Comparative Clinical Trial of 2 Carbon Dioxide Resurfacing Lasers With Varying Pulse Durations

100 Microseconds vs 1 Millisecond

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Objectives: To compare the clinical and histological effects of 2 carbon dioxide lasers with different pulse durations and to evaluate the effect of carbon dioxide laser pulse duration on postprocedure erythema, wound healing, and efficacy of wrinkle treatment.

Design: Prospective, randomized, comparative clinical trial.

Setting: A university-affiliated hospital-based laser center.

Patients: Thirty-five patients with facial wrinkles were enrolled in the study. Treatment sites included 15 perioral, 14 periorbital areas, and 6 full face.

Intervention: A 2-sided comparison was performed. One side of the study site was treated with the TruPulse laser (Tissue Technologies, Palomar Medical Products Inc, Lexington, Mass). The other side of the study site was treated with the UltraPulse 5000 laser (Coherent Medical Inc, Palo Alto, Calif). The 2 sides were treated to equivalent tissue effects rather than maintaining the number of passes.

Main Outcome Measures: Photographs of the treatment areas at baseline, week 1, week 2, month 2, and month 6 were evaluated by a 5-member panel for degree of erythema, amount of edema, and percentage of wrinkle improvement. Silicon skin casts for profilometry measurements before and after the treatment were compared. To evaluate skin shrinkage, surface area before and after treatment of square tattoos on both cheeks of the full-face patients were computed using a digital imaging system. Histological sections before and after the procedure were analyzed.

Results: At week 1, 75% of the patients had more erythema on the UltraPulse than TruPulse sides. The difference in erythema (TruPulse less than UltraPulse) between the 2 treatment sides was clinically mild yet statistically significant for weeks 1 ($P = .05$) and 2 ($P = .05$). Although observed results favored the UltraPulse over the TruPulse, the difference in efficacy between the 2 lasers did not reach statistical significance.

Conclusions: Compared with the longer pulse-duration carbon dioxide laser, the shorter pulse-duration carbon dioxide laser, used with higher energy and more passes, caused slightly less erythema while maintaining efficacy. The longer pulse-duration laser required lower energy and fewer number of passes to achieve an equivalent depth of ablation, level of residual thermal damage, and degree of efficacy. The shorter TruPulse allows for more superficial tissue damage per pass and therefore is best suited for situations requiring superficial or more controlled ablation. The longer UltraPulse achieves a desirable depth of tissue damage with fewer passes. The data did not support the long-term presence of tissue collagen shrinkage in the treated areas.

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PULSED OR SCANNED carbon dioxide lasers with high-peak powers and short laser-tissue interaction times can safely and effectively treat cutaneous photodamage, including mild to moderate wrinkles. Carbon dioxide laser energy, at 10 600 nm, is strongly absorbed by water and in this way heats and destroys tissue. Continuous wave carbon dioxide lasers not only ablate tissue but also cause charring and a surrounding zone of thermal damage 0.2- to 1-mm thick. The newer pulsed or scanned lasers have high-peak power that can ablate tissue without leaving behind a charred surface and short pulse durations that limit the amount of residual thermal damage. Therefore, only a thin layer of tissue (30-80 µm) is removed with each pass of the laser. Besides ablation and smoothing of uneven skin texture, new collagen formation and shrinkage of collagen have been proposed as mechanisms for decreasing the depth of wrinkles.

Following a carbon dioxide laser resurfacing procedure, some patients expe-
PATIENTS AND METHODS

PATIENTS

Thirty-five patients were enrolled in the study to receive laser treatment for facial sun-damaged skin. Inclusion criteria were age 18 to 90 years and the desire to have facial wrinkles improved. Exclusion criteria were having an active infection, an immunocompromised condition, or an anticoagulation disorder. Patients were treated in 1 of 3 anatomical locations: perioral, periorbital, or full face. Six patients were chosen for a full-face treatment so that serial digital images could be taken of their cheeks, as described later. Our study was approved by the Subcommittee of Human Studies at Massachusetts General Hospital, Boston. Informed consent was obtained from all study participants after the objectives, design, and risks of the study had been explained.

Patient pretreatment evaluations included a medical evaluation, review of enrollment criteria, rating of wrinkle severity, and determination of skin type ( Fitzpatrick scale I-III). Rhytides were evaluated by the following scale: 1, superficial fine lines with minimal textural changes; 2, clearly visible, sharply defined lines with moderate textural change; and 3, clearly visible, sharply defined lines with more severe textural change and redundant skin with creases and folds.

After enrollment in the study, patients began a pre-treatment regimen with 0.025% tretinoin cream (Retin-A, Ortho Pharmaceutical Corporation, Raritan, NJ) and 3% hydroquinone solution (Melanex, Neutrogena Dermatologics, Los Angeles, Calif) for at least 2 weeks and 250 mg of dicloxacillin 4 times a day and 125 mg of famciclovir twice a day for 7 days starting 1 day before the procedure. Patients were advised to avoid exposure to sunlight before and after the treatment.

RESULTS

Data analysis was based on the following number of completed patient follow-ups: 32 patients for weeks 1 and 2, 35 patients for month 2 healing, 34 patients for month 2 efficacy, and 33 patients for month 6 efficacy. Thirty-four patients were women; 1 was a man. The average patient age was 50 years. Skin types included 42% type I, 50% type II, and 8% type III. No individuals with skin types IV to VI were enrolled in this study. Pretreatment wrinkle severity did not differ significantly (P = .57) from right to left side of the study areas.

LASER PROCEDURE

The lasers compared in this study were the TruPulse (Tissue Technologies, Palomar Medical Products Inc, Lexington, Mass) and the UltraPulse 5000 (Coherent Medical Inc, Palo Alto, Calif). The TruPulse has a pulse duration of 60 to 100 microseconds, a square spot size of 3 mm, and a maximum pulse energy of 500 mJ. The UltraPulse has a pulse duration of 600 microseconds to 1 millisecond, a collimated beam with a circular 3-mm spot size, and a maximum pulse energy of 500 mJ.

For each patient, one side of the study area was treated with the TruPulse and the other side was treated with the UltraPulse. Laser assignments alternated from left to right side of the treatment site for each consecutive patient and were independent of severity of wrinkles. Both laser treatments were completed at the same session. Two physicians were involved in the patient treatments.

Treatment settings are described in Table 1. The number of passes and laser fluence varied depending on the laser used, severity of wrinkles, and anatomical location. Therefore, the same final tissue effect was obtained on both sides of the treatment site, yet fluence and number of passes were not held constant. Tissue response to the laser, reduction of wrinkles, and color of the tissue were all variables used to determine the final tissue effect. For all treatments, the TruPulse laser was used at an equivalent or higher fluence and with more passes than the UltraPulse.

Anesthesia was obtained with nerve blocks and local dermal infiltration using 2% lidocaine with 1:100 000 epinephrine (Abbott Laboratories, North Chicago, Ill). Patients undergoing a full-face procedure received oral diazepam (3-10 mg), intramuscular meperidine (Demerol, Elkins-Sinn Inc, Cherry Hill, NJ) (25-30 mg), and promethazine hydrochloride (Phenergan, Elkins-Sinn Inc) (12.5-25 mg).

Healing, efficacy, and profilometry data are presented in Table 2 and tattoo surface areas in Table 3. The degree of erythema for each laser and the difference in erythema between the 2 lasers diminished from week 1 to week 2 and from week 2 to month 2. At week 1, 75% of the patients had more erythema on the UltraPulse than TruPulse sides. The difference in erythema and edema between the 2 treatment sides was clinically mild (Figure 1 through Figure 4) yet statistically significant for only week 1 (P = .02). At week 1, the erythema induced by the TruPulse was mildly less than that caused by the UltraPulse. All panel members considered the UltraPulse sides to have improved slightly more than the TruPulse sides at 2 months. The difference in efficacy between the 2 lasers reached statistical significance for month 2 (P = .02), yet no difference was noted at 6 months (Figure 5 and Figure 6). Adverse effects were the same for both laser treatment areas and included 0% scarring, 0% hypopigmentation, 20% hyperpigmentation, and 8% infection (2 patients with a positive culture for Staphylococcus aureus and 1 patient with a herpetic infection). All infections occurred after the full course of the preprocedure and postprocedure medication had been completed.
Postprocedure wound care was the same for both treatment sides and included Second Skin (Spenco Medi-
cal Ltd, West Sussex, England) dressings, dilute vinegar 
solls followed by application of vaseline or healing oint-
ment (Aquaphor, Beiersdorf Inc, Norwalk, Conn), and 
continuation of oral antibiotics and antivirals for a total of 
1 week.

OUTCOME PARAMETERS

Photographs of the treatment areas were taken before treat-
ment, immediately after treatment, and at 1 week, 2 weeks, 
2 months, and 6 months. The same 35-mm camera (Dine 
Macro-light system Model II, LA Dine Inc, Palm Beach Gar-
dens, Fla) and ASA 100 film were used for all photo-
graphs. Standard photographic views (en face, 45°, and 90°) 
were taken at each patient visit. All film was processed by 
the same laboratory.

A 5-member panel, blinded to study objectives and la-
er assignments, evaluated the clinical photographs. All panel 
members were trained for the outcomes evaluation by re-
viewing nonstudy photographs. Erythema and edema were 
scored, using a continuous numeric scale of 1 to 10, for 
the right and left sides of the treatment areas at week 1, 
week 2, and month 2 follow-up intervals. Before treat-
ment and 2 and 6 months after treatment photographs were 
shown to evaluate efficacy. Percentage of wrinkle improve-
ment, on a scale of 0% to 100% improvement from base-
line, was scored for the right and left sides of the treat-
ment areas.

Profilometry measurements using silicone (Silfo, De-
velopments Ltd, England) skin casts were used to quan-
titate wrinkle improvement. Skin casts of a wrinkle on each 
treatment side were obtained before the treatment and at 
2 and 6 months. Placement of follow-up casts was based on 
photographic localization of the baseline cast over a spe-
cific wrinkle. All wrinkle casts were analyzed by the same 
laboratory using depth, area, and shadowing measure-
ments.4

Evaluation of the square tattoos before and after la-
er resurfacing did not demonstrate any significant de-
crease in surface area (Table 3). The measurements 
showed no evidence of long-term collagen shrinkage.

Histological sections demonstrated a larger amount of 
residual thermal damage (defined as the depth of al-
tered collagen measured from the top of the ablated sur-
face) with increasing numbers of passes with the Tru-
Pulse: 1 pass, 0-5 µm, and 5 passes, 85 µm. Additional 
histological data from nonstudy patients treated with the 
TruPulse using the same protocol found additional lev-
els of thermal damage: 2 passes, 17 µm; 3 passes, 25 µm; 
and 4 passes, 40 µm (Figure 7). The UltraPulse laser 
(Figure 8) caused slightly more residual thermal dam-
age: 2 passes, 40 µm; 4 passes, 60 µm with local areas 80 
to 100 µm. Damage to endothelial cells was visualized at 
depths of 250 µm. Six-month postprocedure biopsy 
specimens from 1 patient showed a band of new colla-
gen in the papillary dermis measuring 30 µm on the 
TruPulse side (pretreatment band, 8 µm; 207% 
increase) and 40 µm on the UltraPulse side (pretreat-
ment band, 13 µm; 208% increase). A second patient 
with pretreatment and posttreatment biopsy specimens in 
the periorbital area showed no significant increase in 
collagen for either laser. The epidermis in all postproce-
dure biopsy specimens showed less maturation disarr-
ay, fewer dyskeratotic cells, and a less flattened rete 
ridge pattern.

The carbon dioxide lasers with a short pulse duration can 
effectively treat photodamaged skin and wrinkles.1-3,5,6 
The possibility of pronounced postprocedure erythema, 
which on average lasts as long as 8 to 12 weeks but may 
last as long as 6 months,2 deters some patients from 
electing to undergo this procedure. One week after 
resurfacing biopsy specimens from this study demon-
strate that the erythema correlates histologically with a 
superficial perivascular lymphocytic infiltrate, ectatic 
blood vessels, and neovascularization. These findings 
are normal wound healing responses, and new collagen 
formation, a potential component of wrinkle improve-
ment, is dependent on this inflammatory phase of 
wound healing.

The question arises as to whether an equally effica-
cious outcome can be achieved if the residual thermal 
damage is limited, and in this way the erythematous, or
inflammatory phase of wound healing is diminished. The results from this study found that a shorter pulse duration laser caused slightly less erythema and no significant decrease in efficacy at weeks 1 and 2. The difference in erythema was clinically mild and diminished over time. Panel evaluations of efficacy showed a trend toward the UltraPulse causing more wrinkle reduction, but the difference was not statistically significant. In comparison, the profilometry measurements at month 2 demonstrated that the UltraPulse caused more wrinkle reduction, yet by month 6 there was no significant difference in outcome.

### Table 1. Laser Parameters for TruPulse and UltraPulse Treatment Sites

<table>
<thead>
<tr>
<th>Treatment Sites</th>
<th>Perioral</th>
<th>Periorbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>TruPulse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse energy, mJ</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Spot size, mm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pattern generator</td>
<td>No</td>
<td>Yes†</td>
</tr>
<tr>
<td>No. of passes</td>
<td>3-6</td>
<td>2-4</td>
</tr>
<tr>
<td>UltraPulse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse energy, mJ</td>
<td>350-450</td>
<td>250-350</td>
</tr>
<tr>
<td>Spot size, mm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pattern generator</td>
<td>Yes†</td>
<td>No</td>
</tr>
<tr>
<td>No. of passes</td>
<td>3</td>
<td>2-3</td>
</tr>
</tbody>
</table>

†When the pattern generator (2.25-mm spot size) was used, the pulse energy was decreased so that it was equivalent to 350 to 450 mJ with the 3-mm spot size.

### Table 2. Outcome Scores for TruPulse vs UltraPulse Treatment Sites

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TruPulse Treatment Side</th>
<th>UltraPulse Treatment Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema score, week 1</td>
<td>4.37†</td>
<td>4.60</td>
</tr>
<tr>
<td>Erythema score, week 2</td>
<td>2.14</td>
<td>2.26</td>
</tr>
<tr>
<td>Erythema score, month 2</td>
<td>0.61</td>
<td>0.67</td>
</tr>
<tr>
<td>Edema score, week 1</td>
<td>2.20†</td>
<td>2.38</td>
</tr>
<tr>
<td>Edema score, week 2</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Edema score, month 2</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Percent rhytide improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>by panel evaluation, month 2</td>
<td>39.3†</td>
<td>43.2</td>
</tr>
<tr>
<td>by panel evaluation, month 6</td>
<td>40.0</td>
<td>40.6</td>
</tr>
<tr>
<td>Percent rhytide improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>by profilometry, month 2</td>
<td>11.4†</td>
<td>35.1</td>
</tr>
<tr>
<td>by profilometry, month 6</td>
<td>20.1</td>
<td>25.6</td>
</tr>
</tbody>
</table>

* Erythema and edema scores were rated by a 5-member panel based on a scale of 0 to 10.
†P = .05 comparing TruPulse (Tissue Technologies, Palomar Medical Products Inc, Lexington, Mass) and UltraPulse 5000 (Coherent Medical Inc, Palo Alto, Calif) scores.

### Table 3. Percentage Decrease From Baseline Tattoo Surface Area for Each Follow-up Interval

<table>
<thead>
<tr>
<th>Laser</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Month 2</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>TruPulse</td>
<td>1.2 ± 0.98</td>
<td>1.5 ± 1.0</td>
<td>3.3 ± 0.85</td>
<td>1.9 ± 0.50</td>
</tr>
<tr>
<td>UltraPulse</td>
<td>2.9 ± 1.29</td>
<td>3.1 ± 1.68</td>
<td>3.2 ± 1.69</td>
<td>2.9 ± 1.44</td>
</tr>
</tbody>
</table>

* Values are mean ± SD. There was no statistically significant difference between before and after treatment surface area measurements for each laser (TruPulse, Tissue Technologies, Palomar Medical Products Inc, Lexington, Mass; UltraPulse 5000, Coherent Medical Inc, Palo Alto, Calif) or between lasers.
One should note that the shorter pulse-duration laser was generally used at higher fluences and with more passes than the longer pulse-duration laser. A comparative trial using the 2 lasers at equivalent fluences and number of passes would probably have caused a more distinct difference in both the amount of erythema and the efficacy. Furthermore, profilometry data can be difficult to interpret because a slight alteration from baseline in patient expression, orientation, or wrinkle identification can bias the results. In this study, it is unlikely that the UltraPulse sides had less wrinkle reduction at month 6 than month 2.

The histopathological presence of a wrinkle is often subtle. Some wrinkles are due to repetitive stressing of the skin and may be associated with no visible histological findings. More pronounced frown lines caused by muscular contraction have deeper thickened hypodermal septae. Rhytides arising from photodamage are associated with decreased collagen in the papillary dermis and an accumulation of elastotic material in the mid-dermal elastotic. The finer collagen fibers of the papillary dermis diminish, causing the epidermis to rest on a more condensed papillary dermis. Wrinkles form because the superficial dermis has diminished in size and the epidermis, which has maintained or increased its length, adjusts by crinkling. Chronological aging causes progressive disappearance of the superficial network of perpendicular oxytalan fibers that also may cause the skin to wrinkle because of decreased contractility. This study found several pretreatment wrinkles to contain focal areas of mid-dermal elastolysis and loss of the normal architecture of the superficial papillary dermal elastic structure containing oxytalan and eulanin fibers.

With these concepts of wrinkle development in mind, proposed mechanisms of action for resurfacing include leveling of the skin surface by tissue ablation, new collagen formation resulting from thermal injury, and collagen shrinkage that tightens the skin. For each laser, increasing the number of passes correlated with a greater depth of residual thermal damage. The shorter pulse-duration laser caused less thermal damage with each pass, yet to achieve the same tissue effect, more passes had to be performed. The additional...
passes caused increased amounts of thermal damage to the same depth similar to that seen with fewer passes with the longer pulse–duration laser. This study showed that using the lasers to achieve the same treatment tissue effect led to similar long-term clinical outcomes. As slightly less thermal damage per pass was induced, the shorter pulse–duration laser may be better suited for more superficial resurfacing where the level of ablation and depth of thermal damage need to be more precisely controlled. Superficial resurfacing is appropriate in the periorbital area, for mild photodamage and wrinkles, in darker skin-type individuals, and potentially, with further study, in the neck region with its delicate skin. Increasing the number of passes, or using a longer pulse–duration laser, can achieve deeper thermal damage, which is more desirable when treating more extensive photodamage.

Analysis of the skin following dermabrasion and deep chemical peeling shows a new layer of dense, compact collagen in the papillary dermis arranged in parallel alignment to the epidermis (repair zone), similar to a superficial scar. Behin et al.12 found that the band of new collagen that formed following both phenol peeling and dermabrasion increased from week 2 to week 16. Kligman et al.13 noted an area of dermal collagen 2 to 3 mm wide on skin that had received a phenol peel 15 to 20 years earlier. Thin, randomly located elastic fibers were present within the collagen band. The epidermis is thicker and has restoration of the normal rete ridge pattern, less maturation disarray, and fewer dyskeratotic cells. The long-term effect of laser resurfacing on collagen remodeling is less well documented. Cotton et al.14 examined resurfaced skin 3 months following resurfacing and found a dermal repair zone in an unspecified percentage of 4 patients' biopsy specimens. No quantitative comparison with pretreatment skin was noted. There was more fibrosis with higher laser energies, yet this increase was not statistically significant. It is important to note that there is a thin dermal repair zone in photodamaged skin itself, secondary to years of exposure to UV light.15 Seckel16 found a new layer of collagen present at 1 and 2 months but not at 3 months after resurfacing, suggesting that the zone of repair is not a long-term finding. Other clinical studies17 have found a maintained growth in the collagen repair zone. Wrinkle improvement in patients who have undergone resurfacing appears to increase between months 1 and 6, suggesting that fibroblast activity and collagen remodeling occur during this period to form a sustained band of fibrosis. Documenting increased collagen formation in resurfaced skin by in situ hybridization and Western blot analysis, similar to 12 weeks postdermabrasion results in which Nelson et al.18 showed a 3-fold increase in type 1 procollagen, would provide more evidence to support this proposed mechanism.

Ideally, one would like to establish a dose-response association between depth of thermal damage and amount of new collagen formation after the procedure, yet not all the 6-month biopsy specimens in this study showed a significant band of new collagen. The limited new collagen seen on the postprocedure biopsy specimens may be because patients, especially the one treated in the peri-orbital area, had relatively superficial wrinkles and were treated with fewer laser passes. The mild thermal damage may have induced a less visible amount of new collagen, suggesting that superficial resurfacing causes minimal dermal changes. Limited statistical analysis can be completed because only 4 six-month biopsy specimens were obtained in this study.

Shrinkage of the skin is visible during resurfacing, and heat from the laser probably induces denaturation of some collagen fibers, an event that occurs at 55°C to 62°C.19 The uncoiled and shorter collagen fibers may form a sustained band of fibrosis. Documenting the lack of evidence in this study of collagen shrinkage at 2 and 6 months after the procedure, as demonstrated by minimal change in the surface area of resurfaced skin measured to the pixel unit by a digital imaging system, supports a limited role of collagen shrinkage in wrinkle improvement. In contrast, measurements of collagen bands on electromagnetic images of resurfaced skin have shown a decrease in the length of collagen fibers by 27% up to 2 and 3 months after the procedure.13 Further studies evaluating more specifically the length of collagen fibers at long-term resurfac-
ing follow-ups may be more definitive regarding the issue of collagen shrinkage.

CONCLUSIONS

Compared with the longer pulse–duration carbon dioxide laser, the shorter pulse–duration carbon dioxide laser, used with higher energy and more passes, caused slightly less erythema in the first 2 weeks while maintaining efficacy. The difference in erythema in the first 2 weeks was statistically significant yet clinically less relevant. The longer pulse–duration laser required lower energy and fewer number of passes to achieve an equivalent depth of ablation, level of residual thermal damage, and degree of efficacy. With either laser, increasing the number of passes increased the thermal damage and correlated with increased postprocedure erythema. The shorter TruPulse allows for more superficial tissue damage per pass and therefore appears better suited for situations requiring superficial ablation akin to erbium:YAG laser skin resurfacing.20 The longer UltraPulse achieves a desirable depth of tissue damage with fewer passes. The data on a limited number of patients did not support the long-term presence of collagen shrinkage and found a thin band of new papillary dermal collagen in some posttreatment sites. Further studies involving larger numbers of long-term follow-up skin specimens of laser-treated patients would provide more information regarding the mechanisms of action of laser skin resurfacing.

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