaps between laser pulses. The hand-piece and thus the pattern were rotated by an angle of 45° (Er:YAG) and 90° (CO₂), respectively, between consecutive passes to avoid meeting single spots.

At the end of the treatment, the CO₂-treated area showed pinpoint bleeding and a slight serosanguinous exudate, whereas the Er:YAG-laser treated site had delicate crusts.

Vaseline was applied to the treatment areas immediately after the procedure. Patients were instructed to gently cleanse the peri-orbital region three times a day with cold black tea and to re-apply Vaseline as needed (to maintain moisture) until complete shedding of crusts and scales. Also, they were advised to stay away from direct sun

TABLE 3. Patient Satisfaction

	Which of the s	sides caused mor	re discomfort?	Which of the sides would you undergo again or recommend to others?			
Time	CO_2	Er:YAG	Neither	CO_2	Er:YAG	Both	Neither
1 day after treatment	13 (46.4%)	14 (50.0%)	1 (3.6%)	14 (50.0%)	6 (21.4%)	4 (14.3%)	4 (14.3%)
3 days after treatment	11 (39.3%)	13 (46.4%)	4 (14.3%)	13 (46.4%)	6~(21.4%)	5~(17.9%)	4~(14.3%)
6 days after treatment	15 (53.6%)	11 (39.3%)	2(7.1%)	10 (35.7%)	10 (35.7%)	6~(21.4%)	2(7.1%)
3 months after treatment	17~(60.7%)	9 (32.1%)	2~(7.1%)	8 (28.6%)	13~(46.4%)	5~(17.9%)	2~(7.1%)

exposure and to refrain from picking and rubbing the skin. Prior to follow-up examinations, patients were explicitly asked to avoid any skin-care products since the skin's moisture content might have influenced the assessment of possible side effects and wrinkle depth.

Evaluation

Patients were assessed according to Table 2.

The first primary end point was the objective wrinkle depth (in mm). The wrinkle profile recording was performed by using the optical 3D in vivo measurement system PRIMOS (Phaseshift Rapid In vivo Measurement Of Skin) (GFMesstechnik GmbH, Teltow, Germany). The system is based on the digital fringe projection technique as described by Jaspers et al. [29], and has been validated for rhytide assessment in several clinical studies [30-32]. Briefly, a parallel stripe pattern is projected onto the skin surface by using micro-mirrors and recorded by a CCD camera. The 3D effect is achieved by the minute elevation differences on the skin surface, which deflect the parallel projection stripes. The measurements of these deflections provide qualitative and quantitative data of the skin profile and therefore allow the assessment of the effect of laser skin resurfacing [30]. The PRIMOS measurement was performed with a facial camera mount (Canfield Scientific, Inc., Fairfield, NJ) that was left in place for the photographic documentation. To ensure reproducibility between the images, the baseline image was recalled at half intensity and the subject's head position was adjusted until it was directly aligned with the baseline image prior to image capture.

Photographs were taken with a Canon Digital Camera (EOS 350D with Macro Lens EF-S 60 mm f/2.8 USM, Canon, Inc., Tokyo, Japan) equipped with a lens mounted ring flash (Macro Ring Lite MR-14EX, Canon, Inc.). Standardized views (frontal and 45° oblique) with a defined distance between the camera and skin were used, and the same laboratory processed all photographs. Photographs were assessed according to the Fitzpatrick wrinkle score [23] by a panel of three dermatologists familiar with laser resurfacing but not involved in the study. Photos were evaluated in a blinded fashion, that is, the photographs were mixed intra-individually and the examiners were unaware of whether the photographs were pre-operative or post-operative. The Fitzpatrick score had been validated in previous studies and has shown good inter- and intraobserver reproducibility [33,34]; hence it was chosen as the second primary end point.

Patient satisfaction as the secondary end point was assessed using two simple questions:

- "Which of the sides caused more discomfort?"
- "Which of the sides would you undergo again or recommend to others?"

All undesired effects of the procedures were rated on site by a physician assistant not otherwise involved in the study on a 10-point visual analogue scale 1, 3, and 6 days as well as 3 months after treatment.

Statistical Data Evaluation

All data were analyzed using the Statistical Package for Social Sciences (SPSS/PC+) program (Version 12.0 for Windows), employing the Wilcoxon signed rank test and McNemar test.

The average value was used for the analysis of the continuous variables.

The significance level was set to P<0.05. Descriptive statistics were also calculated (mean, standard deviation, median, minimum, maximum, numbers, percentage rate).

RESULTS

Fitzpatrick Wrinkle Score

Overall, both modalities yielded a significant, albeit only moderate, reduction of the Fitzpatrick score (Fig. 1). The difference between sides was not significant before (P=0.081) and after treatment (P=0.53).

64.3% of the sides treated with the CO_2 laser and 57.1% of those treated with the Er:YAG laser were rated as "improved." Figure 2 shows an example of a patient with a considerable reduction in rhytides on both sides.

Profilometry

The wrinkle depth was significantly reduced by both modalities (from $1.97\pm2.05\,\text{mm}$ to $1.64\pm2.04\,\text{mm}$ on the CO_2 side and from $1.97\pm1.29\,\text{mm}$ to $1.63\pm1.20\,\text{mm}$ on the Er:YAG side), and the relative reduction was somewhat more marked than the values on the Fitzpatrick score (Fig. 3). CO_2 laser treatment was again slightly more efficient, but the differences were statistically not significant and not perceivable. An improvement was considered in 88.9% (CO₂) and 82.1% (Er:YAG) of treated sides, respectively.

Side Effects

Both modalities resulted in marked pinpoint bleeding (CO_2) or crust formation (Er:YAG), respectively.

The intensity of the concomitant and side effects over the course of follow-up is displayed in Table 4. Early after treatment, complaints were substantially more marked on

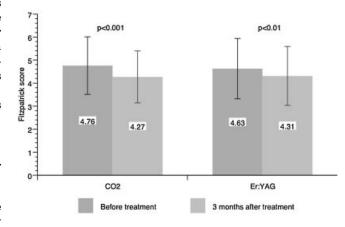


Fig. 1. Mean Fitzpatrick wrinkle score before and 3 months after treatment.

164 KARSAI ET AL.

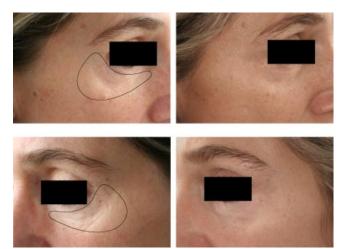


Fig. 2. **Top left**: Pre-operative appearance (the black line demarcates the treatment area); **top right**: 3 months post-operatively (CO₂). **Bottom left**: Pre-operative appearance; **bottom right**: 3 months post-operatively (Er:YAG). Marked reduction in rhytides on both sides. [Figure can be viewed in color online via www.interscience.wiley.com.]

the side treated with the Er:YAG laser with the notable exception of bleeding which occurred more frequently after CO_2 laser treatment.

Six days after treatment, erythema and swelling were more persistent in the sides treated with the $\rm CO_2$ laser, and after 3 months there was a more marked hyperpigmentation on the same sides.

Patient Satisfaction

The patients' rating of both methods showed no appreciable or statistically significant difference (Table 3). There was a certain preference for the CO_2 laser early on during follow-up, more or less correlating to the occurrence of side effects, although later it reversed.

DISCUSSION

Non-ablative fractional methods have been reported to be effective and to have limited side effects [35], but they failed to achieve results comparable to those of conventional

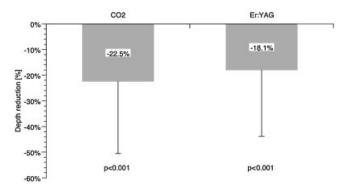


Fig. 3. Mean reduction of profilometrically measured wrinkle depth 3 months after treatment in comparison to pre-treatment values.

ablative techniques, which finally led to the development of ablative fractional devices [16,19]. In contrast to some claims in the literature [19], the present study failed to demonstrate appreciable differences between both methods in treating peri-orbital rhytides in a meticulously chosen experimental setting with randomized, blind allocation of treatment sites in a split-face design. Correspondingly, this confirms previous comparative reports about non-fractional skin resurfacing [4-7]. Basically, the efficacy of both methods was roughly equal, and whereas the discomfort was somewhat more pronounced after Er:YAG treatment during the first days (with the notable exception of bleeding), CO₂ treatment was perceived as more unpleasant in the later course of follow-up. The majority of patients rated both methods as equally disturbing, and a majority would undergo the treatment again without a clear preference for either modality.

Like chemical peels and dermabrasion, laser resurfacing works by injuring the skin to a controlled depth. The question arises as to what extent this ablation has to take place for efficient rhytide reduction. Indeed, a major technical precaution for successful resurfacing is an ablation of the layers of the dermis that are mainly affected by photodamage. Since UV light is the causative agent, it is obvious that the more superficial strata of the dermis should be mainly altered, and histological findings confirm this assumption [36,37].

With energy settings in the same order of magnitude as in the present study, the penetration depth of CO_2 lasers is $400-450\,\mu m$ [16] and the one of Er:YAG lasers is $150-200\,\mu m$ [18]. According to an histological study by Gonzalez-Ulloa et al. [38], the penetration depth of Er:YAG lasers is sufficient to reach the papillary dermis in every facial region except the forehead, where the epidermis is $202\,\mu m$ thick. Especially in the peri-orbital region, the epidermis is delicate with a thickness of only $130\,\mu m$, rendering the dermis easily accessible by Er:YAG laser light.

For the CO₂ laser, some of the laser-induced heat is diffused into the surrounding tissue due to the relatively long pulse duration (10 milliseconds), which is higher than the thermal relaxation time of water (1 milliseconds). The greater degree of thermal exposure in turn yields a more "aggressive" treatment leading to collagen shrinking. This seems beneficial in regions of the face where severe elastosis is the prevailing reason for rhytide formation (e.g., the upper lip) and with higher epidermis thickness, but less so in the peri-orbital region. Moreover, stacking of repetitive Er:YAG laser pulses has been demonstrated to cause deep collagen denaturation and remodeling on human lid skin despite the limited thermal exposure [39].

The literature to date fails to convincingly demonstrate the superiority of either method. Whereas Waibel et al. [19] consider fractional CO_2 laser treatment superior to fractional Er :YAG, this conclusion is based on a limited number of patients and was therefore declared preliminary by the authors themselves. Bodendorf et al. [18] found no difference between both modalities based on the published material and their own experience; this conclusion is in complete agreement with our own results.

TABLE 4. Concomitant and Side Effects

	Time after treatment							
	1 day		3 days		6 days		3 months	
Symptom	CO_2	Er:YAG	CO_2	Er:YAG	CO_2	Er:YAG	CO_2	Er:YAG
Pain	2.1 ± 2.1	2.9 ± 2.5**	0.3 ± 0.8	0.4 ± 0.9	0.04 ± 0.2	_	_	
Burning, itching	2.0 ± 2.5	$2.8\pm2.7^{**}$	0.5 ± 0.9	$1.4\pm1.6^*$	0.4 ± 0.8	0.3 ± 0.4	0.2 ± 0.9	_
Erythema	6.6 ± 2.1	6.2 ± 2.4	3.6 ± 1.5	3.6 ± 1.2	$2.5\pm1.2**$	1.2 ± 1.2	0.1 ± 0.6	0.04 ± 0.2
Swelling	6.9 ± 2.3	6.0 ± 3.2	2.2 ± 1.9	2.0 ± 1.9	$0.6\pm1.0^*$	0.3 ± 1.0	0.3 ± 1.0	0.1 ± 0.6
Blistering	0.3 ± 0.8	0.9 ± 2.5	0.04 ± 0.2	0.1 ± 0.8	_	_	_	_
Secretion	0.7 ± 1.4	$2.2 \pm 3.2**$	0.1 ± 0.3	$0.4\pm1.0^*$	0.04 ± 0.2	_	_	_
Bleeding	$3.6 \pm 2.9***$	0.6 ± 1.8	0.1 ± 0.6	0.1 ± 0.6	_	_	_	_
Crusting	4.1 ± 2.6	3.4 ± 3.2	2.0 ± 1.9	2.1 ± 2.0	0.1 ± 0.4	0.04 ± 0.2	_	_
Hypopigmentation	_	_	_	_	_	_	_	_
Hyperpigmentation	_	_	0.1 ± 0.4	0.04 ± 0.2	_	_	$1.5\pm2.4**$	0.1 ± 0.3
Scars	_	_	0.1 ± 0.4	0.1 ± 0.6	_	_	_	_
Atrophy	_	_	0.1 ± 0.4	_	_			
Sum	27.3 ± 10.2	26.0 ± 15.1	9.3 ± 4.9	10.6 ± 8.4	$3.9 \pm 1.9***$	1.8 ± 1.6	$2.2 \pm 2.9**$	0.3 ± 0.7

Gray background: significant difference between groups (significantly higher values marked with *P < 0.05, **P < 0.01, ***P < 0.001).

As for ablative fractional methods in general, the efficacy of various laser modalities for rhytide reduction has been demonstrated (e.g., [2,5,12,13,15,17,18]) but the effect of a single treatment session may not be comparable to conventional ablative methods. There is published material opposing this statement; for instance, Trelles et al. [14] published very encouraging results about a single treatment with a fractional Er:YAG laser, albeit in a very inhomogeneous sample in terms of treated region and treatment parameters. Another major shortcoming is illustrated in Figure 3 of the article under discussion: The photographs showing the pre- and post-treatment findings are different both in dimension (distance from camera to skin) and lighting, making it virtually impossible to objectively assess the degree of improvement [40]. Moreover, at the time the photograph was taken, there was obviously still a substantial edema present. We therefore suggest that photographic evaluation take place no less than 12 weeks after treatment (as in the present study).

Furthermore, histological specimens are often included in clinical studies to confirm the clinical effects of laser treatment. Indeed, histological examination of specimens is very valuable in basic research on laser effects (e.g., [16]); in a clinical longitudinal study setting where tissue is sampled several times during follow-up (e.g., [41]), its utility is limited because by definition a given specimen can only be obtained and examined once, and adjacent tissue is not necessarily comparable.

The present trial has shown that the dilemma of efficacy versus tolerability in laser therapy of facial rhytides is far from being resolved. Whereas side effects were easily identifiable, and treatment specifications were chosen according to the best available evidence and established local end points (such as pinpoint bleeding in CO₂-treated sites), the treatment result was overall satisfactory, albeit

rather moderate. From a practical and therapeutic point of view, the surgeon would have suggested one or more follow-up sessions in most cases, which puts the lower down time in comparison to non-fractional laser ablation in perspective. Just as for the non-ablative modalities [42], the ostensible advantage of fractional methods seems to diminish substantially when results are analyzed meticulously.

As a final note, we should like to enumerate a number of methodological requirements for future studies:

- Patient satisfaction has been included in only very few studies on fractional resurfacing so far [2], but should be a mandatory part of the evaluation.
- Reproducibility and consistency of evaluation conditions (photography, scoring) and methods are paramount [40].
- Randomized split-face comparison to one of three modalities (sham treatment, non-fractional laser or a different fractional modality) is likely to enhance the evidence of the results.
- A lack—or thorough documentation—of manufacturer affiliations will be helpful in assessing the meaningfulness of trials.

CONCLUSIONS

According to the present study, a single ablative fractional laser session has an appreciable yet limited effect on peri-orbital rhytides. When fractional ${\rm CO_2}$ and ${\rm Er:YAG}$ lasers are used in such a manner that there are comparable post-operative healing periods, comparable cosmetic improvement occurs.

The limited success suggests that more than one treatment cycle is required to achieve sustainable patient

166 KARSAI ET AL.

satisfaction. With this in mind, the ostensible advantage of fractional over traditional ablation modalities may have to be challenged. Whether or not our findings can be extrapolated to include other facial regions is a question that can only be answered in a separate clinical study designed according to the principles of evidence-based medicine. In particular, a direct comparison of fractionated and traditional ablative treatment methods would be desirable.

In contrast to the promises and suggestions of the industry, selecting a particular device is obviously not the decisive factor in terms of achieving good results and avoiding complications in laser skin resurfacing. This means that a careful eye should be kept open for company affiliations when analyzing published data [43,44].

REFERENCES

- Tierney EP, Hanke CW. Recent trends in cosmetic and surgical procedure volumes in dermatologic surgery. Dermatol Surg 2009;35:1324–1333.
- Cohen SR, Henssler C, Johnston J. Fractional photothermolysis for skin rejuvenation. Plast Reconstr Surg 2009;124: 281–290.
- Riggs K, Keller M, Humphreys TR. Ablative laser resurfacing: High-energy pulsed carbon dioxide and erbium:yttriumaluminum-garnet. Clin Dermatol 2007;25:462–473.
- 4. Fleming D. Controversies in skin resurfacing: The role of erbium. J Cutan Laser Ther 1999;1:15–21.
- Alexiades-Armenakas MR, Dover JS, Arndt KA. The spectrum of laser skin resurfacing: Nonablative, fractional, and ablative laser resurfacing. J Am Acad Dermatol 2008;58: 719-737.
- Khatri KA, Ross V, Grevelink JM, Magro CM, Anderson RR. Comparison of erbium:YAG and carbon dioxide lasers in resurfacing of facial rhytides. Arch Dermatol 1999;135:391– 397.
- 7. Ross EV, Miller C, Meehan K, McKinlay J, Sajben P, Trafeli JP, Barnette DJ. One-pass CO_2 versus multiple-pass Er :YAG laser resurfacing in the treatment of rhytides: A comparison side-by-side study of pulsed CO_2 and Er :YAG lasers. Dermatol Surg 2001;27:709–715.
- Sriprachya-Anunt S, Fitzpatrick RE, Goldman MP, Smith SR. Infections complicating pulsed carbon dioxide laser resurfacing for photoaged facial skin. Dermatol Surg 1997; 23:527-535.
- 9. Nanni CA, Alster TS. Complications of carbon dioxide laser resurfacing. An evaluation of 500 patients. Dermatol Surg 1998;24:315–320.
- 10. Hantash BM, Gladstone HB. Current role of resurfacing lasers. G Ital Dermatol Venereol 2009;144:229–241.
- 11. Geronemus RG. Fractional photothermolysis: Current and future applications. Lasers Surg Med 2006;38:169–176.
- Dierickx CC, Khatri KA, Tannous ZS, Childs JJ, Cohen RH, Erofeev A, Tabatadze D, Yaroslavsky IV, Altshuler GB. Micro-fractional ablative skin resurfacing with two novel erbium laser systems. Lasers Surg Med 2008;40:113–123.
- erbium laser systems. Lasers Surg Med 2008;40:113–123.

 13. Lapidoth M, Yagima Odo ME, Odo LM. Novel use of erbium:YAG (2,940-nm) laser for fractional ablative photothermolysis in the treatment of photodamaged facial skin: A pilot study. Dermatol Surg 2008;34:1048–1053.
- 14. Trelles MA, Mordon S, Velez M, Urdiales F, Levy JL. Results of fractional ablative facial skin resurfacing with the erbium:yttrium-aluminium-garnet laser 1 week and 2 months after one single treatment in 30 patients. Lasers Med Sci 2009;24:186–194.
- Hunzeker CM, Weiss ET, Geronemus RG. Fractionated CO₂ laser resurfacing: Our experience with more than 2000 treatments. Aesthet Surg J 2009;29:317–322.
- Hantash BM, Bedi VP, Kapadia B, Rahman Z, Jiang K, Tanner H, Chan KF, Zachary CB. In vivo histological

- evaluation of a novel ablative fractional resurfacing device. Lasers Surg Med 2007;39:96–107.
- Christiansen K, Bjerring P. Low density, non-ablative fractional CO₂ laser rejuvenation. Lasers Surg Med 2008;40: 454-460.
- Bodendorf MO, Grunewald S, Wetzig T, Simon JC, Paasch U. Fractional laser skin therapy. J Dtsch Dermatol Ges 2009;7: 301–308.
- Waibel J, Beer K, Narurkar V, Alster T. Preliminary observations on fractional ablative resurfacing devices: Clinical impressions. J Drugs Dermatol 2009;8:481–485.
- Ross EV, Swann M, Soon S, Izadpanah A, Barnette D, Davenport S. Full-face treatments with the 2790-nm erbium:YSGG laser system. J Drugs Dermatol 2009;8:248–252.
- Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: A new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers Surg Med 2004;34:426–438.
- Dixon WJ, Mood AM. The statistical sign test. J Am Stat Assoc 1946;41:557–566.
- Fitzpatrick RE, Goldman MP, Satur NM, Tope WD. Pulsed carbon dioxide laser resurfacing of photo-aged facial skin. Arch Dermatol 1996;132:395–402.
- Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988;124:869–871.
- Kaufmann R, Hibst R. Pulsed Erbium:YAG laser ablation in cutaneous surgery. Lasers Surg Med 1996;19:324–330.
- Avram MM, Tope WD, Yu T, Szachowicz E, Nelson JS. Hypertrophic scarring of the neck following ablative fractional carbon dioxide laser resurfacing. Lasers Surg Med 2009;41:185–188.
- Fife DJ, Fitzpatrick RE, Zachary CB. Complications of fractional CO₂ laser resurfacing: Four cases. Lasers Surg Med 2009;41:179–184.
- 28. Tierney ÉP, Hanke CW. Ablative fractionated CO_2 laser resurfacing for the neck: Prospective study and review of the literature. J Drugs Dermatol 2009;8:723–731.
- Jaspers S, Hopermann H, Sauermann G, Hoppe U, Luderstädt R, Ennen J. Rapid in vivo measurement of the topography of human skin by active image triangulation using a digital micromirror device. Skin Res Technol 1999;5: 195–207.
- Friedman PM, Skover GR, Payonk G, Kauvar AN, Geronemus RG. 3D in-vivo optical skin imaging for topographical quantitative assessment of non-ablative laser technology. Dermatol Surg 2002;28:199–204.
- 31. Lagarde JM, Rouvrais C, Black D, Diridollou S, Gall Y. Skin topography measurement by interference fringe projection: A technical validation. Skin Res Technol 2001;7:112–121.
- 32. Hatzis J. The wrinkle and its measurement—A skin surface profilometric method. Micron 2004;35:201–219.
- Kopera D, Smolle J, Kaddu S, Kerl H. Nonablative laser treatment of wrinkles: Meeting the objective? Assessment by 25 dermatologists. Br J Dermatol 2004;150:936–939.
- Reynolds N, Thomas K, Baker L, Adams C, Kenealy J. Pulsed dye laser and non-ablative wrinkle reduction. Lasers Surg Med 2004;34:109–113.
- 35. Geraghty LN, Biesman B. Clinical evaluation of a single-wavelength fractional laser and a novel multi-wavelength fractional laser in the treatment of photodamaged skin. Lasers Surg Med 2009;41:408–416.
- Ma W, Wlaschek M, Tantcheva-Poór I, Schneider LA, Naderi L, Razi-Wolf Z, Schüller J, Scharffetter-Kochanek K. Chronological ageing and photoageing of the fibroblasts and the dermal connective tissue. Clin Exp Dermatol 2001;26:592– 500
- Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, Datta S, Voorhees JJ. Mechanisms of photoaging and chronological skin aging. Arch Dermatol 2002;138:1462–1470.
- Gonzalez-Ulloa M, Castillo A, Stevens E, Fuertes GA, Leonelli F, Ubaldo F. Preliminary study of the total restoration of the facial skin. Plast Reconstr Surg 1954;13: 151–161.
- 39. Drnovsek-Olup B, Beltram M, Pizem J. Repetitive Er:YAG laser irradiation of human skin: A histological evaluation. Lasers Surg Med 2004;35:146–151.

- 40. Niamtu J. Image is everything: Pearls and pitfalls of digital photography and PowerPoint presentations for the cosmetic surgeon. Dermatol Surg 2004;30:81–91.
- 41. Trelles MA, Vélez M, Mordon S. Correlation of histological findings of single session Er:YAG skin fractional resurfacing with various passes and energies and the possible clinical implications. Lasers Surg Med 2008;40: 171–177.
- 42. Riggs K, Keller M, Humphreys TR. Ablative laser resurfacing: High-energy pulsed carbon dioxide and erbium:yttrium-aluminum-garnet. Clin Dermatol 2007;25:462–473.
- 43. Field LM. Laser resurfacing hysteria. The media, the marketers, the companies, and us. Dermatol Surg 1998;24: 684–686.
 44. Field LM. Never, ever a twinkle from billboard advertising—
- Field LM. Never, ever a twinkle from billboard advertising— Nor from advertising budgets. Dermatol Surg 1999;25:828– 829